Knowledge is...

2018 Annual Report

Stanford MEDICINE | Department of Medicine

Knowledge is...

...creating

...sharing

...applying

...translating

FATIMA RODRIGUEZ, MD (LEFT), ROBERT HARRINGTON, MD, AND JUSTIN PARIZO, MD (RIGHT), ENJOY A CALM MOMENT IN CLINIC.

Welcome!

As we undertook the construction of this year's annual report, we agreed upon a theme pretty quickly. We're an academic institution, so we're in the business of dealing with knowledge: we create it, we share it, we apply it, and we translate it. The theme **KNOWLEDGE IS...** became the backbone of our report, and it fits well with the four strategic priorities of our department:

1) invest in science and research
2) educate and train the next generation
3) elevate the culture of clinical care
4) connect science to the clinical

Each of the 20 articles in this report has a direct line to the theme and our priorities. Four articles describe how *we* **CREATE KNOWLEDGE** *by investing in science and research:* through the work of the Quantitative Sciences Unit, the creation of the Arrhythmia Center, new programs in Oncology, and the efforts of three young Nephrology faculty.

We **SHARE KNOWLEDGE** *as we educate and train the next generation.* You'll read about our residents' quality improvement research course, Stanford's translational investigator program, our growing community of advanced practice providers, recent findings that were shared in a prestigious GI journal, and the scribe program for recent college graduates.

As *we* **APPLY KNOWLEDGE**, *we elevate the culture of clinical care,* seen here in articles about the use of ultrasound in rheumatology, a bone marrow recipient and his donor, the impressive presence of our pulmonary colleagues at our new Emeryville clinic, one of our faculty who volunteers in Haiti, improving medication safety at the VA, and one of our faculty who is a national preventive health leader.

And *we connect science to the clinical when we* **TRANSLATE KNOWLEDGE** from the bench to the bedside as told in articles about the Project Baseline study, an emeritus professor's career in prevention, discovering a medical basis for chronic fatigue syndrome, and a quest to define the relationship between weight gain and insulin resistance.

Both our priorities and our theme are critically dependent on the attention and devotion of our talented staff. Whatever aspect of the department's activities we think about—creating, sharing, applying, or translating knowledge—it cannot be accomplished without them. We showcase them through two pages of photos and commentary beginning on page 18.

This report barely scratches the surface of what the Department of Medicine does on a daily basis. It is, however, a nice representation of our recent past, our present, and in many cases our future. I'm pleased to share our **2018 ANNUAL REPORT** with you.

Sincerely,
Robert Harrington, MD
Chair, Department of Medicine

Quantitative Sciences Unit:
It's Not About the **SAMPLE SIZE**

When Manisha Desai, PhD, a professor of biomedical informatics research, arrived at Stanford in 2009, she says she "kept hearing that there are just not enough statisticians on campus to provide all the necessary statistical support. And I felt that it shouldn't be that way."

There were some statistical groups, she noted, who were "wonderful at addressing consultative needs. When we started the Quantitative Sciences Unit (QSU), we wanted to make sure we complemented those statistical groups, which meant that we wanted to meet researchers' needs with long-term collaborative partnerships. That's really how we got established."

First, there was a need to educate faculty in search of "just a sample size." Desai talks about a typical scenario and how she changed it: "We got a lot of knocks on the door and someone would say, 'I've got this grant; it's due tomorrow. All I need is for you to bless it and give me the sample size calculation. I'm sure this will be quick and easy for you.'"

The education started immediately. Desai explains: "We had those people sit down and talk with us about their science: What are you trying to learn? What questions are you trying to address? We went back and forth about what's known, what are the gaps, what are you trying to contribute scientifically. It's a very different conversation than they were expecting to have."

As that conversation continued, the dynamic changed. Desai goes on: "We showed them that we are actually scientists and can partner with them to help shape their questions, to make sure the questions are sensible and are getting at their goals. We also worked on refining hypotheses. Once all of that was done and we were on the same page, we talked about how best to design the set of experiments, the data to be generated that would be relevant for addressing the questions. Eventually, they began to see that this is a long iterative process. We would go back and forth, and that required scientific engagement. And now we write into NIH grant proposals that we need a biostatistical team for doing the data management and analyses and for partnering with the investigators."

QSU MENTORS HOSPITALISTS IN RESEARCH METHODS

Since 2011, Neera Ahuja, MD, a clinical associate professor of hospital medicine, has grown her division from a faculty of seven to one of 36 in four distinct sections: surgical co-managers, hospitalists, nocturnists (who are hospitalists with overnight responsibility for inpatients), and Stanford Health Care–ValleyCare staff. With her faculty in place, she was ready to have them start doing research.

But she realized, "We had only two or three faculty who had some research background, and we lacked biostatisticians. First we thought about hiring our own full-time biostatistician to have in our group. But Manisha [Desai, PhD, a biomedical informatics professor] very keenly said that person will feel isolated and won't have the support of people who do what they do. So we partnered with the Quantitative Sciences Unit. Manisha was very open to a collaboration and in fact said that is what her group is meant to do because they are purely a research group. They want to support clinical groups like ours and find ways to guide and mentor. Now we fund a quarter of the salaries of two biostatisticians. Most of our research is quality improvement, medical education, and some informatics, where we have some biomedical informatics research experts run some data and do some analyses."

Desai explains that the role of the QSU with young researchers such as the faculty in hospital medicine "has to do with mentoring them in research methods. We are partnering with Neera to help build up that research infrastructure. We want to help them understand such things as the grant submission process."

MANISHA DESAI, PHD, LEADS THE QUANTITATIVE SCIENCES UNIT.

Sometimes investigators come to the QSU too late in the grant cycle for a proposal to be completed and successful. In those instances, Desai doesn't hesitate to advise faculty to wait a cycle; in the current economic climate, such postponements have always proven to be advantageous for investigators. "They need to give it their best shot," she says. "So in cases where people are really not ready, we encourage them to give us enough time to work together with them and show what we can bring to the table. We become a part of the team."

In addition to spending a significant portion of their time collaborating on nascent and ongoing scientific projects, the QSU mentors faculty members who are new to research and are interested in learning the correct way to do their own studies. One such case is the Division of Hospital Medicine [see sidebar].

The QSU currently has 30 members, and five of them form an administrative core to triage new work. Desai explains that "we find out from our intake form how they came to our door and which department they are in. Depending on their resources and whether they need help with a grant proposal or unfunded data analyses, we figure out how to allocate our resources, how to prioritize the work, and then look for statistical expertise to match the need."

While the teaching and collaborating take up a significant portion of the time available from the QSU, Desai stresses, "We are a research group, and we're building our careers with those of our collaborators. And that's the difference between consulting and collaborating. We are team members and coinvestigators, and we seek opportunities provided by our collaborators to lead research that is directly relevant and beneficial to them."

The New Stanford Center for Arrhythmia Research: A **MULTIDISCIPLINARY** Approach at Heart

The Division of Cardiovascular Medicine has launched the Stanford Center for Arrhythmia Research with the aim of bringing a larger multidisciplinary approach to build on the success of the longstanding Cardiac Arrhythmia Service.

In recent years, the Cardiac Arrhythmia Service has assembled a team that has significantly increased patient volume; grant and extramural support for research, presentations, publications, and patent submissions; as well as trainees who are supported by a variety of fellowship awards.

But by creating a research center, co-directors Paul Wang, MD, and Sanjiv Narayan, MD, PhD, plan to bump the achievements up a notch.

The center's inaugural event was a September 8, 2017, symposium that brought together researchers and clinicians from varied departments, divisions, and centers to discuss the latest advances at Stanford.

"Our vision is to be an international magnet for arrhythmia research. This will allow us to develop novel technologies and to treat arrhythmias in a way that hasn't been done before. We want to attract people from many disciplines in an effort to tackle some important problems," says Wang, who also serves as director of the Cardiac Arrhythmia Service.

Interdisciplinary Approach

"It is our goal to make Stanford a leading arrhythmia research and clinical care facility where we can bring people from many disciplines together and work toward some really ambitious goals in advancing the treatment of arrhythmias," Wang says.

He and Narayan believed that without a true interdisciplinary approach, it was unlikely their center would make the major breakthroughs that will be needed in the field. They had already attracted a large number of key faculty members, many of whom are leading experts in such diverse fields as mathematics, chemistry, pulmonary medicine, engineering, biology, social science, the humanities, imaging, stem cell biology, psychology, computer science, sleep medicine, cardiac surgery, and bariatric surgery.

Narayan is a good example of interdisciplinary expertise. After studying mathematics and biology and training as a computational biologist with plans to become a neuroscientist, he became fascinated with the heart and its electrical signals and decided to become a cardiac electrophysiologist—the specialty of all eight cardiologists in the Cardiac Arrhythmia Service.

"The Stanford Center for Arrhythmia Research provides a place where innovators can work in this exciting field. Other centers such as the Stanford Byers Center for Biodesign have been instrumental in creating such a vibrant and supportive community. It's a model for how people from many disciplines at Stanford come together to promote innovations," Wang says.

