INSIDE STANFORD MEDICINE

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The fall issue of *Stanford Medicine* magazine showcases new approaches to pediatric care.

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Ex-49er back at Stanford to finish residency

By Patricia Hannon

PAUL SAKUMA

Milt McColl, a successful medical device entrepreneur and former linebacker for the San Francisco 49ers, is a second-year resident in the Stanford Health Care-O'Connor Hospital Family Medicine Residency program. McColl earned his medical degree from Stanford in 1988.

When Milt McColl, MD, decided to finish his residency after nearly 30 years away from clinical medicine, he didn't expect to be back at Stanford, where he played football and earned his bachelor's and medical degrees.

That, he said, was a stroke of luck, or what he said his father calls the moment "when preparation meets opportunity."

McColl, 58, admits that brand of luck determined most of his professional life after college. It was there when he was signed as a free agent by the 49ers — the same week he was accepted to Stanford's medical school — as well as when he landed his first medical internship, and when the medical device industry captured his attention.

But deciding to finish his residency was different.

"Nothing I've done in life is because I planned it. Usually it was because the opportunity sort of arose," McColl said recently as he grabbed a quick lunch at a bustling café at Santa Clara Valley Medical Center. "This was the most thought-out, planned-out thing I've done in my career because it was really difficult two years ago to make the decision to do it."

It was especially tough to leave his CEO position at Gauss Surgical, which developed a real-time blood loss measuring device for operating rooms. "I think the hardest discussion was with the investors that I've been running a company with for five years," McColl said.

But McColl handed the CEO role to company founder Siddarth Satish, whom he met at Stanford, making a full commitment to the Stanford Health Care-O'Connor Hospital Family Medicine Residency program, where he is a second-year resident.

An unusual career trajectory

McColl's trajectory from a successful startup CEO to resident isn't as circuitous as it might appear. He always kept a hand in medicine, volunteering at a free clinic and working with medical professionals in device development. But by his mid-50s, the business demands weighed on him, and he and was looking for something new.

"I was kind of worn out, and was volunteering at a primary care clinic in San Francisco," he said. "About once a month I would go up there, and I started realizing how much I enjoyed working with patients and doing medicine."

So, he explored the feasibility of finishing his residency. He had his medical license, which he got after his first internship in 1989, but some program directors intimated that he didn't fit the profile of a typical resident. At O'Connor, Grace Yu, MD, the residency program director, admitted that McColl was an unusual candidate, but his enthusiasm for the program and clinical medicine impressed her. Yu, a clinical assistant professor of medicine at Stanford and graduate of its medical school, said she and former program director Robert Norman, MD, talked in-depth with McColl about his goals and the potential pitfalls. But clinical work wasn't new to him, and recommendations from the physicians at the clinic where McColl volunteered stood out.

"They said, 'Nobody else in their 50s would be thinking about this, or if they See MCCOLL, page 6

Study finds mechanical heart valves can be safer option for certain patients

By Tracie White

LESLIE WILLIAMSON

Joseph Woo and his colleagues found that for some patients, mechanical heart valves may be a safer option than valves made of tissue.

Mechanical heart valves may be safer in certain cases than valves made of animal tissue and should be used more, especially in younger patients, according to a study by researchers at the School of Medicine.

The study also found that unlike what's recommended in the national guidelines, which say patients 50-70 years old undergoing aortic or mitral valve replacement should be given a choice of either a mechanical or biological valve, the best choice in fact can hinge on whether the aortic or mitral valve is being replaced.

The study shows that for patients undergoing mitral valve replacement, a mechanical valve is actually beneficial until the age of 70. On the other hand, for patients undergoing aortic valve replacement, the benefit of implanting mechanical valves ceased after the age of 55.

"This has potential to significantly impact the current national practice guidelines," said Joseph Woo, MD, professor and chair of See VALVE, page 7

Algorithm can diagnose pneumonia better than radiologists, study says

By Taylor Kubota

Researchers have developed an algorithm that offers diagnoses based off chest X-ray images. It can diagnose up to 14 types of medical conditions and is able to diagnose pneumonia better than expert radiologists working alone.

A paper about the algorithm, called CheXNet, was published Nov. 14 on the open-access, scientific preprint website *arXiv*.

"Interpreting X-ray images to diagnose pathologies like pneumonia is very challenging, and we know that there's a lot of variability in the diagnoses radiologists arrive at," said Pranav Rajpurkar, a graduate student in the Machine Learning Group at Stanford and co-lead author of the paper. "We became interested in developing machine learning algorithms that could learn from hundreds of thousands of chest X-ray diagnoses and make accurate diagnoses."

The work uses a public data set initially released by the National Institutes of Health Clinical Center on Sept. 26. That data set contains 112,120 frontal-view chest X-ray images labeled with up to 14 possible pathologies. It was released in tandem with an algorithm that could diagnose many of those 14 pathologies with some success, designed to encourage others to advance that work. As soon as they saw these materials, the Machine Learning Group — a group led by Andrew Ng, PhD, adjunct professor of computer science — knew they had their next project.

The researchers, working with Matthew Lungren, MD, MPH, assistant professor of radiology at the School of Medicine, had four Stanford radiologists independently annotate 420 of the images for possible indications of pneumonia. The researchers chose to focus on this disease, which brings 1 million Americans to the hospital each year, according to the Centers for Disease Control and Prevention, and is especially difficult to spot on X-rays. In the meantime, the Machine Learning Group team got to work developing an algorithm that could automati- See X-RAY, page 6

Med school finances explained at meeting

PAUL SAKUMA

Marcia Cohen, Lloyd Minor and Samuel Zelch fielded questions from the audience at the town hall.

The School of Medicine is on solid financial ground.

That was a key message from Samuel Zelch, MBA, chief financial officer and associate dean, during his presentation Nov. 13 at a town hall meeting on the school's finances. For the hundreds of employees who attended the event in Berg Hall, at the Li Ka Shing Center for Learning and Knowledge, it was an opportunity to learn more about the financial state of the school, as well as to ask questions about it. Two more town halls on the subject are scheduled for 2018 — one in the winter and another in the spring.

"We'll all be able to do a better job of stewarding and managing our resources responsibly if we understand where those resources are coming from and where they sit and what they're intended for," Dean Lloyd Minor, MD, said in introductory remarks. He, Zelch and Marcia Cohen, MBA, senior associate dean for finance and administration, later fielded questions from the audience.

Zelch said that financial troubles had not prompted the meeting.

"In fact, we're doing very well," Zelch said. "We have significant resources, and we're quite fortunate compared to many of our peer schools."

Rather, the town hall was an effort to promote greater financial transparency, he said.

Big revenue growth

The school's revenue for fiscal year 2017 was $2.4 billion — an increase of 46 percent from four years ago, Zelch said. Payments to the school from Stanford Health Care and Stanford Children's Health accounted for 43 percent of that figure, and another 28 percent came from sponsored research, such as grants from the National Institutes of Health. The rest came from student tuition, endowment income, gifts and other sources.

Overall, Stanford Medicine, which includes the medical school, Stanford Health Care and Stanford Children's Health, generated 69 percent of the university's total revenue of $9.8 billion for fiscal year 2017. This is largely due to the strong revenue growth at Stanford Health Care and Stanford Children's Health: It totaled $5.9 billion, up 53 percent from four years ago.

On its website, the school's Office of Fiscal Affairs has posted a link where employees can pose questions or suggest topics they would like to see covered at a future finance town hall event. **ISM**

Stanford scientists among those funded by Stand Up To Cancer

Several Stanford Medicine researchers are on "dream teams" that will receive funding from the organization Stand Up To Cancer to develop strategies to detect and treat early-stage cancer.

Maximilian Diehn, MD, PhD, assistant professor of radiation oncology, is a co-leader of the SU2C-LUNGevity American Lung Association Lung Interception Translational Research Team, which received a $2 million grant. The team will work on developing a diagnostic tool that uses information from low-dose CT scans and from blood-based assays, which detect circulating tumor DNA and cells. The funding will support development and pilot testing of the tool, which aims to speed the detection of lung cancer. Ash Alizadeh, MD, PhD, assistant professor of medicine, and postdoctoral scholar Young-Jun Jeon, PhD, also are on the team.