One of the center's goals is to ensure that translational components are in place so that what is being discovered at the laboratory level is brought all the way to the patient.

A CARDIAC ARRHYTHMIA PRIMER

An estimated 300 million people in the world have an arrhythmia, a condition in which the heart beats with an irregular or abnormal rhythm. The most common arrhythmia, affecting 30 million people worldwide, is atrial fibrillation (AFib).

Cardiac electrophysiologists at the Stanford Center for Arrhythmia Research treat AFib, sudden cardiac death, and other arrhythmias using catheter ablation, a minimally invasive procedure using catheters (thin, flexible tubes) inserted through blood vessels. Catheter ablation uses heat or cold energy to treat heart tissue that triggers arrhythmias.

Ablation

The current standard for treating arrhythmias is ablation. That involves locating a specific area of the heart that is malfunctioning, then destroying, or ablating, the problem cells.

Ablation can be done surgically or minimally invasively. Cardiac surgeons can approach arrhythmias by opening the chest cavity and precisely carving out parts of the heart and then carefully sewing the muscle back together, or they can use less invasive tools that provide direct access to the heart. An even less invasive technique is catheter ablation, which accesses the heart using catheters, then uses extreme heat or cold to kill the cells that are causing the arrhythmia.

Cardiologists also use medications to treat arrhythmias by affecting different ion channels of the malfunctioning cells.

Innovative Technologies

Cryoablation and focal impulse and rotor modulation (FIRM) ablation are two technologies that were invented by the Stanford team and have become standard arrhythmia treatments.

Wang is the coinventor of cryoballoon ablation, a cardiac catheterization procedure that uses extreme cold to treat the heart tissue that triggers an arrhythmia. Cryoablation has been used to treat more than 250,000 patients with atrial fibrillation (AFib) worldwide. In the procedure, physicians insert a catheter through a blood vessel and guide it to the heart. They then inflate a tiny balloon at the end of the catheter with a special gas coolant to freeze the atrial tissue triggering the arrhythmia. During one application, the cryoballoon can treat a large surface of atrial tissue.

PAUL WANG, MD (LEFT), AND SANJIV NARAYAN, MD, PHD, DIRECT THE STANFORD CENTER FOR ARRHYTHMIA RESEARCH.

Applying his computational biology expertise using mathematical tools to understand the nature of arrhythmias, Narayan invented FIRM ablation, a mapping technology that cardiologists use to precisely target the electrical sources of AFib. With the help of sophisticated computer software, FIRM accurately identifies key areas of the heart for ablation. It is a very effective treatment that provides long-term relief of AFib and its symptoms.

Hybrid Program

One example of the center's multidisciplinary collaboration is the Hybrid Surgical-Catheter Ablation Program, which combines the efforts of cardiac surgeons and cardiologists.

"We don't think it comes down to whether it's surgeons or cardiologists who are better at treating arrhythmias. We think the issue is how we can optimize our working together to achieve the best results for the patient," says Wang.

A big part of that effort was the recruitment of Anson Lee, MD, a young cardiac surgeon who came to Stanford to specialize in arrhythmia surgery.

"Arrhythmia surgery largely went away as a standard technique for treating arrhythmias, so many of its tools are no longer available. We believe that surgical approaches can be very appropriate, and it's important to rejuvenate this area of surgery. That's why we are working to invent the next wave of technologies to enable arrhythmia surgeons to work with cardiac electrophysiologists," Wang explains.

In hybrid surgical-catheter ablation, electrophysiologists and cardiac surgeons are working in partnership to treat the heart from both inside and out. This innovative approach provides better long-term outcomes and greatly improves patients' quality of life.

During a two-step procedure, catheter ablation is combined with thoracoscopic surgery, a minimally invasive chest surgery in which a minuscule camera is placed into the chest through tiny ports. During that surgical step, the team can see the heart directly, but without having to open the chest cavity. The surgeon then uses specially designed equipment to treat those parts of the heart that are responsible for the heart rhythm problem.

In step two, the cardiac electrophysiologist inserts catheters into the heart from a peripheral vein well outside the cardiac area to identify and treat additional areas that are harder to access from the outside.

"This is a really exciting development that gives us the best of both worlds. Some things are more easily accessed from the outside, and some things are more easily accessed from inside. By working together, we can get better results than by either of our groups working independently," says Wang.

Conversations on **COMBATING** Cancer

Two new programs exemplify Stanford's strengths in clinical care and translational research in cancer.

PAMELA KUNZ, MD, ASSISTANT PROFESSOR OF MEDICINE AND DIRECTOR OF THE NEUROENDOCRINE TUMOR PROGRAM

SHIVAANI KUMMAR, MD, PROFESSOR OF MEDICINE AND OF RADIOLOGY, DIRECTOR OF THE PHASE I CLINICAL RESEARCH PROGRAM, AND DIRECTOR OF THE TRANSLATIONAL ONCOLOGY PROGRAM

In recent decades it's become increasingly clear that cancer is an incredibly complex disease. No two cancer types are exactly alike, no two patients are alike, and treating tumors involves attacking them from all angles. At Stanford, oncologists are tackling many sides of cancer research and patient care through innovative collaborations and programs. Two new programs in the Division of Oncology demonstrate this: the Neuroendocrine Tumor Program brings together professionals from many specialties to treat patients with these rare tumors; and the Phase I Clinical Research Program helps bring experimental new drugs to Stanford patients—while giving basic scientists vital research opportunities to study the drugs. Recent conversations with the directors of the two programs convey what makes them unique and important.

To start out with, what are neuroendocrine tumors?

Neuroendocrine tumors, or NETs, are rare cancers that can originate in almost any part of the body. We most commonly see them in the gastrointestinal tract and lungs. They tend to be slower growing than other cancers; even patients with metastatic disease can live for many years. The incidence is very low—only about seven people per 100,000 are diagnosed each year in the US. But because many patients live for years with their disease, the prevalence is actually quite high. There are more people living with NETs in the US than with esophageal, stomach, and pancreatic cancer combined.

Why is it important to have a distinct program focusing on NETs?

These are so different from other cancers; they're really a different entity and they require different therapies. Knowing how to select the initial treatments for a patient, then tailor those treatments, requires some expertise. Because NETs are not common, a community oncologist may only see a handful of cases ever. In addition, we are especially interested in meeting the long-term needs of these patients, and we have established a new NET survivorship program focused on addressing symptoms of cancer, side effects of treatment, nutrition, and mental health.

What does managing the NET program at Stanford involve?

This disease requires complex coordination among many disciplines—medical oncology, surgical oncology, nuclear medicine, interventional radiology, endocrinology, cancer genetics, and psychiatry. So it's really about pulling together the expertise to make sure patients get the best care. We see about 200 NET patients a year at Stanford, and they often travel long distances. We try to not only treat patients here, but partner with the patients' oncologists back home.

Is the NET program involved in research as well as clinical care?

Yes. We have participated in many key clinical trials and other clinical research projects. This last year we participated in the study of a new drug called ^{177}Lu-Dotatate, which delivers radiation in a very targeted way to NETs; this is really the quintessential definition of a targeted therapy. The results of our work were published in the January 2017 issue of *The New England Journal of Medicine*, and the drug is now being reviewed by the FDA. It will very likely be the focus of future generations of studies. We want to know whether we can combine other treatments with ^{177}Lu-Dotatate, which patients respond best to the drug, and whether there are any long-term side effects. We are also looking for new diagnostic tests to better identify which patients may have more aggressive cancers so we can tailor selection of treatments.

What plans do you have for the NET program?

With so many new therapies for NETs, we are emphasizing patient and physician education. Three continuing medical education events in the next year will teach community physicians and other health care providers about NETs. We also host an annual NET patient education event. Lastly, we are thrilled to have received funding for a fellowship to train the next generation of NET specialists. Our first NET fellow will start in mid-2018.

How did the Phase I Clinical Research Program come about and what are its goals?

First of all, a phase I trial is when you're testing a drug for the first time in humans; you're trying to figure out safety, dosing, and which patient population to target. This is the key stage between preclinical development and clinical development. I was recruited to Stanford from the National Cancer Institute in 2015 and started the Phase I Clinical Research Program for patients with advanced solid tumors. The goals are to leverage the broad clinical and research expertise that exists at Stanford and to work with various stakeholders, including industry, to develop new therapies for cancer. The program is designed to facilitate development of promising anticancer therapies while ensuring the highest standards of patient safety.

What does the Phase I program at Stanford do to help ensure quality trials?

If researchers have a molecule that they're interested in moving forward into phase I trials, we sit down with them and go through their information, we see if they need additional data, and we talk to them about what it will take to get a trial in place. We also help identify what resources will be needed to advance the research into the clinic. Then, we help design the clinical protocols and conduct the trials. Basically, we provide expertise that bench scientists may need to translate their findings.

You also work on phase I trials coming out of industry, right?

Yes. The majority of drug discovery and development happens in industry, where they're identifying novel targets and developing new molecules for testing. Therefore, it is very important that we build that collaboration. It gives us access to cutting-edge molecules, and it creates opportunities for our patients to participate in clinical trials of these agents and for our scientists to conduct scientific studies with these molecules.

Why are phase I trials so important?

Phase I studies are at the interface of preclinical and clinical development. It's basically where we make the decision about whether a new drug should be moved forward into later stage clinical development. A lot of drugs go all the way through clinical development and fail to work, so it's important to have a strong phase I program that can help prioritize promising drugs early and expedite their development.

Why is Stanford a good place for phase I trials?

Stanford is very strong in basic and translational science. The sense of innovation here makes it a great place for phase I trials. Our Bay Area location is advantageous because we are able to interface easily with companies. The Phase I program provides opportunities to translate the discoveries into the clinic and facilitate the development of new treatments.

Is there a phase I trial going on at Stanford right now that you're particularly excited about?

Currently the Phase I program is investigating a number of novel agents with a variety of mechanisms of action, ranging from immune therapies to genetically targeted agents. In collaboration with Loxo Oncology, our program is involved in the development of their new drug, larotrectinib, which targets solid tumors—including brain, breast, colorectal, thyroid, and lung cancers—with a particular genetic alteration. The drug has shown a 76 percent response rate in both adult and pediatric patients with metastatic tumors. The company is moving forward toward applying for drug approval, based in part on the results observed at Stanford.

Young Nephrologists Asking **BIG QUESTIONS** About Kidney Diseases

A trio of early-career researchers have wide-ranging projects that aim to improve kidney health around the world.

Your kidneys, nestled in your lower back on either side of your spine, are the kind of organ system you don't think about much until something goes wrong with them. If you're healthy, your kidneys filter your blood to keep it clean, removing waste and producing urine. But if both kidneys stop doing this job, then you either need a new kidney—a transplant—or something else to mechanically filter your blood—dialysis.

The rate of kidney diseases in the United States and the rest of the developed world is on the rise, so research into how to prevent and treat these diseases is needed more than ever. At Stanford, a trio of early-career researchers exemplify the breadth of current nephrology research, and the energy and creativity needed to tackle some tough questions.

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These early-career researchers exemplify the creativity needed to tackle some tough questions about kidney disease: http://stanford.io/2B7Yvrt

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A Medical Mystery

Halfway around the world, in rural Sri Lanka, a mysterious kidney disease is killing farm workers. In the last decade, more than 20,000 deaths have been blamed on the disease, which is called chronic kidney disease of unknown etiology, or CKDu. Here in Palo Alto, nephrologist Shuchi Anand, MD, is on the hunt to find out what's causing it and help spearhead new ways to screen and manage the thousands of patients who need ongoing care.

"The concern is that it's a single toxin that's causing the disease," says Anand, who completed her fellowship in nephrology at Stanford in 2012 before joining the faculty as a nephrology instructor. "But at this point, we still don't know."

In the United States and developing countries, most cases of chronic kidney disease (CKD) are seen in older individuals with risk factors like diabetes, high blood pressure, and cardiovascular disease. But in Sri Lanka—as well as small regions of southern India, Nicaragua, and El Salvador—the disease has been appearing in young, otherwise healthy adults.

A similar outbreak of kidney diseases occurred in the 1950s and 1960s in the Balkans. Years later, researchers discovered that an herb growing in nearby fields was causing the cluster of cases. That historical case is why today's scientists have a hunch that a toxin—in the groundwater, soil, or plants—may play a role in the current outbreaks.

Anand, who has traveled to affected areas in Sri Lanka, is working on setting up a study to analyze what CKDu patients in Sri Lanka have been exposed to. So far, she and her colleagues have collected kidney biopsy data on about a hundred patients, with the goal of testing for infections, pesticides in their bodies, and other chemical levels.

"In the past, there's been a lot of single-hypothesis research on CKDu," says Anand. "There's this new momentum toward creating collaborations that guide a more systematic approach, and Stanford has been a leading part of that effort."

The results of their effort are still forthcoming, and the group hopes to eventually collect data on a total of 300 patients. Somewhere in the molecules contained in blood samples, they hope, is an answer.

Putting Numbers on a Disease

There are different ways that the kidneys can stop working. The blood vessels leading into the organs can become damaged, cysts can grow, stones can block the flow of urine, or the immune system can attack the kidneys. One subset of these diseases is dubbed glomerular diseases: They affect the tiny filters, called glomeruli, that help the kidneys function. But not all glomerular diseases are the same, and they have diverse causes—patients can develop them due to an autoimmune disease like lupus, after contracting an infection or taking certain drugs, or because of a genetic disease.

Michelle O'Shaughnessy, MD, an assistant professor of nephrology who moved to Stanford from Ireland in 2013, wants to sort out the differences between each type of glomerular disease, by quantifying the patients who contract them, how they contract them, and which treatments work.

"We see a huge spectrum of outcomes with glomerular disease," says O'Shaughnessy. "Some patients do really well, while others do very poorly, and lots are in a spectrum between those two extremes."

FROM LEFT: DRS. SHUCHI ANAND, COLIN LENIHAN, AND MICHELLE O'SHAUGHNESSY ARE ADDRESSING SOME OF NEPHROLOGY'S TOUGHEST CHALLENGES.

The challenge in figuring out which patients have which outcomes, she says, stems from the fact that there's no national—or worldwide—registry of glomerular disease patients. As a result, studies tend to be small, focused only on patients within an individual hospital system. O'Shaughnessy is working on ways to mine large health record databases for information on patients with glomerular disease.

In 2017, O'Shaughnessy published the results of a large epidemiological study of more than 21,000 glomerular disease patients referred to the University of North Carolina, Chapel Hill, over a 30-year time span. She and collaborators found the rate of diabetes-related kidney disease to increase dramatically—accounting for nearly a fifth of all biopsy-proven glomerular disease by 2015.

"That's really concerning because having diabetes and kidney disease portends a much poorer prognosis than having diabetes alone," says O'Shaughnessy. "From a public health perspective, we as physicians need to be aware that this is increasing."

Her next steps are to assemble a larger study of glomerular disease patients, following the course of disease beginning at diagnosis and including people who aren't typically included in small controlled trials—those with other chronic diseases, and elderly people, for instance.

Targeting Transplants

Whether patients have glomerular disease or CKDu, they may need a kidney transplant if their kidney function deteriorates enough. Today, more than 100,000 people in the United States are on the waiting list for a kidney, yet only around 17,000 transplants are performed each year. While much of this lag is due to a shortage of organs, matching donors with recipients can also be a problem because patients can have antibodies that make them reject an organ. These antibodies react to proteins on the donor kidney called human leukocyte antigens, or HLAs.

"Our tissues are covered in these HLA proteins, and they're kind of like a fingerprint," explains Colin Lenihan, MD, an assistant professor of nephrology who—like O'Shaughnessy—hails from Ireland. If you're exposed to these HLA molecules from someone else's body—through pregnancy, blood transfusion, or a previous transplant—you can develop anti-HLA antibodies, a process called sensitization. However, some patients are sensitized but have no history of pregnancy, transfusion, or transplant, and it's not clear why they have developed anti-HLA antibodies.

"Sensitization is a big problem," Lenihan says. "Highly sensitized patients are less likely to find a compatible donor, and they also don't tend to do as well after the transplant." Some 20 percent of people waiting for a deceased donor kidney transplant, he says, are sensitized to more than 80 percent of all HLA types, limiting the organs they can receive.

Lenihan is studying whether the flu vaccine may play a role—he and his colleagues are testing levels of HLA antibodies in patients on the transplant waiting list at Stanford before and after they get a routine flu shot.

"The flu vaccine is really beneficial and saves lives, but there may be a subset of people who develop unwanted anti-HLA antibody after they get vaccinated," Lenihan says. Of course, he admits, the study could also show no effect on HLAs from the flu vaccine, so it's too early to make any changes to vaccine policies.

Residents' Elective **TACKLES** Quality Improvement Research

A unique offering of Stanford's medicine residency program is one month spent exclusively on research. One research opportunity that has been growing in popularity is devoted to quality improvement (QI).

Lisa Shieh, MD, PhD, a clinical professor of hospital medicine, has been involved in the QI elective and explains its premise: "The goal of the quality improvement elective, which we've been running for five to seven years, is to give the residents a combination of seeing how the institution does QI and doing it themselves. When residents sign up we have them think about a QI project, we give them the support they need, and we try to align their project with institutional goals. We also provide opportunities for them to see how QI is done throughout the hospital: They sit in on leadership QI meetings and on working groups."

The 'What Matters Most' Letter Project

One QI project pursued by several residents aimed to help patients inform their physicians about the things that most mattered to them. Shieh describes how the residents approached this topic: "Three of our projects this year were on the same theme: How can we help our patients share with us what is most important to them? This could be considered goals of care or end of life planning, which is challenging to talk about. It's hard for both patients and families."

This project was done in partnership with V.J. Periyakoil, MD, a clinical associate professor of primary care and population health, who created a "what matters most" letter that the residents used, and with Rabbi Lori Klein, JD, MA, from the Stanford Spiritual Care Program. The letter is a template for patients to explain to their doctors and their families the things that are most important to them as they approach the end of life. A patient can write, for example, that attending a daughter's wedding or a son's graduation is a primary concern or that dying at home matters most. Unlike advance directives and living wills, however, the letter is not a legal document.