In addition, Sanjiv "Sam" Gambhir, MD, PhD, professor and chair of radiology and director of the Canary Center for Cancer Early Detection at Stanford, is the principal Stanford investigator of the SU2C-LUNGevity American Lung Association Lung Cancer Interception Dream Team. This $5 million, four-year project entails creating a molecular atlas of pre-cancerous lung tissue; developing blood tests capable of identifying patients with early lung cancer recurrence and nasal, blood and radiological techniques to discern whether abnormalities on chest imaging are cancerous; and developing tests to determine who is most likely to benefit from particular treatment strategies. The team is a collaboration between Stanford, Johns Hopkins University, UCLA, Boston University, Harvard University and the Francis Crick Institute.

Stand Up To Cancer is a program of the Entertainment Industry Foundation. **ISM**

Researchers identify attributes of high-value oncology, primary care

By Krista Conger

Mounting pressure on U.S. physicians to control skyrocketing health care spending has led to a demand to understand how to provide the best possible care at the lowest possible cost.

Now, two overlapping teams of researchers at the School of Medicine have identified tangible changes that physicians can make to meet goals to improve the value of health care specified by the Medicare Access and CHIP Reauthorization Act of 2015 and reinforced by private health insurers. Beginning in 2019, Medicare payments to physicians will be adjusted up or down by annually increasing amounts according to how a doctor meets national benchmarks for high-value care.

> "No one has ever conducted this type of research in physician office sites before."

In two separate studies, the researchers outline several tangible attributes of cancer care and primary care that will allow physicians and their teams to rise to this challenge.

"No one has ever conducted this type of research in physician office sites before," said Arnold Milstein, MD, professor of medicine at Stanford. "These studies are unprecedented, not only in what they examined, but in their potential to affect the practice of medicine on a national level."

"Cancer care is expensive, and physicians and insurers sometimes question the value of the nonmedical or nonclinical services that we provide for patients," said Douglas Blayney, MD, professor of medicine. "Here, we identify for the first time specific aspects of high-quality, low-cost care that provide value for patients and payers and that can be adopted by doctors and organizations across the country."

Blayney is the lead author of the cancer-care study, which was published Nov. 16 in *JAMA Oncology*. Milstein is the senior author of that study, as well as the senior author of the study that identified the distinguishing features of high-value primary care practices, which was published online Nov. 13 in *Annals of Family Medicine*.

Arnold Milstein

Douglas Blayney

Milstein is the director of Stanford's Clinical Excellence Research Center, the first university-based research center exclusively dedicated to discovering, testing and evaluating cost-saving innovations in clinically excellent care. Blayney is a member and the former medical director of Stanford's Cancer Institute.

Digging into national data

For both studies, the researchers used never-before-available claims data from insurance companies to identify physician-practice sites across the country that deliver high-quality care with less total health care spending.

The oncology study analyzed data from thousands of cancer patients at oncology sites throughout the Pacific Northwest and Midwest from January 2007 to May 2014; the primary care study analyzed commercial health insurance claims from 2009 to 2011 from more than 40 million patients and 53,000 primary care practice sites.

The researchers then compared the average annual total health care spending per primary care patient or spending per cancer treatment episode at each of the high-quality care sites. Practice sites that ranked at the top of both measures (delivering both high-quality and low-cost care) were designated as high-value sites for further study.

The researchers then conducted extensive site visits of high-value and average-value physician practices to tease out attributes of care that distinguished high-value sites — sites that deviate positively from the norm.

"We wanted to understand what's different about the care of the high-performing clinical teams that allows them to lower the cost of excellent care, which is an aspiration of both Congress and of private insurers," said Milstein. "These studies are the first to distinguish attributes of physicians who provide great, more affordable care."

Three broad themes capture the distinguishing features of high-value U.S. cancer care: an early discussion with each patient of the limitations, expectations and goals of cancer care; the early involvement and normalization of palliative care — not just for end-of-life issues, but also to help alleviate or manage treatment side effects; and a dedicated outpatient facility for cancer patients to address their urgent care needs in an ambulatory care setting.

A fourth attribute — the presence of a go-to point person, often a nurse or a nurse practitioner, to help patients problem-solve difficulties around self-care and navigate a sometimes confusing health care system — was also important, the researchers found.

"Our findings suggest that many of the places that provide high-value care are also particularly good at providing these often

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STANFORD MEDICINE

Town hall event focuses on Stanford Health Care's future plans

By Grace Hammerstrom

Stanford Health Care's challenges and its plans for the future were among the topics addressed at the State of Stanford Health Care meeting Nov. 6 at the Li Ka Shing Center for Learning and Knowledge.

SHC President and CEO David Entwistle and School of Medicine Dean Lloyd Minor, MD, addressed a standing-room-only crowd of almost 400, with another 1,500 employees watching the first-ever online, interactive broadcast of the annual event.

STEVE FISCH

(Top) The State of Stanford Health Care meeting at the Li Ka Shing Center for Learning and Knowledge drew nearly 400 people, and another 1,500 watched an online, interactive broadcast of the event. (Bottom) David Entwistle and Lloyd Minor spoke at the Nov. 6 event.

The two Stanford Medicine leaders laid out the collaborative work being done across all three organizations — Stanford Health Care, Stanford Children's Health and the School of Medicine — and they used the interactive polling system to get input from employees attending both onsite and online.

> "There are a number of areas in which we have already had an impact in a short period of time."

Later that week, Entwistle also shared his presentation with an employee audience at a tech facility on Embarcadero Road in Palo Alto, and with employees at the SHC office in Newark.

Entwistle shared a performance snapshot of SHC, which showed high scores in customer service and patient satisfaction, as well areas where improvement in quality is needed. "It's important to know where you are on the track, and where you are currently headed," he said. "Numbers are not the core of everything we do, but they certainly tell us where we are making progress on the things we value as an organization."

He also shared SHC's plans for sustainability in an increasingly competitive marketplace. "Stanford is not on a trajectory to acquire more ambulatory hospitals," he said. "Instead, we will continue to develop strategic alliances with the people who are already sending us patients."

Entwistle also addressed areas in which the organization needs to improve. Using the interactive polling system, he asked employees to guess where SHC ranks on the University Health System Consortium/Vizient quality measurement of 107 hospitals. Only 30 percent of the responding employees knew that it ranked 71st.

"When you look at all the amazing things we do, there are still opportunities for improvement," said Entwistle. He outlined SHC's "value equation," which attributes success to a combination of quality, service, cost and employees.

"We are looking at the things we can do to make a difference," he said. "There are a number of areas in which we have already had an impact in a short period of time, and a number of areas where there are still significant opportunities to improve, such as mortality, infection and surgical cost containment."

Strategic planning

The second half of the meeting was devoted to the integrated strategic planning process involving Stanford Health Care, Stanford Children's Health and the Stanford School of Medicine. The dean described how collaborative working groups are helping to develop the plan.

"In my five years at Stanford, and from what I know from before I arrived, never before have we worked so well together as we do now," Minor said. "All three entities share the same mission of patient care, research and teaching, and all are remarkably aligned around that vision."

As an example, Minor noted that the working group on care delivery models includes Robert Harrington, MD, from the school; Quinn McKenna from SHC; and Kim Roberts from Stanford Children's Health. The team is looking at what the services across the care continuum will look like in 2025, taking into account intensive competition and the fact that Stanford is a high-cost system. Another working group is focusing on safety, quality and value, with a goal of positioning Stanford as one of the top 10 academic medical centers in the country by 2025.

These working groups will continue to meet to finalize their recommendations; the final plan will be presented to the Stanford University Board of Trustees in 2018. **ISM**

Care

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unreimbursed, nonmedical services," said Blayney.

Shepherding each primary care patient

A similar concept, identified as "care-traffic control," was one of the takeaways from the study of high-value primary care sites. "We found that physicians at these sites were thinking more deeply about what each individual patient needs to navigate in the periods between primary care office visits," said Milstein. "Does their illness affect their executive functioning? Are they following through on laboratory tests? Are they taking their medicines as prescribed? Are all of the doctors and specialists a patient sees aware of important aspects of their care plan, such as the existence of an advance directive? Although this is unknown territory to physicians in average-performing primary care practices, it is actively surveilled and supported by their high-value peers."