One resident, Silvia McCandlish, MD, randomized a group of inpatients in her study so that half of her patients completed the letter and gave it to their physicians and half of her patients did not. Her study focused on the reaction of the physicians who received the letter from patients, in particular whether they found it useful. Shieh reports that "They found the letter to be more useful than other types of advance directives, which are often very vague. Most doctors don't find such documents helpful to guide recommendations for treatment. While they are good things to have, the what-matters-most letter adds to them."

> The letter is a great **TOOL** because it's more personal...

For the residents who complete a project, there are multiple opportunities to submit their results to association meetings and often to both present and publish them. Several residents have recently received awards for their projects after presentations at regional and national meetings.

McCandlish's project won a regional American College of Physicians (ACP) QI section competition and competed at the national Society of Hospital Medicine meeting, where it was among the top 15 abstracts out of hundreds submitted.

Other residents worked on different aspects of the what-matters-most letter. Ilana Yurkiewicz, MD, studied the demographics of the patients who filled out the letter. Jessica Langston, MD, surveyed the providers of patients who filled out the letter and learned that many of them were unaware of the letter. When she showed them the letter, they found it very useful and wished they had known about it. As a result, workflows were changed so that the letter is pulled into the electronic medical record, where it will be available to each patient's physician.

LISA SHIEH, MD, PHD (RIGHT), MAKES A POINT ABOUT QUALITY IMPROVEMENT WITH MEDICAL RESIDENTS.

These QI projects don't necessarily come to an end when the residents complete the elective. The what-matters-most letter, for instance, is now being worked on by palliative care fellows who are trying to get the letter to inpatient medicine and oncology patients. While there is much work still to be done, Shieh feels that the letter is a "great tool because it's more personal and focuses on what matters to patients as opposed to the typical 'do you want to be intubated' kinds of questions that scare patients."

Inappropriate Thrombophilia Testing Project

Shieh notes that the medicine residency program has been studying the impact of educational interventions. "One recent QI project educated residents about choosing wisely; we called it 'the high value care curriculum.' We talked about the cost of care and how it's rising and that there is waste, and we talked about things in medicine to do and not to do," she says.

One recommendation in hematology is not to order a number of labs that look for an increased risk of blood clotting—known as thrombophilia—in patients who don't need it. In the inpatient setting a thrombophilia workup is almost never necessary. Two residents set about determining how prevalent such workups were among Stanford inpatients and how to educate physicians about not doing wasteful things that provide little or no value.

Eric Mou, MD, undertook a massive chart review to learn "how often we inappropriately ordered these tests at Stanford Hospital," says Shieh. "Of the 1,817 orders analyzed, 777 (42.7 percent) were potentially inappropriate." Mou was invited to present his project at a regional ACP meeting where it won the research competition; he also presented it at a national ACP meeting and American Society of Hematology meeting. *The Journal of Hospital Medicine* published his manuscript in September 2017.

Henry Kwang, MD, who worked with Mou on this project and coauthored the resulting manuscripts, looked at the impact of an educational intervention on inappropriate thrombophilia workups. He showed that the intervention was effective, which Shieh describes as "very unusual for educational interventions." Kwang's project went on to be a finalist at both the national ACP meeting and the national Society of Hospital Medicine meeting. In addition, it was a top 10 winner in the Stanford QI symposium.

In addition to learning the basics of research methods, residents who opt for the QI elective have the opportunity to see their projects come full circle from proposal to publication—plus another several lines on their curriculum vitae.

CHAD WELDY, MD, PHD

The **TIPPING** Point:

How Stanford's Translational Investigator Program Supports—and Propels—the Careers of Early Physician-Scientists

Chad Weldy, MD, PhD, found his calling deep in the toxicology laboratory at the University of Washington (UW), while he was working alongside physician-scientists to investigate the effects of air pollution on cardiovascular and pulmonary health. Weldy always knew that he loved scientific research, and it was this interest that propelled him through college at Western Washington University and a subsequent PhD program. But he had never considered a career in medicine. His work at UW—along with his exposure to a blend of cardiology and basic science—was "my first introduction to the possibility of doing both," he recalls. "I decided that was my goal."

After earning his doctorate, Weldy pursued that goal in earnest—completing a postdoctoral fellowship at UW in the lab of a prominent cardiologist, and receiving his MD from Duke University. He landed at Stanford in 2017 as one of nine residents in the Department of Medicine's Translational Investigator Program (TIP).

TIP is designed to provide unparalleled training and mentorship to individuals like Weldy, who are planning careers as physician-scientists. It's an important goal, says Joy Wu, MD, PhD, one of three co-directors of the program. Physician-scientists bring a unique perspective to the practice of medicine—bridging the divide between the bench and the bedside. And recent reports from organizations like the National Institutes of Health suggest their numbers are dwindling.

"It's becoming harder to retain physician-scientists in a research career," Wu explains. "This program exists to reach them as early as possible—when they're applying to residency—and to support a robust pool of physician-scientists that will become faculty here or at other leading academic medical centers."

For current residents in the TIP program, this support takes many forms. Participants are guaranteed a salary at the full Accreditation Council for Graduate Medical Education level even during their American Board of Internal Medicine–mandated research years,

> I love being able to get away from the wards for an hour to sit with other physician-scientists and talk **SCIENCE**

along with additional supplements for housing and education. They're also guaranteed a fellowship position at Stanford after successfully meeting residency requirements. Weldy, for example, will be joining the cardiovascular medicine fellowship after he completes two years in the internal medicine fast track program.

Additionally, TIP provides myriad mentorship opportunities—from quarterly dinners hosted by faculty to involvement in the Pathways of Distinction program, a mentorship initiative that allows residents to select one of several individual pathways that best aligns with their academic interests. These initiatives help build a sense of community, says Weldy.

"We've had several lunches where we have had amazing investigators present some of their research, as well as their path to how they ended up as faculty at Stanford. I love being able to get away from the wards for an hour to sit with other physician-scientists and talk science."

Training is another key component. Wu elaborates: "We have sessions on everything related to career development, including grant writing, how to seek a mentor, how to apply for faculty positions, and more."

Participants also benefit from Stanford's collaborative and innovative spirit. "At many medical centers the university is separate from the medical school and the hospital," Wu explains. "At Stanford everything is in close proximity. I think that leads to a rich array of opportunities for research and collaboration."

Weldy agrees, adding: "The TIP program stood out to me because of the unique culture of innovation and discovery that is infused across campus. There's not only a history of discovery—there's a palpable sense that Stanford is on the tip of changing the practice of medicine."

GARRETT CHAN, PHD, RN, TEACHING IN A SIMUATION LAB.

Embracing a Growing COMMUNITY of Advanced Practice Providers

Garrett Chan, a clinical associate professor of primary care and population health and emergency medicine, spent his 20s pursuing a career as an art curator, taking classes like art history and humanities, with the eventual goal of working at a museum.

But then he met with a counselor, who prompted him to scrap the curatorial track and explore a career in nursing. Chan was surprisingly receptive. "I said sure!" he explains, "so she handed me a paper with a list of courses like chemistry, anatomy, and biology." Clutching his new curriculum, he set off to embark on an entirely new path.

Chan spent the next several years acquiring degrees (an RN and BSN from San José State and a MS and PhD from UC-San Francisco), and clinical experience (in the emergency department and palliative care services of the San Jose Medical Center and at Stanford) at breakneck speed.

He joined Stanford Health Care as a nurse-scientist in 2006, and the Department of Medicine as a faculty member in 2014. Chan is not exclusively a nurse. His interests—and identities—vary widely. "My daily work as a faculty member includes administration in Stanford Health Care, direct care of patients, and work as a research scientist and an educator." On any given day, he can be found in the emergency department, helping faculty evaluate the efficacy of a new critical care program; in the lab, acting as principal investigator on a multi-site clinical trial of an FDA-approved device designed to test subepidermal moisture and writing up the results; in the office, creating the curriculum for an RN postdoctoral fellowship in palliative care; or in the classroom, leading the advanced practice provider fellowship program and training interdisciplinary staff as the director of the Center for Professional Development.

Chan is also part of a growing community of advanced-practice providers—including registered nurses, nurse practitioners, and physician assistants—working alongside medical doctors on campus. There are several nurse scientists employed by the department. And in August Stanford welcomed the inaugural class of 27 students in the master of science in physician assistant studies program. It's an exciting and beneficial shift, Chan explains. "A significant part of physician education and practice is focused on disease management," he says. "And while nurses always have disease management in mind, they bring a very holistic perspective to health care. We're paying attention to how patients and families are coping, patient education, and other psycho-social aspects of care." Chan predicts that the inclusion of different care perspectives will both complement—and enhance—the practice of medicine and delivery of health care at Stanford.

A Unique SCRIBING Model

The COMET Fellowship for College Graduates

Like many of her recent college graduate peers, Cat Carragee was unsure how to get from *here* to *there*. *There* was a job in the health professions, perhaps as a doctor, but *here* wasn't where she needed to be.