Other important themes in primary care include the use of treatment protocols — for example, standing orders supported by electronic health care records to ease the cognitive burden on the care staff — and a system to ensure that the compensation packages for physicians and care staff members reflect the quality and affordability of the care they provide.

"No one has ever studied this intersection of high-quality and low-cost health care at a national level for individual physician offices," said Milstein. "We're hopeful that these studies will help American physicians and policymakers better understand what tangible changes in care-delivery practices will allow physicians to meet our national thirst for more with less."

"Our research uses the concept of positive deviants to uncover existing solutions to health care challenges that can be adopted by clinicians around the country to produce similar results," Blayney added.

The studies are examples of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors of the *JAMA Oncology* paper are Melora Simon, MPH, a former project director at the Clinical Excellence Research Center; former visiting instructor Beatrice Podtschaske, PhD; former research coordinator Margaret Shyu; and visiting scholar Craig Lindquist, MD, PhD. A researcher from the Hutchison Institute for Cancer Outcomes Research also contributed to the paper.

Other Stanford co-authors of the *Annals of Family Medicine* paper are Simon and Julia Murphy, former project leader at Stanford's Clinical Excellence in Research Center. Researchers from Harvard Medical School, Case Western Reserve University School of Medicine and QuintilesIMS also contributed to the study.

Blayney has consulted for the Michigan Oncology Quality Consortium, is a volunteer leader of ASCO's QOPI program and is a consultant for and stockholder in PRM/CARET. Simon has an immediate family member who is employed by and is a shareholder of Guardant Health Inc.

The research in both papers was supported by the Peterson Center on Healthcare.

Stanford's Department of Medicine also supported the work. **ISM**

Researchers awarded grant from NIH to study autism

By Bruce Goldman

Researchers at Stanford and UCLA have received a $9.3 million grant from the National Institutes of Mental Health to study the ways that many genes associated with autism spectrum disorder may converge to affect a smaller number of molecular pathways or cellular processes responsible for the condition.

Sergiu Pasca

The Stanford team — led by Sergiu Pasca, MD, assistant professor of psychiatry and behavioral sciences — will receive about $4 million.

Pasca's laboratory has devised a way to produce three-dimensional neuronal cultures called human brain spheroids — tiny round balls of more than 1 million cells each — from induced pluripotent stem cells, or iPS cells. These spheroids, which resemble specific brain regions, can be assembled to serve as a window through which scientists can observe, in a dish, key molecular and cellular processes that take place in a developing human brain.

Pasca and his Stanford colleagues will genetically engineer iPS cell lines carrying mutations in various genes linked to autism spectrum disorder. They will use the resulting iPS cell lines to derive cortical spheroids containing excitatory neurons and ventral-forebrain spheroids containing inhibitory neurons. His group will work closely with co-investigator John Huguenard, PhD, professor of neurology and neurological sciences, and collaborators at UCLA to seek abnormalities in cells derived in these 3-D brain cultures.

The goal is to better understand the roots of the disorder by looking for areas where mutations in numerous disparate genes lead to deficiencies in a much smaller number of biochemical pathways. **ISM**

Dolphin mouths house 'the dark matter of the biological world'

By Nicoletta Lanese

Researchers have identified two deep lineages of bacteria that have never been characterized before — and they found them in a dolphin's toothy grin.

These deep lineages are known as phyla. A phylum is a broad taxonomic rank that groups together organisms that share a set of common characteristics due to common ancestry. The discovery of two bacterial phyla, as well as additional novel genes and predicted products, provides new insights into bacterial diversity, dolphin health and the unique nature of marine mammals in general, said David Relman, MD, professor of medicine and of microbiology and immunology at the School of Medicine.

A paper describing the research was published Nov. 16 in *Current Biology.* Relman, who holds the Thomas C. and Joan M. Merigan Professorship, is the senior author. The lead author is Natasha Dudek, a graduate student at UC-Santa Cruz.

The U.S. Navy's Marine Mammal Program reached out to Relman more than 10 years ago for help in keeping its dolphins healthy. The animals are highly trained and perform missions at sea.

Previous research by Relman's group, in collaboration with the Marine Mammal Program, revealed a surprising number of never-before-seen bacteria in dolphin and other marine mammal samples, particularly those swabbed from the dolphins' mouths, said Relman, who is also chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System. Some of the bacteria found in the current study are affiliated with poorly understood branches of the bacterial tree.

NATIONAL MARINE MAMMAL FOUNDATION

Studying the bacteria found in the mouths of dolphins is giving researchers insight into dolphin health and the unique nature of marine mammals in general.

Striking gold

"These organisms, about which we have known just a tiny bit, are basically the dark matter of the biological world," he said. "We knew there was gold in those dolphin mouths, and we decided it was time to go after it with more comprehensive methods."

In the new study, the researchers identified bacterial lineages by reconstructing their genomes from short bits of DNA. The genome of a given cell serves as its blueprint and contains all its operating instructions, encoded in DNA. The researchers named one of the newly identified lineages Delphibacteria, in honor of the dolphins (Delphinidae is the Latin name for oceanic dolphins).

By looking at the genes encoded in the genomes of Delphibacteria representatives, the researchers gained insight into the bacteria's lifestyle. The bacteria are predicted to express a property called denitrification that may affect dolphins' oral health: The chemical process can cause inflammation and could be connected to gum disease. Denitrification also occurs in plaque on human teeth, suggesting that something about mammalian mouths selects for this process.

Putting puzzle together

The researchers differentiated between bacteria and predicted their behavior by looking broadly at their genomes. "What we do first is shear the DNA into a bunch of little bits and pieces, the mix of DNA is sequenced and we then try to figure out how the genomes were originally assembled," said Dudek. If a gene is one piece of a puzzle, the researchers put together the whole puzzle. This approach has been spearheaded by collaborator and study co-author Jillian Banfield, PhD, at UC-Berkeley.

David Relman

By taking this approach, the researchers spotted bacteria that had long eluded characterization. They also identified a number of unusual proteins, including previously unknown forms of Cas9. Cas9 proteins are part of a bacterial immune system called CRISPR-Cas, a system well-known for its use in gene-editing technology. Scientists can use this system to modify genomes and control how cells function. It can be used to turn genes on or off, replicate human diseases in animals and possibly prevent disease in humans.

"Typically, people are interested in small Cas9 proteins that might be easy to manipulate and deliver into cells," said Relman. "These are the opposite — they're enormously big." Different structures in the genes that encode these proteins account for the size difference, and the researchers suggest these large Cas9 proteins have different properties from those known before. Dudek plans to pursue this line of research further.

The study also feeds nicely into ongoing work in Relman's lab. A large, comparative study is underway to investigate how adaptation to life in the sea might affect marine mammal microbiomes. Beyond discovering and characterizing novel bacteria, Relman wants to apply his research to conservation.

"Marine mammals are becoming increasingly endangered," he said. "They are sentinel species for the health of the sea, and the more we can understand their biology, the better we can anticipate changes in the health of their environment."

Other Stanford co-authors are postdoctoral scholars Christine Sun, PhD, and Daniela Aliaga Goltsman, PhD, and former research associate Elisabeth Bik, PhD.

Researchers from UC-Berkeley also contributed to the study.

The Office of Naval Research supported the study. Stanford's departments of Medicine and of Microbiology and Immunology also supported the work. ISM

Stanford Medicine magazine showcases new approaches in pediatric care

By Patricia Hannon

There's something special about children and how they approach their world — wide-eyed, curious, energetic, creative, playful and trusting. They're also vulnerable, and that's why they count on the adults in their lives to take good care of them.

But when they're sick, that can be a challenge, especially for the medical professionals who are trying to make them better in an environment that's traditionally been designed around adult care.

The new issue of *Stanford Medicine* magazine, which was produced in collaboration with Lucile Packard Children's Hospital Stanford, shows how physicians, researchers and caregivers are transforming pediatric care to ensure that treatment puts children — and their families — at the center of their health care more than ever before.

Lloyd Minor, MD, dean of the School of Medicine, writes in his letter to readers that finding better and more precise medical options for children depends on a close "collaboration between Stanford Medicine researchers and clinicians who routinely bring medical advances from their laboratories to the benefit of our pediatric patients." Caring for children, he said, calls for special tools and strategies.