Here was work she was doing as a scribe in the emergency department at O'Connor Hospital in San Jose, California, for minimum wage. While she was getting some exposure to clinical medicine, she wasn't really learning clinical medicine. "As a scribe I was there to help the doctors," she says. "Any clinical learning was just a sideline." She also knew that she needed research experience to strengthen an application to medical school, but to get such a job would require years of experience including work in the field.

Then a friend told her about COMET, and her life changed.

COMET (Clinical Observation and Medical Transcription Fellowship) is the brainchild of Steven Lin, MD, a clinical assistant professor of primary care and population health, who proposed a scribe service model with a twist.

Lin was interested in scribing after seeing his colleagues burn out from what he describes as "an explosion of administrative work being put on the shoulders of primary care physicians, plus frustration with the inefficiencies of electronic health record (EHR) systems like EPIC."

But he also knew that many scribes are interested in a health career, perhaps as physician assistants, doctors, or nurse practitioners. He thought that having a longitudinal relationship with one or more providers would be valuable in the eyes of admissions committees, as would "opportunities to stand out and get experience."

Scribing, he thought, "was an obvious place to go to, but I wanted to do it in a way that was a win-win-win scenario. Could we provide an experience that would benefit the scribes so they could go on to achieve their dreams of working in the health profession?" At the same time, could this model "be of tangible help to our primary care physicians, be meaningful, and decrease their work responsibilities in terms of charting and the EHR so they could spend more time with their families?"

Lin further describes COMET: "That's how the post-baccalaureate scribe fellowship came about. In our unique model a mentoring relationship is central. We're committed to the scribes and their education. They work with one to three physicians for an entire year. These are faculty members who mentor them, teach them at the bedside, do scholarly research projects with them that scribes then present at national conferences. We write recommendation letters for them and mentor them on their applications and their career development. It's been a really good experience for both our scribes and our providers."

Carragee could not agree more. After being one of the two pilot COMET fellows in 2015, she spent an additional year as chief scribe, orienting and supporting the incoming class of six fellows and finding ways to expand COMET to more clinics. She's finished with that now, though; in September 2017 she started medical school at University College Dublin. She has reached her *there*.

As for the providers, Lin reports that "the scribes relieve the documentation burden. They increase our physicians' ability to complete their charts on schedule. They can go home on time and have weekends free with family. It's really been a great benefit to them."

STEVEN LIN, MD, HAS THE HELP OF SCRIBE KEVIN LEE (LEFT) DURING A PATIENT ENCOUNTER.

LAREN BECKER, MD

OLD Gut, **YOUNG** Gut: What's the Difference?

Why do our digestive systems become finicky as we age?

Growing old can be a pain in the neck—or a pain in the stomach. As you age, you're more prone to constipation, acid reflux, and bowel control problems. Some of that's due to medications older people are more likely to take, chronic diseases, or inactivity, but it may also be due to changes in the gut, according to Laren Becker, MD, PhD. A physician-scientist in the Division of Gastroenterology & Hepatology and an instructor of medicine, Becker has advised undergraduate and graduate students during their research rotations during the past several years.

Recently, Becker studied the guts of mice, which led him to discover another factor driving gut problems: immune cells change with age and drive inflammation, which in turn, changes the function of the GI tract.

"If this is also true in humans, and we could find a way to prevent these changes, we wouldn't have this overwhelming burden of GI problems in older people," says Becker, whose research was published in *Gut* in February 2017.

Immune System to Blame

Like every other system in the body, the digestive system is chock full of immune cells that patrol for invading pathogens that we might have swallowed with our food. In the muscle layer of the gut, the most plentiful of these cells are muscularis macrophages, immune cells that surround the nerve cells of the intestines. Becker wanted to study how these macrophages—which, aside from their defensive role, are known to help coordinate the cross-talk between the nervous system and GI tract—change during aging. In initial studies, he turned to young and old mice to make the comparisons. Here's what he found:

HOW AGING AFFECTS THE GUT

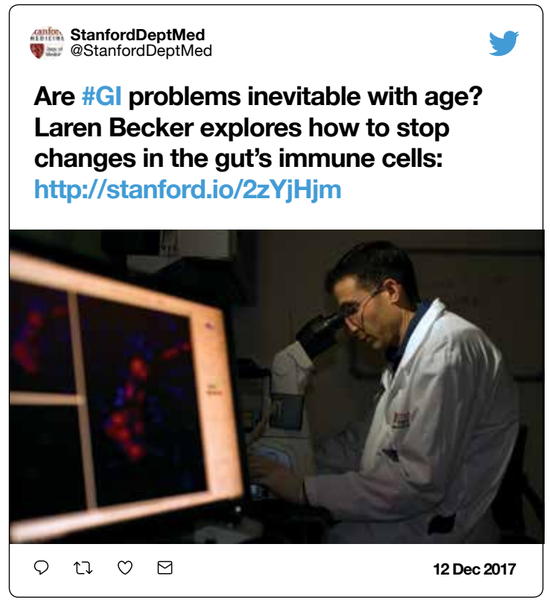
	Young mice	Old mice
Protein levels	Young mice have high levels of a protein called FoxO3 in the muscularis macrophages of the gut.	As mice age, levels of FoxO3 decrease, causing a change in macrophage behavior.
Macrophage types	Most macrophages in the gut are anti-inflammatory "M2" macrophages.	Macrophages shift towards the "M1" type, which promote inflammation and recruit other immune cells to the area.
Neurons around the GI tract	Neurons responsible for controlling the movements of the gut tend to be healthy.	Neurons show signs of chronic neuroinflammation and cell death.
Gut motility	The gut is able to correctly coordinate the movement of food and digestive products through the body.	Without enough functioning neurons in the gut, the whole system slows down. Food takes longer to travel along the intestines.

> targeting these cells could be a way to **RESTORE** many parts of the body to a more youthful state

To sum up, the entire population of muscularis macrophages in the gut changed as the mice aged, promoting inflammation and killing off lots of neurons in the gut. This could lead to all sorts of gastrointestinal conditions, Becker says, since those neurons are critical to keeping the gut moving.

Next, Becker wants to see whether the findings made in mice hold true in humans. He's also curious which factors are initially responsible for the shift in FoxO3 levels and macrophage function. The microbiome—the collection of bacteria that live in your gut—may play a role, for instance. And more work is needed to reveal whether macrophages in other organs of the body make similar shifts toward inflammation during aging.

"If we have a better understanding of how macrophages change with age, targeting these cells could be a way to restore many parts of the body to a more youthful state," Becker says.



2017 EMPLOYEES OF THE MONTH	
January	**JEANETTE CONLEY** Stanford ValleyCare
February	**INES CAMPERO** Stanford Prevention Research Center
March	**ARNOLD SHIR** Stanford Health Policy
April	**MIHAELA BOZDOG** Faculty Affairs Group
May	**HANBANG ZHANG** Upi Singh Lab
June	**ERIN AVERY** Nutrition Research Group and WELL
July	**JASMIN STEINER** Primary Care and Population Health
August	**BETH DUFF-BROWN** Center for Healthcare Policy and Center for Primary Care and Outcomes Research (CHP/PCOR)
September	**MICHELLE LEE** Medicine Residency and Educational Programs
October	**DONNA MEDVED** Medicine—Gastroenterology & Hepatology
November	**JULIE J. ANDERSON** Med/HIP/BeWell
December	**CHIKA EGEMBA** Center for Healthcare Policy and Center for Primary Care and Outcomes Research (CHP/PCOR)

Invaluable **TEAM** members

With the support of our many talented and dedicated staff employees, the Department of Medicine is pursuing an array of ambitious goals as its members create, share, apply, and translate knowledge. Staff are involved in myriad activities, reducing much of the administrative burden on faculty and allowing them to pursue the department's strategic priorities.

On the research side, department employees play crucial roles in managing and operating both laboratory and medical clinic facilities. Assured that these critical pieces of the job are well handled, physician-scientists and their associates are free to focus on their basic science and clinical research projects.

On the educational front, departmental staff support trainees as they begin and develop their careers, colleagues as they learn more about a current position or learn skills to move into a new position, and new staff as they are brought on board.

Where patient care is concerned, departmental employees are responsible for scheduling patients and procedures, seeing that clinics and other facilities meet or exceed all criteria of licensing and accrediting bodies, and staffing areas of service to ensure that the needs of patients are met at all times.

There is much crossover within the department's priorities, requiring a high level of cooperation and coordination among the staff. It is in large part owing to this collegiality that the department is able to reach, and often exceed, its goals.

Among all the outstanding staff in the Department of Medicine, 12 stood out as Employees of the Month in 2017, and they are noted in the chart at left.

Musculoskeletal Ultrasound Clinic is a **BOON** to Patient Care, Education, and Research

As a fellow in immunology and rheumatology, Rob Fairchild, MD, noticed something lacking in the care of rheumatology patients, and he set out to change that.

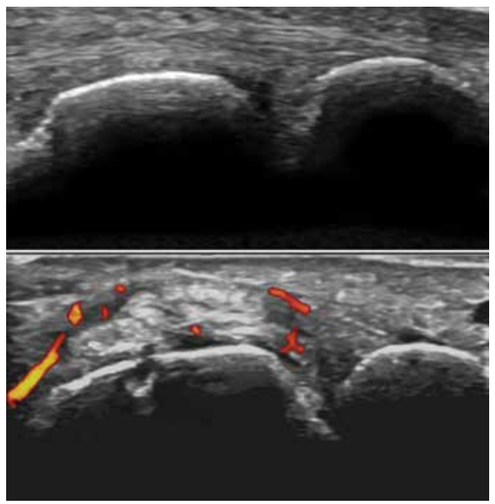
“The use of ultrasound by rheumatologists is more common in Europe than in the United States,” Fairchild observed. He was intrigued because ultrasound is a relatively easy tool that can be performed quickly in the clinic, and it’s an effective means for aiding diagnosis and treatment.

“I did some training on ultrasound during my first year of fellowship, and that led me to devote one of my fellowship electives to starting a musculoskeletal ultrasound clinic dedicated to rheumatology evaluations and interventions,” he says.

Now, as the newest full-time member of the immunology and rheumatology faculty, Fairchild is seeing that the clinic continues not only for the benefit of patients, but also for the education of other trainees.

In fact, the American College of Rheumatology is moving toward incorporating ultrasound as part of rheumatology training, so Fairchild will be building that training into the fellowship curriculum.

ULTRASOUND IMAGES OF BIG TOE



Top image shows a normal big toe. Bottom image shows a large gouty tophus, inflammation, and bony erosion in the big toe of a 32-year-old man complaining of recurrent swelling and pain.

The Craft So Long to Learn

The rheumatologist admits that ultrasound is very complicated and takes a long time to master. It requires learning separate views for each of the joints, and there are a lot of structures to know.

But ultrasound has long been an effective and accepted modality among many specialties, so what makes the Rheumatology Ultrasound Clinic distinct from other musculoskeletal ultrasound clinics?

“There’s actually a really big distinction. First and foremost, I’m a rheumatologist/immunologist. While most specialties use musculoskeletal ultrasound for soft tissue ailments like tendonitis, bursitis, and other joint abnormalities, rheumatologists are also trained to evaluate and manage conditions specific to our field, such as inflammatory arthritis or gout. So, we are often looking for very different things than other ultrasonographers.”

While Fairchild heads the clinic, two other attending rheumatologists—Jison Hong, MD, and Janice Lin, MD—also perform several procedures.

Evaluation and Treatment

Ultrasound helps Fairchild, Hong, and Lin when they are on the lookout for unusual disease manifestations like glandular disease in Sjogren’s syndrome, a debilitating condition that causes the eyes, mouth, or other parts of the body to dry out. It’s also useful in diagnosing polymyalgia rheumatica, an inflammatory disorder that causes muscle pain and stiffness, especially in the shoulders and hips. And ultrasound is a great aid in looking at temporal arteries to spot giant cell arteritis, which, if left untreated, can lead to blindness.

Two of the most frequent referrals the clinic receives are inflammatory arthritis evaluations and interphalangeal joint injections of the hands.

In one recent case Fairchild was asked to evaluate whether there was evidence of an underlying inflammatory arthritis in a patient, as diagnosed by the patient’s previous rheumatologist.

According to Fairchild, “The patient had been on significant immunosuppression with a combination of steroids, methotrexate, and weekly TNF-alpha inhibitor injections, which all have the potential for serious side effects, require frequent clinical and laboratory monitoring, and are expensive. Our clinic’s ultrasound evaluation of the hands showed no synovial hypertrophy, synovitis, joint effusion, or erosions, which are the hallmarks of rheumatoid arthritis. Using this additional information coupled with the patient’s history and clinical evaluation, the referring provider at Stanford felt confident

ROB FAIRCHILD, MD, USES ULTRASOUND FOR MANY DIAGNOSTIC AND TREATMENT PURPOSES, INCLUDING EVALUATING INFLAMMATORY ARTHRITIS.

that the patient’s immunosuppression was not warranted and began to wean the patient off the medications.”

Another recent referral was for intra-articular injections for severe inflammatory/erosive osteoarthritis. “This aggressive, debilitating disease causes severe damage to the distal joints of the fingers with bony proliferation coupled with inflammation, pain, and dysfunction,” he explains.

“One way to reduce swelling, pain, and inflammation in these joints is through steroid injection. However, these joints are very small, and needle injection can be quite painful and technically challenging because of the bony mass surrounding the joint, making needle guidance difficult. When referred these patients, I use ultrasound to accurately guide the needle into the joint in one pass, greatly improving procedure tolerability and accurate steroid placement. As a testament to the efficacy and tolerability of these ultrasound guided procedures, I frequently have patients request repeat visits for additional therapeutic intervention once the steroid has worn off,” he says.

‘Old’ and ‘New School’ Practitioners

Not everyone is convinced of the value of ultrasound.

Many rheumatologists are familiar and comfortable with “classic” examination techniques like feeling a patient’s joints for warmth, swelling, and tenderness to make an excellent diagnosis.

“That’s very different from the ‘new school’ practitioners who can pull out an ultrasound and combine it with a clinical exam to give even greater accuracy. A lot of ‘old school’ rheumatologists would balk at that, but studies have shown that ultrasound is superior in finding active disease, particularly when the disease is mild, where it can be missed with a clinical exam alone,” Fairchild notes.

His interest in ultrasound is convincing other, more established rheumatologists that this technique is important for everyone to know and incorporate into their practice. In fact, some providers who may not have appreciated the value of ultrasound initially are now warming up to it.

Plans for Research

Several areas of research fit into Fairchild’s plans for the clinic. One has to do with how patients perceive their disease when they see it by ultrasound.

“I can tell patients that their disease is really active as a means of encouraging them to take a very serious medication, but that’s quite different from putting an ultrasound on them, pointing to the inflamed area and showing them how the joint is abnormal or damaged. They have an immediate response to that,” he says when explaining his desire to develop a research project in that area.

Another research interest involves scleroderma patients, who can be very sick with soft tissue and skin manifestations. There’s been a lot in the literature recently that has looked at ultrasound and how it can be used to assess disease severity, the kind of disease that the patient actually has, and how it can help with treatments. Fairchild is pursuing a project in that realm with Lorinda Chung, MD, MPH, who runs Stanford’s Autoimmune Skin Disease Clinic in Redwood City with David Fiorentino, MD, PhD.

Training Tomorrow’s Ultrasonographers

Resident and fellow training is another facet of the ultrasound clinic.

“Coupled with their training in the clinic, we also do training at the bedside as part of Stanford 25,” says Fairchild. “Last year Dr. Hong and I did several musculoskeletal ultrasound teaching sessions for the residents in the hospital—hands-on things to show them how to look for knee effusions and other simple things that would be useful on the floor. I want to try to expand that as much as possible in the future.”

Bone Marrow Transplant **SURVIVOR** Connects with Donor Halfway Around the World

How a Transplant Donation Saved One Life and Forever Changed Two

When Ron Gross went to his local hospital in Las Vegas in 2011 for routine tests prior to a cervical spine fusion, he had no idea how dramatically his life was about to change. Overnight he went from being a seemingly healthy middle-aged man to a seriously ill patient in need of a bone marrow transplant, then became a transplant survivor with an important new person in his life.

A blood test disclosed abnormalities soon determined to be myelodysplastic syndrome (MDS), a cancer of the bone marrow that affects its ability to make healthy blood cells. Gross needed an immediate transfusion of platelets to prepare him for the spinal surgery; soon thereafter he began 10 months of chemotherapy.

Gross talks about his experience in a matter-of-fact way: "At first everything seemed to be working with the chemotherapy, but I was needing supplementary infusions. My blood wasn't working out too good as far as the counts went. As I progressed, I was averaging two to three transfusions a week of red blood alone and then platelets once or twice a week."

The Frightening Search for a Bone Marrow Donor

It wasn't long before his oncologist suggested that he needed to think about finding a donor for a bone marrow transplant. That's when Gross began to do some research, ultimately deciding to come to Stanford in hopes of having that transplant.

"I was all for the possibility of a transplant from the beginning," he says. "I was educated very well by the reading material that Stanford provided. They diagrammed what to expect and how successful things have been over the last several years."

Sally Arai, MD, an associate professor of blood and marrow transplantation, was Gross's physician. She talks about what kind of patient he was: "He presented for transplant with high-risk disease. What distinguished him was how very optimistic he was. He was just a lovely person from the beginning and very trusting. He started things off by saying, 'Here I am and I know you can take care of me.'"

Gross started looking for a donor within his family—two sisters and a brother—and, he reports, "the best was eight out of 10 antigens from a sister. But that wasn't going to be good enough for my condition, so they went to the Be the Match Registry."