"The risk-to-benefit relationship is very different in children," Pejman Ghanouni, MD, PhD, assistant professor of radiology, said in a story about how he and other physicians are reimagining an adult-focused ultrasound treatment to successfully shrink some bone tumors in children. The procedure prevents children from having to undergo invasive surgery or radiation treatments that can be more harmful to them than to adults. "Kids are not small adults, so we really need different treatment options," he said.

Hospital expansion

Lucile Packard's belief in the importance of family and nature in the healing process is reflected in every corner of the 521,000-square-foot addition to the children's hospital that bears her name. The issue provides an inside look at the new facility, where every room has a planter box outside it and a view of a sweeping garden where children can play. The patient rooms are designed for families to use as gathering spaces, with extra sleeping space for two people. Animal sculptures and mosaics help families find their way around the hospital.

The facility includes the most advanced equipment and technologies to improve diagnostics and treatment with children and teens in mind.

Also featured in this pediatrics-themed issue:

- A story about a promising immunotherapy treatment known as CAR T-cell therapy, which relies on the use of a patient's own genetically modified immune cells to track down and attack leukemia cells.
- A look at how the shortage of affordable housing in the Bay Area puts the health care of children at risk, and how Stanford pediatricians are working with social service and housing agencies to help tackle the problem.
- An interview with Save the Children CEO Helle Thorning-Schmidt, who said that for her organization, "There is nothing more urgent than protecting children in armed conflict."
- A story about how virtual reality is being used to calm anxieties in fearful children and teens undergoing sometimes frightening medical procedures, as well as to help them understand their illnesses and how their physicians plan to treat them.

The issue also includes a look at how Joseph Woo, MD, professor and chair of cardiothoracic surgery, and his colleagues are increasingly using a patient's own tissues to repair, rather than replace, damaged aortic valves to give patients better long-term outcomes.

In addition, the issue includes an excerpt from a book by wilderness medicine experts Paul Auerbach, MD, a professor of emergency medicine at Stanford, and Jay Lemery, MD, an associate professor of emergency medicine at University of Colorado. In *Enviromedics: The Impact of Climate Change on Human Health*, the authors lay out the adverse health effects linked to global warming and call on physicians to lead the way in raising awareness of the problem.

The magazine is available online at http://stanmed.stanford.edu. Print copies are being sent to subscribers. Others can request a copy at 723-6911 or by sending an email to medmag@stanford.edu. ISM

Stem cells express genes differently in the lab dish than in the body

By Krista Conger

Stem cells in the body have a significantly different gene-expression profile than do the same cells when they're isolated in a lab dish, according to researchers at the School of Medicine.

The research suggests that any conclusions about stem cell function based on studies of isolated stem cells may now need to be reconsidered in light of the fact that the cells' biology changes during isolation. In particular, the researchers found that levels of certain RNA molecules increased when stem cells were isolated, whereas the levels of many other RNA molecules decreased.

"The cells in the animal clearly differ from those that are removed for study," said Thomas Rando, MD, PhD, professor of neurology and neurological sciences. "It's likely that some of these notable differences will skew our view of what the quiescent state entails for many types of adult stem cells. We and other researchers will need to rethink about how to profile stem cells in a way that accurately reflects their in vivo state."

"Cells in the animal clearly differ from those that are removed for study."

A study describing the research was published Nov. 14 in *Cell Reports*. Rando, the director of Stanford's Glenn Center for the Biology of Aging, is the senior author. Postdoctoral scholar Cindy van Velthoven, PhD, is the lead author.

New technology

Previous studies of stem cell gene expression have been largely based on cells that had been removed from their native environment within an animal and purified through a process called fluorescence-activated cell sorting, or FACS. Researchers then studied the function, biology and RNA content of the isolated cells.

In contrast, Rando and his colleagues used a new technology that allowed them to specifically label RNA molecules at the moment of their birth in muscle stem cells in mice. These molecules could then be rapidly extracted for study, in contrast to the several hours it can take to isolate whole stem cells from an animal. This approach allowed them to distinguish the patterns of gene expression in vivo from those observed in stem cells that had been isolated before analysis of their RNA.

The results confirmed what previous research in Rando's laboratory has shown: Despite their seemingly sleepy lifestyle, muscle stem cells are actually hotbeds of activity concealed by a tranquil outer membrane. The researchers were particularly surprised to learn that many of the RNAs made by the muscle stem cells in vivo are either degraded before they are made into proteins, or they are made into proteins that are then rapidly destroyed — a seemingly shocking waste of energy for cells that spend most of their lives just cooling their heels along the muscle fiber.

Effects of cell isolation

"Historically, we've thought of quiescence as an 'everything off,' or dormant, state," said Rando. "But our work has shown that the reality is quite different. Not only have we been missing transcripts that are present in vivo, but we are also puzzled as to why so many transcripts that are made in vivo are not made into proteins. It's possible that this is one way the cells stay ready to undergo a rapid transformation, either by blocking degradation of RNA or proteins or by swiftly initiating translation of already existing RNA transcripts."

STEVE FISCH

Thomas Rando and his colleagues used a new technology that allowed them to specifically label RNA molecules at the moment of their birth in muscle stem cells in mice.

The researchers found that isolated cells make large numbers of RNA molecules known to be involved in cellular stress and in cellular proliferation. Conversely, stem cells in the body make more RNAs involved in maintaining the quiescent state, in which they exist until called upon to make new muscle fibers.

The researchers additionally found that the process of isolating whole muscle stem cells for study caused some important RNA molecules to be degraded, rendering them undetectable in previous studies. These findings further support the notion that this quiescent state is not one of dormancy, but one of active regulation and controls — controls that are no longer needed once the cells are awakened to begin the process of tissue repair.

Rando and his colleagues expect that the new RNA labeling technique will be used by many other researchers studying adult stem cells.

"It's so important to know what we are and are not modeling about the state of these cells in vivo," said Rando. "Are we modeling it correctly when we look at stem cells isolated by FACS? This study will have a big impact on how researchers in the field think about understanding the characteristics of stem cells as they exist in their native state in the tissue."

Other Stanford authors of the study are postdoctoral scholars Antoine de Morree, PhD, and Ingrid Egner, PhD; and graduate student Jamie Brett.

The research was supported by the Glenn Foundation for Aging Research, the Muscular Dystrophy Association, the National Institutes of Health, the California Institute for Regenerative Medicine and the Department of Veterans Affairs.

Stanford's Department of Neurology and Neurological Sciences also supported the work. ISM

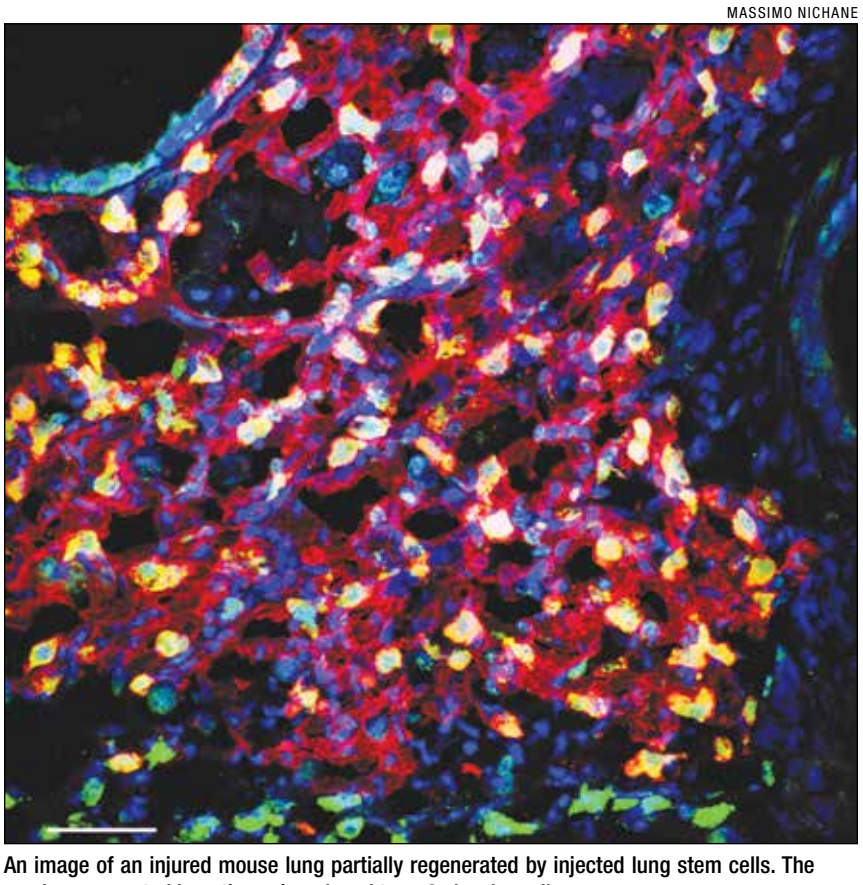
Researchers use stem cells to repair lung injuries in mice

By Christopher Vaughan

A researcher at the School of Medicine and his colleagues have succeeded in isolating mouse lung stem cells, growing them in large volumes and incorporating them into injured lung tissue in mice.

The work raises hopes for regenerative therapies that could heal currently intractable lung diseases.

MASSIMO NICHANE



An image of an injured mouse lung partially regenerated by injected lung stem cells. The newly regenerated lung tissue is red, and type-2 alveolar cells are green.

A study describing the research was published online Nov. 6 in *Nature Methods*. Kyle Loh, PhD, an investigator at the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and Bing Lim, MD, PhD, an investigator at the Genome Institute of Singapore, share senior authorship. The lead author is Massimo Nichane, PhD, currently a research scientist at the Stanford stem cell institute.

Kyle Loh

The lungs are among the most vital organs of the body. In conjunction with the cardiovascular system, they allow air to travel to every cell and get rid of the waste products of respiration, such as carbon dioxide. For many people with end-stage lung diseases, the only option is lung transplantation.

"Scientists have previously had little success in putting new lung cells into damaged lung to regenerate healthy tissue," Loh said. "We decided to see if we could do that in an animal model."

The researchers started by working to improve on current knowledge of lung stem cells. The lung is divided into two compartments, Loh said: the airway, which allows for passage of air in and out of the lung; and the alveoli, where gases pass in and out of the blood. Other researchers had previously isolated one stem cell for the airway and another stem cell for the alveoli. Loh and his colleagues searched for and found a single lung stem cell that could create cells in both the airway and the alveoli. These multipotent lung stem cells were typified by their display of a protein marker called Sox9.

From one to 100 billion billion

Once they had isolated the stem cells, they were able to make them multiply dramatically. Each mouse lung stem cell that they start started with was able to grow into 100 billion billion lung stem cells over the course of six months. Previously, researchers had not had much success expanding any lung stem cell populations in the laboratory.

Finally, they injected the stem cells into mouse lungs that had been injured by a variety of toxins. "What we saw was that these multipotent stem cells repaired the injured tissue and were able to differentiate into the many different kinds of cells that make up the healthy lung," said Nichane.

"Our newfound ability to grow these mouse multipotent lung stem cells in a petri dish in very large numbers, and the cells' ability to regenerate both lung airway and alveolar tissue, constitutes a first step towards future lung regenerative therapies," Loh said. "Future work will focus on whether analogous multipotent stem cells can be found and cultivated from humans, which may open the way to eventually replenishing damaged lung tissue in the clinic."

Researchers at the Genome Institute of Singapore, the Jackson Laboratory for Genomic Medicine in Connecticut and Clarkson University also contributed to the study. This work was supported by the Stanford-UC Berkeley Siebel Stem Cell Institute in addition to the Singapore A*STAR and National Medical Research Council. ISM

McColl

continued from page 1

were maybe you'd be wondering what their underlying motives were. But his are absolutely sincere, and you should really be thinking about him strongly,'" Yu said.

'Testament to his character'

After he was matched to O'Connor, McColl wanted to improve his clinical knowledge before the internship year of the residency started, so he accompanied doctors on rounds and reviewed medical references. "He put in all of that extra work because he knew it was going to be harder coming in, after being away from that rigor of clinical medicine for so many years," Yu said. "I think it was a testament to his character."

Yu believes that McColl's background in professional athletics and in medicine makes him aware of the work that goes into "crafting your profession."

"He appreciates … how wonderful the field of medicine can be — how deeply rewarding — and the impact that physicians can have, not only on their individual patient's lives but a community," she said.

Yu and McColl, and even other residents, worried about whether he would fit in. But Jeff Peng, MD, a chief resident this year, said McColl's humble and friendly personality squelched any uncertainty.

"It's so effortless," Peng said. "He just fits in so well."

He said McColl is always enthusiastic and doesn't hold himself above anyone else. "He doesn't really talk about all of his accomplishments," Peng said. "He focuses on learning and medicine, and he's just a great guy to have around."

McColl is thankful that other residents have accepted him. "Technically I'm not the strongest among any of them because they're fresh out of medical school and their minds are like sponges," he said. "But I think I have some other values that they appreciate in terms of just being around life for a while."

McColl wasn't naïve about the demands of a residency. His father, William "Bill" McColl, also played professional football (for the Chicago Bears) while earning his medical degree, and as a Presbyterian missionary took his family — including young Milt — to Korea and treated leprosy patients before settling into his orthopedic surgery practice in California.

Still, Milt McColl said he had his wife, Cindy, and their four sons to consider in returning to medicine. But their youngest had just left for college, making the timing good.

Cindy McColl said the idea of finishing his residency was always on her husband's mind and that because their kids are grown, it's workable in a way that it might not be for younger residents. "It's a much different thing to do when you have a young family. … I feel like at this age we have a lot more flexibility," she said.

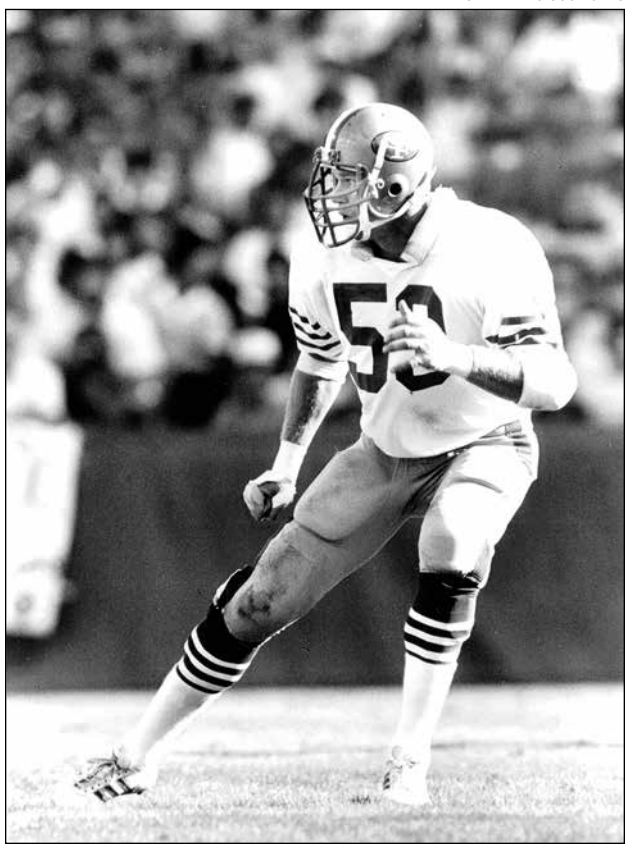
Following in father's footsteps

Milt McColl agreed. "I wouldn't have wanted to miss my kids growing up" or playing sports. His youngest is now a junior at Harvard and playing baseball there. The other boys, like McColl, his wife and all of McColl's siblings, have attended Stanford. One played water polo and now plays rugby; another played baseball, and the fourth was a swimmer. None of them are pursuing medicine.

McColl aspired early to follow his father into both football and medicine, and the elder McColl gave his son advice about doing both, including suggesting that he take first-year medical school classes during his senior year, even while playing college football. Following that advice brought Milt McColl his first encounter with the kind of "luck" that defined his next move.

After graduating from Stanford in 1981, he was accepted to a number of medical schools, including UCLA and his father's alma mater, the University of Chicago, but he also thought the NFL would draft him. When that didn't happen, he focused on medical school, accepting UCLA's offer. By summer, he had

SAN FRANCISCO 49ERS



McColl attended medical school at Stanford while playing professional football. Earlier, he played college football at Stanford.

secured an apartment in Los Angeles and registered for classes, but he had a few months before the move. That's when then-San Francisco 49ers head coach Bill Walsh, who had known McColl since he was his head football coach at Stanford, suggested he try out for the 49ers as a free agent.