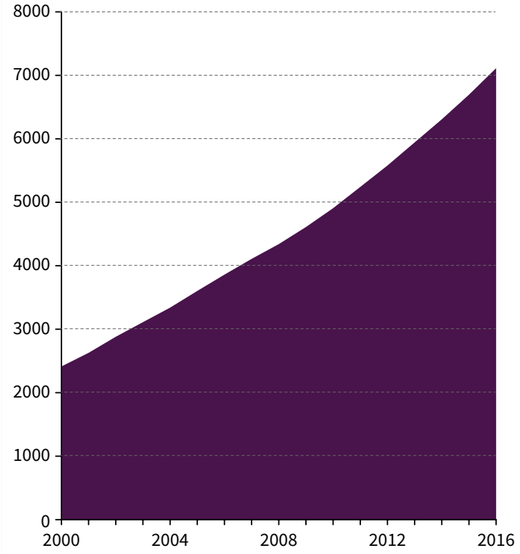
In February, 2014, Gross received his bone marrow transplant from a stranger who was a fully matched, unrelated donor and turned out to be from the other side of the world. His recovery went well, and he reports that he started to feel well about six months later. He had no episodes of rejection.

Arai points out how lucky Gross was: "Mr. Gross's course was pretty smooth in terms of the transplant, just some minor ups and downs, but his overall attitude was just great. Fortunately, he never had to go beyond a fully matched unrelated donor. At the time of his transplant we didn't have much to offer beyond a fully matched unrelated donor transplant, but that has since changed. For example, cord blood (using stem cells from umbilical cord blood) and haploidentical (partially matched) transplants became other approaches for us and increased our numbers of transplants dramatically." (See the table.)

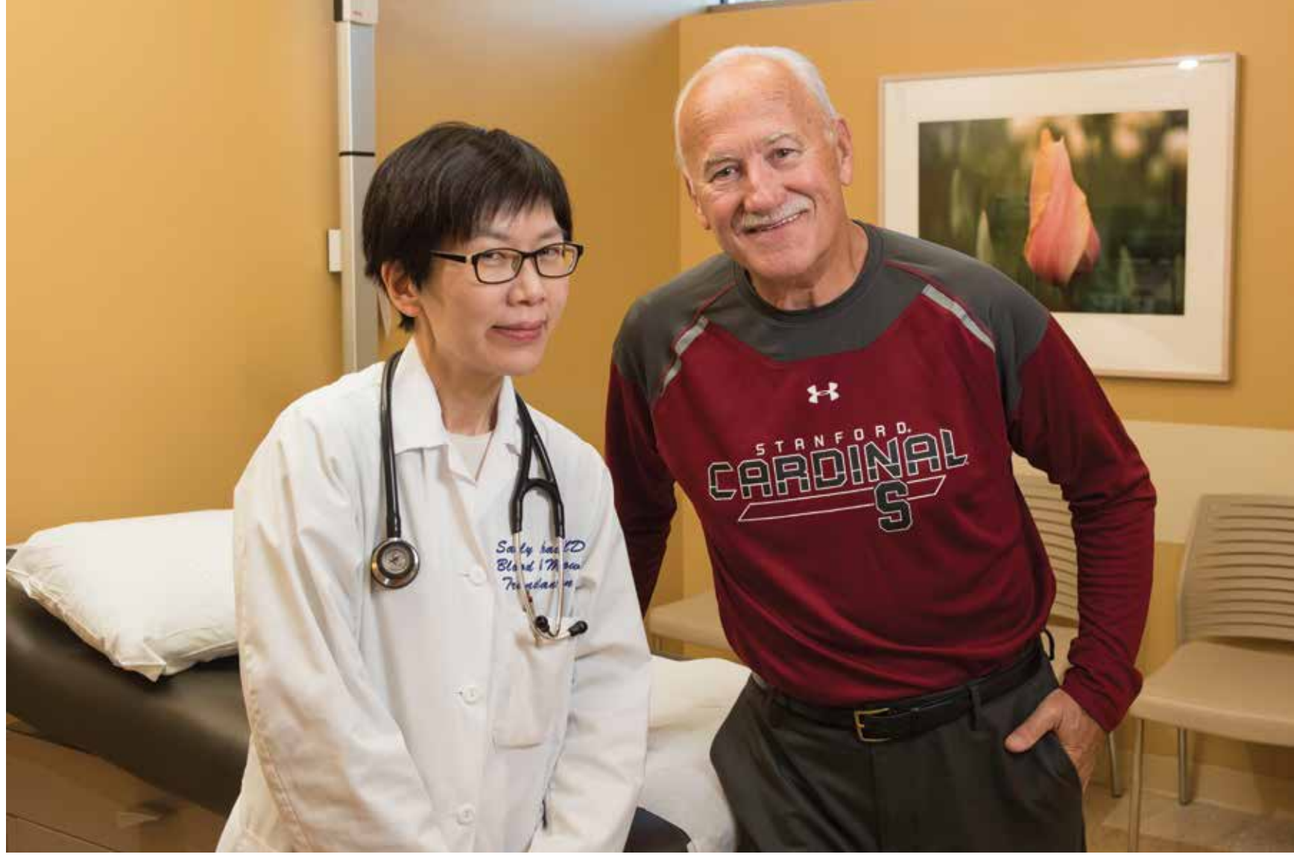
A Two-Year Wait to Meet His Donor

The rules about transplants dictate that donor and recipient cannot learn the identity of one another until, for international transplants,

CUMULATIVE NUMBER OF BONE MARROW TRANSPLANTS AT STANFORD SINCE 2000



The Bone Marrow Transplant program started in 1987 and has both clinical and research significance: It is a national leader both in offering patients the most efficacious treatment and in advancing bone marrow transplant science.



SALLY ARAI, MD, WITH HER BONE MARROW TRANSPLANT PATIENT RON GROSS DURING A RECENT CHECKUP.

two years have passed. But Gross received many unsigned letters and cards from his donor and responded to them. On the day that he celebrated the second anniversary of his transplant, he dialed the phone number of his donor that he had been given. When the phone rang busy he hung up to try again in a few minutes, and his own phone immediately rang. His donor's number was busy because she was dialing his number.

Karolina Wierciak lives in Szczecin, Poland. She signed up to be an organ donor in honor of a cousin who had lost his life to throat cancer. Because the rules in Poland reserve all donated organs for Polish citizens, she chose to enroll in a registry in Germany, making it possible for anyone in the world to receive her donation if she was a match.

Donor and recipient quickly found how alike they are, down to having birthdays two days apart. Recently Gross traveled to Poland and spent time with Wierciak, cementing their strong friendship. They are in touch via email and Facebook, and they text daily even now. As Gross says, "Even though she is the CEO of her company, working long hours, she decided to drive 211 miles to Germany and donate her bone marrow for international distribution, a decision that saved my life."

The Field Continues to Evolve

Arai talks about the changes over just the last several years for patients with blood cancers. "For certain diseases, there have been recent exciting advancements like CAR-T cell therapy. That therapy is open to certain diseases like lymphomas and leukemias. But MDS, which was Ron's diagnosis, is still treated with chemotherapeutic agents from many years back. Ultimately for a cure for these patients, it has to be a transplant."

Patient characteristics have also changed to favor patients who were once considered too old to undergo transplant. "It used to be that transplants were for younger people who could handle the toxicity," says Arai, "but now we have reduced-intensity transplants. Ron represents older patients, and they have become the norm for us. The average age is now in the 60s."

So Ron Gross was lucky on several levels. Perhaps the most important piece of luck to him was the opportunity to form his close relationship with Wierciak. Asked how he would introduce Wierciak to a friend, he says, "I would introduce her as my sister Karolina and my hero."

Pulmonary and **CRITICAL CARE** Medicine Expands to Emeryville

Arthur Sung, MD, a professor of pulmonary and critical care medicine, spends a bit more time getting to some of his patients than he used to, and that's fine with him. When he commutes to the multi-specialty Stanford Health Care Clinic in Emeryville in the East Bay, a variety of patients with diseases of the lung await him in a recently renovated building. The same is true for many of Sung's colleagues at Stanford, and Sung is proud to describe what they have done as "a village effort, with early adopters and dedicated faculty. It is truly a programmatic and division integration of the community aligned with both the School of Medicine and Stanford Health Care's vision."

Sung explains the motivation for many Stanford pulmonologists to commute 40 miles to the East Bay to treat patients: "There was a need gap there in terms of both the presence of disease and the difficulty patients had accessing the Stanford campus. For patients in the East Bay it may be a short distance by absolute miles to go to Stanford, but because of the traffic it's quite a chore to cross the bridges. So this was an underserved population, and that was the main stimulus for our coming to Emeryville. We wanted to offer a comprehensive pulmonary program that manages lung diseases from the more common to the more complex."

The new clinic's patients are both similar to and different from those seen at Stanford, Sung says. "In Emeryville, I see a lot more patients with common lung ailments such as emphysema and asthma, some smoking-related, that we don't see commonly at the Palo Alto campus. We also see a lot of complex lung diseases including pulmonary hypertension, lung fibrosis, and lung cancer in the East Bay. And we see general pulmonology problems that community pulmonologists would like us to consult with them about."