"As happenstance had it … the guy ahead of me got injured the first day of practice, and he stayed injured for six weeks. I ended up getting every play, and after training camp, I made the team," McColl said.

That was in September. Now he had to make a choice; UCLA wanted a full commitment to medical school, and no football. Luckily, as he was trying to figure out what to do, a spot opened up at Stanford, where he had been waitlisted for medical school.

He said he told the dean: "Hey, I just made the 49ers. Can I go to medical school here? And, by the way, I already have completed a number of the first-year classes so I don't even need to go to class the first quarter." He did need to take anatomy, but the quarter was otherwise clear. The dean agreed, so McColl practiced and played football during the day and worked in the anatomy lab at night.

The 49ers won the Super Bowl that season, and McColl spent the next six years balancing a professional football career with the demands of medical school.

More luck

Then in 1988, during his last year of medical school, he had another stroke of luck: The dean told him that Santa Clara Valley Medical Center needed a transitional intern because one had dropped out mid-year. McColl had enough credits to graduate that day, so again he made a deal, this time with the medical center's internship director, who let McColl work the internship for three months, break for football season, then return to finish the internship, which he did in the spring.

But that left McColl with a couple months to fill before his residency began in July. That's when he met three guys with an orthopedic-device startup. They asked McColl to join them, and he became one of Origin Medsystem's first employees. By the time his residency was set to start, he said he "was the guy who knew the most about their first product."

"When all of a sudden it started not working very well, I felt like I couldn't leave the company because I felt terrible," he said.

So, he delayed his residency for a year "and it turned into 28." Now, McColl has come full circle, back to both medicine and Stanford. The Stanford connection is one he didn't expect. But a year after McColl matched with O'Connor, which is owned by Verity Health Systems, the hospital transferred institutional sponsorship of its residency program to Stanford. That means McColl's residency class is part of the Stanford Health Care-O'Connor Hospital Family Medicine Residency program.

Now, McColl has one goal: "I wake up every day thinking, 'What can I do today to pass my boards?'" He's confident he'll pass but believes his strengths are in connecting with patients.

"Oh my, the stories I hear from the patients about things they've been through," he said, recounting the story of a woman whose mother and unborn baby died two days apart. "People go through really hard things in life. Anything I have is nothing compared to what these people are going through."

Ultimately, McColl's wants to work in community-based facilities like the San Francisco clinic where he volunteered, the Indian Health Center of Santa Clara Valley, O'Connor Hospital or Valley Medical Center, where residents in his program rotate through. McColl said he gets "more satisfaction" working with traditionally underserved patients at community clinics.

"That's what I want to do for the rest of my life," he said. **ISM**

X-ray

continued from page 1

cally diagnose the pathologies.

Within a week, the researchers had an algorithm that diagnosed 10 of the pathologies labeled in the X-rays more accurately than previous state-of-the-art results. In just over a month, their algorithm could beat these standards in all 14 identification tasks. In that short time span, CheXNet also outperformed the four Stanford radiologists in diagnosing pneumonia accurately.

Why use an algorithm

Often, treatments for common but devastating diseases that occur in the chest, such as pneumonia, rely heavily on how doctors interpret radiological imaging. But even the best radiologists are prone to misdiagnoses due to challenges in distinguishing between diseases based on X-rays.

"The motivation behind this work is to have a deep learning model to aid in the interpretation task that could overcome the intrinsic limitations of human perception and bias, and reduce errors," explained Lungren, who is co-author of the paper. "More broadly, we believe that a deep learning model for this purpose could improve health care delivery across a wide range of settings."

Many options for the future

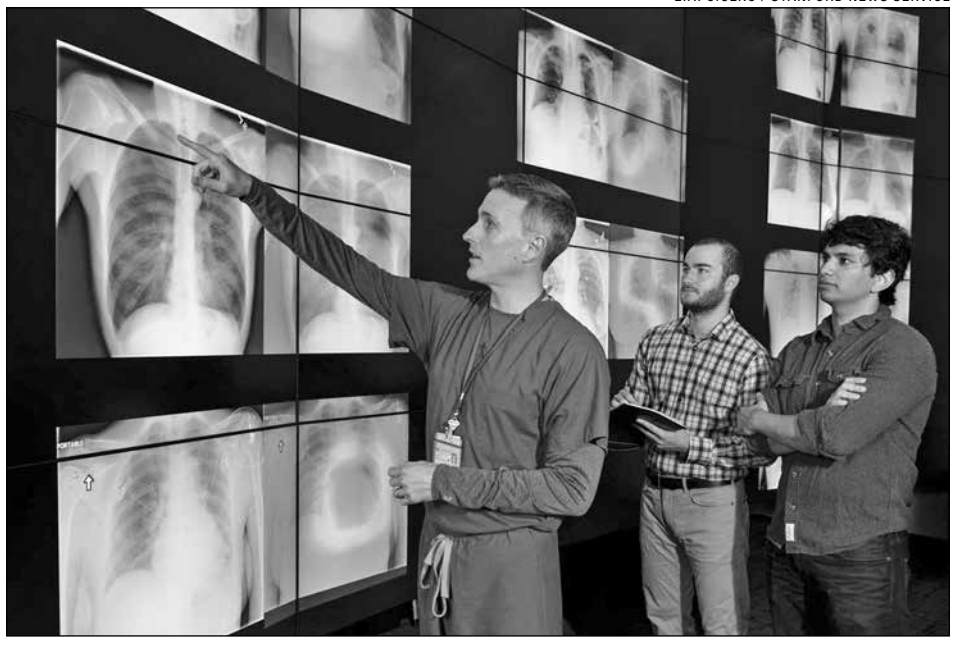
After about a month of continuous iteration, the algorithm outperformed the four individual Stanford radiologists in pneumonia diagnoses. This means that the diagnoses provided by CheXNet agreed with a majority vote of radiologists more often than those of the individual radiologists. The algorithm now has the highest performance of any work that has come out so far related to the NIH chest X-ray data set.

Also detailed in their *arXiv* paper, the researchers have developed a computer-based tool that produces what looks like a heat map of the chest X-rays — but instead of representing temperature, the colors of these maps represent areas that the algorithm determines are most likely to represent pneumonia. This tool could help reduce the amount of missed cases of pneumonia and significantly accelerate radiologist workflow by showing them where to look first, leading to faster diagnoses for the sickest patients.

In parallel to other work the group is doing with irregular heartbeat diagnosis and electronic medical record data, the researchers hope CheXNet can help people in areas of the world where people might not have easy access to a radiologist.

"We plan to continue building and improving upon medical algorithms that can automatically detect abnormalities, and we hope to make high-quality, anonymized medical datasets publicly available for others to work on similar problems," said Jeremy Irvin, a graduate student and co-lead author of the paper. "There is massive potential for machine learning to improve the current health care system, and we want to continue to be at the forefront of innovation in the field." **ISM**

L.A. CICERO / STANFORD NEWS SERVICE



Radiologist Matthew Lungren, left, meets with graduate students Jeremy Irvin and Pranav Rajpurkar to discuss the results of detections made by the algorithm.

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Randall Stafford on new blood pressure guidelines

A panel of the nation's leading heart experts issued new blood pressure guidelines Nov. 13 that redefine for the first time in 14 years what constitutes high blood pressure.

Tens of millions more Americans now meet the criteria for having high blood pressure and must consider changing their lifestyles or taking medications — or both — to reach the lower levels considered safe. High blood pressure has been redefined as a reading of 130 over 80, down from 140 over 90, said Randall Stafford, MD, PhD, professor of medicine and director of the Program on Prevention Outcomes and Practices at Stanford. He was one of the 21 experts who worked on developing the new guidelines. The project was jointly sponsored by the American Heart Association and the American College of Cardiology.

The new guidelines seek to reduce hypertension levels nationwide to improve public health. The condition can lead to heart attack, stroke, kidney failure and death if not detected early and treated appropriately, he said. Stafford, who underwent two kidney transplants and is an avid cyclist, is an advocate for physical activity as a means of helping to control blood pressure. He has lived with high blood pressure since his early 20s. As both a physician and a patient, he knows firsthand how complicated it can be to determine the best strategy for each person with high blood pressure.

Stafford spoke with writer Tracie White about why the new guidelines are important and how they can be implemented.

1 How are the new guidelines different from the previous ones, and why were they needed?

STAFFORD: The changes were motivated largely by data from a federal study published in 2015 called SPRINT [the Systolic Blood Pressure Intervention Trial], which showed that lowering blood pressure well below 140 over 90 had substantial benefits, including for older people.

There are two main messages: First, people at a higher risk of a future heart attack or stroke should be treated more intensively to achieve a blood pressure below 130 over 80. In particular, older people should be treated just as intensively as younger people. Second, the new guidelines define normal blood pressure as less than 120 over 80 or less. While medication should not necessarily be used to achieve this blood pressure, other nondrug strategies should be employed to lower blood pressure toward this level.

2 How many people have high blood pressure, and what do these changes mean for them?

STAFFORD: It is estimated that under these new guidelines, 103 million Americans have high blood pressure, up from 72 million under the previous standard.

Nearly half of all American adults, and nearly 80 percent of those aged 65 and older, will find that they qualify for blood pressure medication and will need to take steps to reduce their blood pressure.

High blood pressure increases the risk of having a heart attack or stroke, as well as several other diseases affecting the arteries in the body. The impact of blood pressure is strongest at very high levels of blood pressure (greater than 180 over 110) but is still significant at any level above 120 over 80. For someone in their 50s, a blood pressure of 160 over 100 increases the risk of having a heart attack or stroke by 50 percent compared with a blood pressure of 120 over 80.

3 Can you discuss the various treatments for lowering high blood pressure and how these will change under the new guidelines?

STAFFORD: While medications that lower blood pressure are a key tool, many nondrug strategies are also useful, but often neglected. Lifestyle changes are not easy, but should be central to how we approach high blood pressure. Changes in physical activity, diet, sleep and weight not only lower blood pressure with few side effects, but also favorably impact the risk of other important outcomes such as cancer and cognitive decline. Many drugs work more effectively when combined with lifestyle changes. The new guidelines hinge on people at higher risk for future bad events — like heart attacks and strokes — being treated more intensively. This requires being more aggressive about lifestyle changes, as well as being more willing to prescribe multiple medications for blood pressure. A good first step for many people is to begin a routine of walking each day with a gradual increase in the distance covered.

Randall Stafford

4 Despite scientific evidence that shows the tremendous health benefits of lifestyle changes such as diet and exercise, why does it remain so difficult for health care professionals to motivate patients to make these changes?

STAFFORD: Increasing physical activity is a potent strategy for reducing the risk of multiple chronic diseases, yet in the United States, most of the population is sedentary or near-sedentary.

In many ways, this is a failure of our health care system. This system is really a "sick care" system that is organized around dealing with acute, short-term problems rather than issues that need continued attention over time.

Physicians similarly want quick solutions and often don't have the training needed to provide persuasive advice about lifestyle change. We live in environments that promote obesity and that make healthy choices difficult. Surrounded by advertising promises and hype, consumers themselves want an easy fix to their problems, rather than the hard work required to live a healthier lifestyle. In the end, however, the substantial benefits can make the hard work worth it.

5 You're an advocate of a "risk-based care" approach for treating high blood pressure. Is this model of disease treatment useful in other clinical situations?

STAFFORD: The new blood pressure guidelines stress that people at higher risk of future harmful events should be treated more aggressively. More widespread use of this concept would lead to more effective and less costly care for many conditions. In fact, we already use this risk-based care approach in other clinical situations.

For example, treatment recommendations for high cholesterol, asthma and reduced bone mineral density are based on future risk. We could easily broaden this approach to how we treat other conditions, such as diabetes and bronchitis. The downside, of course, is that we need to give up the simplicity of a one-size-fits-all approach.

In addition, if we understand that our true goal is to reduce future risk, this implies that we need to treat all of the factors that contribute to high risk. For example, if we are really "treating" the future risk of stroke and heart attack, we should emphasize lifestyle changes and simultaneously consider blood pressure medicines, statins and aspirin. **ISM**

Valve

continued from page 1

cardiothoracic surgery at Stanford, who routinely performs these surgeries. "While our preference is always to repair heart valves whenever possible, there are certain disease processes which necessitate valve replacement. For these patients, given the study's new and unexpected findings, I am already pondering, 'How am I going to counsel my patients today?' The advice may not be the same as the current national guideline recommendations."

The study was published Nov. 8 in *The New England Journal of Medicine*. Woo is the senior author. Postdoctoral scholar Andrew Goldstone, MD, PhD, is the lead author.

Most patients who need open-heart surgery to remove a diseased heart valve face complicated conversations with their heart surgeons about whether to use a natural-tissue or mechanical valve as a replacement.

Mechanical valves can last a lifetime, but they come with increased risks of blood clotting and bleeding, as well as the need to take the blood-thinning medication warfarin. Biological valves, which are most often made from pig or cow tissue, don't increase the risk of bleeding or clotting, but they wear out within about 10 to 15 years, making a second surgery likely.

'A perplexing question'

"This is a perplexing question and comes up for me every single day with patients," said Woo, who holds the Norman E. Shumway Professorship. The decision has been made difficult by the lack of sufficient scientific evidence to back up either choice, he said. Instead, it becomes something of an educated-guessing game based on the age of a patient, comorbidities, a patient's personal preferences and the somewhat vague national guidelines published by the American Heart Association and American College of Cardiology. For those younger than 50, a mechanical valve is currently recommended, and for those older than 70, a biologic tissue valve is recommended, Woo said.

However, the associations' guidelines don't distinguish between whether the mitral or aortic valve is being replaced.

"If you think about this just in terms of age, the older you are, the less likely that you will outlive the durability of a biological valve," Woo said. He added that surgeons have noted in recent years a trend toward younger patients choosing biological valves, primarily because they don't want to deal with a lifetime of taking blood thinners and with the accompanying dietary restrictions and routine blood testing necessitated by a mechanical valve.

The American Heart Association estimates that 5 million Americans suffer from heart-valve disease, which forces the heart to work harder to pump blood and can lead to heart failure and sudden death. The disease can be present at birth or result from infections, heart attacks or other heart conditions.

When a valve becomes so diseased that it impedes the delivery of blood to the body, open-heart surgery to replace the valve with a new one generally is recommended. Each year, more than 50,000 people in the United States undergo either aortic- or mitral-valve replacement surgery, according to the study.

To compare the long-term risks and benefits of mechanical versus biological heart valves, researchers examined rates of mortality, stroke, bleeding and reoperation in patients who underwent heart-valve surgery at 142 hospitals in California between 1996 and 2013. Patient records were obtained from the California Office of Statewide Health Planning and Development databases.

Researchers examined the records of 9,942 patients who underwent aortic-valve replacement and 15,503 patients who underwent mitral-valve replacement during the study period.

"Our research likely contains the largest number of patients ever studied to examine this issue," Woo said.

A stark difference

Results showed a stark difference in health benefits depending on which valve was being replaced, Woo said. The long-term mortality benefit associated with a mechanical valve compared with a biological valve persisted until age 70 in patients undergoing mitral-valve replacement, the study found. For those undergoing aortic-valve replacement, this benefit persisted only until age 55.

"This study will definitely change the information that I give my patients," said Jennifer Lawton, MD, professor of surgery and chief of the Johns Hopkins University Division of Cardiac Surgery, who was not involved with the study. Lawton, like Woo, faces the same daily discussion with her patients about which valve to choose. "The benefit of this study is that it looks at so many patients over a period of time," she said. "Up until now, there have only been small studies on which the guidelines are based."

The current national guidelines are based on data from studies that are not only small, but which examined the use of now-obsolete valves that were implanted more than 30 years ago, the new study said.

Sharing the results of this study with patients is particularly urgent right now because of this growing trend toward younger patients choosing biological valves, Woo said.

"People just don't want to take blood thinners," Woo said, adding that patients are also hoping that experimental transcatheter technology, which could allow valve replacement without the need for open heart surgery, will be available for them in 10 or 15 years when they would potentially need another surgery.

This new study should give both patients and their surgeons valuable new information, Woo said.

"For most heart surgeons who have to face this conversation every single day, this choice is very much on our minds," he said.

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

Other Stanford co-authors are cardiothoracic surgery resident Peter Chiu, MD; Michael Baiocchi, PhD, assistant professor of medicine; statistical programmer Bharathi Lingala, PhD; medical student William Patrick; and Michael Fischbein, MD, PhD, associate professor of cardiothoracic surgery. **ISM**

Researchers seek citizen scientists to help with mosquito tracking

By Taylor Kubota

It's a sound that can keep even the weariest among us from falling asleep: the high-pitched whine of a mosquito. This irritating buzz already makes us run, slap and slather on repellent. But if Stanford researchers have their way, it may also prompt us to take out our cellphones and do a little science.

Manu Prakash, PhD, assistant professor of bioengineering, and his lab are looking for citizen scientists to contribute to Abuzz, a mosquito monitoring platform.

The lab wants citizen scientists to contribute to Abuzz, a mosquito monitoring platform the lab developed to produce the most detailed global map of mosquito distribution. All that's required to participate is a cellphone to record and submit the buzz of a mosquito, which means almost anyone from around the world can take part in this work.

More than mere pests, mosquitoes can carry deadly diseases, including malaria, yellow fever, dengue, West Nile virus, chikungunya and Zika. Diseases spread by mosquitoes result in millions of deaths each year, and the burden of their effects is carried most strongly by places with the fewest resources.

"We could enable the world's largest network of mosquito surveillance — just purely using tools that almost everyone around the world now is carrying in their pocket," said Prakash, who is the senior author of a paper that demonstrates the feasibility of this approach, published Oct. 31 in *eLife*. "There are very limited resources available for vector surveillance and control, and it's extremely important to understand how you would deploy these limited resources where the mosquitoes are."

With enough contributions from citizen scientists around the world, Abuzz could create a map that tells us exactly when and where the most dangerous species of mosquitoes are most likely to be present, and that could lead to highly targeted and efficient control efforts.

"If you see a mosquito and you swat it, you've saved yourself an itch for one day. But if you see a mosquito and you record it and you send the data to the Abuzz project, then you've potentially contributed to an effort that can reduce the burden of mosquito-borne disease for many generations in the future, hopefully," said Haripriya Mukundarajan, a graduate student in the Prakash lab and lead author of the paper.

KURT HICKMAN

Felix Hol, Haripriya Mukundarajan and Manu Prakash record mosquitoes on the Stanford campus.

Matching the buzz to the species

Abuzz is a low-cost, fast, easy way to gain an incredible amount of new data about mosquitoes. Contributing to this research is as simple as holding a cellphone microphone near a mosquito, recording its hum as it flies and uploading the recording to the Abuzz website. The researchers take the raw signal, clean up that audio to reduce background noise and run it through an algorithm that matches that particular buzz with the species that is most likely to have produced it.

Once the match is found, the researchers will send the submitter information about the mosquito and mark every recording on a map on the website, showing exactly where and when that mosquito species was sighted.

Critical to the success of Abuzz is the fact that mosquito species can be differentiated by the frequency of their wingbeats, which is what produces their characteristic whine. Knowing this, Prakash and his team created a mosquito sound library, organized by species, which powers the matching algorithm. Overall, the researchers captured about 1,000 hours of mosquito buzzing from 18 lab-reared and two wild mosquito species, all of which were species relevant to human health.

Recognizing that people who could benefit most from Abuzz may not have access to the latest smartphones, the researchers designed the platform so that it can work off recordings from almost any model of cellphone. Most of the data they focused on in the study was recorded on a $20 clamshell-style cellphone from 2006.

Further simplifying the process, the Abuzz algorithm has worked using as little as one-fifth of a second of sound — although recordings that are 1 second or longer are the most desirable. Such basic requirements mean that merely recording near a mosquito just as it takes off from a surface is enough to create an Abuzz-worthy recording.

To assure that Abuzz works the way they've intended, the researchers ran a field test with 10 local volunteers in a village in Ranomafana, Madagascar, in 2016. It took about 10 minutes to train these citizen scientists. The next day, they returned with 60 recordings that spanned three hours.

Enlisting citizen scientists

"It was very easy to tell people what to do, and people were very eager to participate," recalled Felix Hol, PhD, a postdoctoral scholar and co-author of the paper who helped conduct this field study. "Just 10 minutes of training and they could actually produce a lot of very usable data. That was a very beautiful experience for me."

For any of the grandest aims of Abuzz to be possible, it needs engagement from citizen scientists. Without those contributions, it cannot reach its full potential. The group intends to release an app to facilitate community engagement in the near future and has already produced detailed training videos.

"What I would love to see is people engaging in the problem," Prakash said. "Try to join the platform. Record mosquitoes. Learn about the biology. And in that process, you will be supporting the kind of research and scientific data that we and medical entomologists around the world so desperately need and, at the same time, you will be making your own community safer."

Additional Stanford co-authors of the paper are graduate student Erica Castillo and former graduate student Cooper Newby. Prakash is also a member of Stanford Bio-X and Stanford ChEM-H, an affiliate of the Stanford Woods Institute for the Environment and senior fellow at Center for Innovation in Global Health.

The work was funded by Stanford University, the Stanford Woods Institute for the Environment, the Howard Hughes Medical Institute, NWO Rubicon, the National Science Foundation, the Bill and Melinda Gates Foundation, the PEW Foundation, the MacArthur Foundation, the Coulter Foundation, the National Institutes of Health and the United States Agency for International Development.

Stanford's Department of Bioengineering also supported the work. The department is jointly operated by the School of Medicine and the School of Engineering. ISM

OF NOTE

reports on significant honors and awards for faculty, staff and students

JOHN HARRIS JR., MD, professor of surgery, was elected president of the Western Vascular Society. He will serve a one-year term. His clinical interests include the collaborative role of vascular reconstruction during complex tumor resections.

THEODORE LENG, MD, was appointed associate professor of ophthalmology, effective July 1. His research interests include imaging informatics, artificial intelligence and machine learning, telemedicine, cell-based therapies and clinical trial design. He is the director of clinical and translational research and director of ophthalmic diagnostics for the Department of Ophthalmology.

RONGLIH LIAO, PhD, was appointed professor of medicine, effective Dec. 1. Her research focuses on defining the mechanisms underlying amyloid heart disease. She will establish and lead basic and translational research at the Stanford Amyloid Center, which will integrate clinical, research and training efforts related to amyloidosis.

JON-PAUL PEPPER, MD, was appointed assistant professor of otolaryngology-head and neck surgery, effective Aug. 1. He specializes in aesthetic and reconstructive surgery of the face, particularly surgery for the treatment of facial paralysis, as well as rhinoplasty, facial reconstruction following skin cancer, and facelift surgery.

SCOTT SOLTYS, MD, was promoted to associate professor of radiation oncology, effective Oct. 1. His work focuses on the development of new techniques involving stereotactic radiosurgery and radiotherapy for the treatment of malignant and benign tumors of the brain and spine, as well as functional disorders such as trigeminal neuralgia.

John Harris Jr.

Theodore Leng

Ronglih Liao

Jon-Paul Pepper

Scott Soltys

Tulio Valdez

Leanne Williams

Jamie Zeitzer

TULIO VALDEZ, MD, was appointed associate professor of otolaryngology-head and neck surgery, effective Oct. 1. He specializes in voice, breathing and swallowing problems in pediatric patients, including surgical management of dysphagia and approaches for managing chronic cough. His research focuses on developing imaging technology to improve diagnosis of middle ear conditions and swallowing dysfunction.

LEANNE WILLIAMS, PhD, professor of psychiatry and behavioral sciences, has received a $3.8 million, four-year U01 grant from the National Institutes of Health Human Connectome Project. Her team plans to use advanced imaging to map human brain circuits with the goal of detecting brain-circuit dysfunctions, allowing for a better understanding of emotional disorders.

JAMIE ZEITZER, PhD, was appointed associate professor (research) of psychiatry and behavioral sciences, effective Nov. 1. He investigates the impact of light on circadian rhythms and is working to develop countermeasures to jet lag, shift work and altered sleep timing. He is also interested in the use of technology to track and improve sleep. ISM