A Collaborative Relationship with Community Physicians

Critical to the success of the partnership at the Emeryville Health Clinic is a cordial and cooperative relationship among all the pulmonologists who practice there. Sung believes the groundwork for their success came from significant effort on all sides. He explains, "Stanford wants to establish close relationships with communities. From the beginning there was a lot of communication between us and the community physicians. This is a partnership. It isn't really like cutting a pie; it is like sharing and treating the patients holistically."

"We took many trips to Emeryville to reassure that we were not there to take away business; we were there to add tertiary care. Patients often come to us for just a consultation and then go right back to their community pulmonologist. We don't keep patients unless it's necessary; for example, the community pulmonologists don't really have the bandwidth to take care of diseases like lung fibrosis and pulmonary hypertension, and we can provide those resources."

Designing the Pulmonary Clinic

In addition to enhancing the local lung disease expertise, all the pulmonologists had the common goal of being able to care for their patients in a completely renovated, state-of-the-art building. Working jointly on that project meant that, as Sung says, "both the community physicians and the Stanford physicians had a lot to say about the design. We had multiple sessions to discuss both the type of patients we wanted to serve and the way they would flow through the building. We took trips to some of the more progressive centers across the country to see how they did things so that we could emulate them."

The building's design ensures that patients have a smooth and logical pathway from the entrance to the building to their discharge after being treated. As Sung sees it, "The patient flow is very well thought out. We are able to deliver very simple care and handle diseases that require a lot more expert testing, such as biopsies and procedures, as well as those needing advanced CT scanners and operating rooms. We have all of that."

> The building's design **ENSURES** that patients have a smooth and logical pathway

Exposure to Community Medicine for Trainees

Emeryville also offers a different opportunity for younger doctors than clinics at Stanford. Because of the complexity of so many patients with lung diseases who travel to Palo Alto, Sung believes that "the fellows sometimes miss the opportunity of seeing how it would be practicing in the community. Having Emeryville is a win-win situation. Not only do we provide complex care, but that exposure to community medicine is there for our fellows to experience as well."

ARTHUR SUNG, MD

EMERYVILLE'S PULMONARY SPECIALTIES

The Stanford Health Care Clinic, Emeryville offers every subspecialty of Stanford's pulmonary program, and each subspecialty is led by Stanford physicians.

Subspecialty	Physician leaders
Pulmonary hypertension	Cyrus Kholdani, MD, and Andrew Sweatt, MD
Transplant	Laveena Chhatwani, MD
Interstitial lung disease	Rishi Raj, MD
Interventional pulmonology	Harmeet Bedi, MD
Asthma	Chunrong Lin, MD
Pulmonary nodules	Visman Nair, MD, and Ryan Van Wert, MD
General pulmonology	Arthur Sung, MD

Chunrong Lin, MD, a clinical assistant professor of pulmonary and critical care medicine, agrees that the Emeryville population is different. "At Emeryville I see patients from Oakland, where there are a lot more African Americans than I see at Stanford. I am seeing some patients with severe asthma who have never seen an asthma specialist, and I'm able to introduce them to some new therapies."

Sung's own practice in Emeryville mirrors his practice at the main campus. As Sung says, "I do interventional pulmonology for patients who require minimally invasive procedures such as bronchoscopy, severe asthma, lung nodules, and emphysema."

Sung returns to the unique characteristics of the situation in Emeryville and the advantages it offers both patients and their physicians: "It is uncommon to have such a comprehensive building as we have in Emeryville that provides a lot of the things that you would otherwise send the patient back to the main campus to be tested for."

Doctoring in **HAITI** Twice a Year

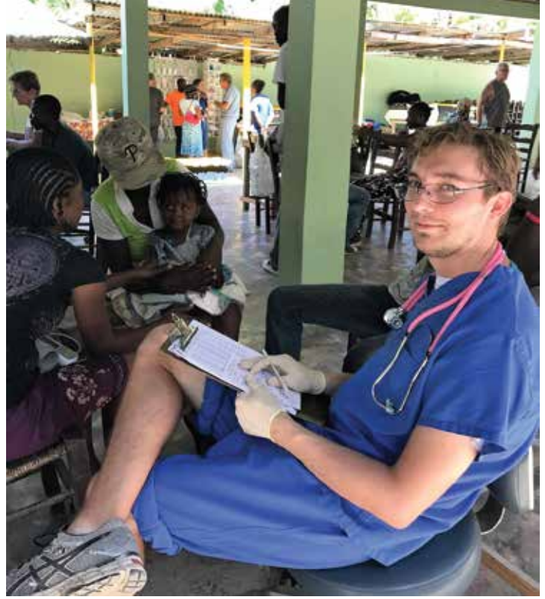
As measured by per capita income, Haiti is the poorest country in the western hemisphere. It has a lot of things working against it: crumbling infrastructure, political instability, an undernourished population, and a location that makes it prone to hurricanes and earthquakes. Its medical resources are few.

In La Croix, population approximately 600, 12 to 14 medical missionaries arrive twice yearly, paying their own expenses, to attend to whatever medical needs they encounter. Word travels fast, because Timothy Foeller, MD, a clinical instructor of hospital medicine, and three other physicians each treat about 100 patients a day for two weeks. There are also four nurses, a maintenance person, a pharmacist, and a police officer who organizes the 600-plus patients who show up every morning. “Our catchment area is much bigger than La Croix,” says Foeller.

> We see **EVERYTHING** ...from pediatrics to geriatrics.

“Once an 85-year-old woman showed up. She seemed a little demented, which is rare because people there usually don’t live long enough to develop dementia. She looked confused and wasn’t responding appropriately. It turned out she was from a town 30 miles away over a mountain, and she had walked most of the way.”

What leads a doctor to a medical mission to Haiti? For Foeller it’s a family trait: “I got involved with Haiti about six years ago through my wife, Megan [Foeller, MD, a clinical instructor in obstetrics and gynecology]. Her uncle, a semi-retired emergency medicine doctor in Rockford, Illinois, and his wife, a cardiac nurse, got involved with missions to Haiti 20 years ago through their church. Megan got involved when she started medical school, and I started going when I met her. The 501(c)3 organization we are affiliated with is Friends of the Children Haiti.”



TIMOTHY FOELLER, MD, ON A TWO-WEEK MEDICAL MISSION IN HAITI.

The illnesses they treat run the gamut. “We see everything,” says Foeller: “high blood pressure, acid reflux, badly infected machete wounds, burns, TB, HIV, malnutrition, birth defects. Everything from pediatrics to geriatrics.”

The group has developed several initiatives aimed at controlling some of the population’s greatest needs in the six months between their visits.

The first initiative concerns high blood pressure, which is the source of many strokes and heart events in Haiti. Addressing it requires both medications and education. “We explain that patients must take one pill a day, and that’s a foreign concept to them,” says Foeller. “We give them a six-month supply and tell them to bring back the bag with any pills they missed taking. If they don’t bring it back they don’t get more pills; they always bring it back.”

The second initiative selects several local individuals and teaches them to be emergency medicine technicians. “We give them gauze pads and teach them basic wound care,” says Foeller. “We have them take blood pressures in hypertensive patients. We give them glucometers so they can check on the diabetics. They do a good job.”

“The third initiative is Megan’s. Nine years ago she learned that midwives deliver most babies. She asked all the midwives to come to the clinic so she could meet them, and 20 showed up, mostly 60-year-olds with no formal training. She spends one day each visit re-educating them and giving them sterile materials like razors and latex gloves. It takes a long time to teach someone to put gloves on who has never seen gloves.”

In summary, says Foeller, “lots of things are very rewarding about our time there. We provide a good service and we help a lot of people.”

A Medical **TASK FORCE** that Impacts Virtually Every Primary Care Patient and Practice

Most Americans outside the field of medicine likely would give you a puzzled look if you asked what they thought of the US Preventive Services Task Force.

But ask primary care clinicians and they’ll tell you the task force is one of the key sources for recommendations about preventive health care. The guidelines issued by the 16-member task force—a volunteer panel of nationally recognized experts in prevention and evidence-based medicine—impact virtually every primary care patient and practice in the United States.

Douglas K. Owens, MD, MS, the Henry J. Kaiser, Jr. Professor and director of both the Center for Primary Care and Outcomes Research in the Department of Medicine and the Center for Health Policy at Freeman Spogli Institute for International Studies, was named vice chairperson of the task force in spring 2017. He will serve as vice chair for two years, then chair the independent body of experts who issue evidence-based guidelines about preventive care.

“Our goal is to provide guidelines clinicians trust. To do that, we review the scientific evidence very comprehensively, we get input from some of the nation’s leading experts in primary care and evidence evaluation, and we have very robust policies to prevent conflicts of interest,” Owens says. “Under the Affordable Care Act, preventive interventions that we recommend as grade A or B must be covered by commercial payers without a co-pay, which means our guidelines can have a huge impact on preventive services delivered in primary care.”

The task force assigns each recommendation a letter grade based on the strength of the evidence and the balance of benefits and harms of a preventive service.

Task force members come from health-related fields including internal medicine, family medicine, pediatrics, behavioral health, obstetrics and gynecology, and nursing. They have a broad portfolio that covers child, adult, and obstetrical primary care, with some 70 active guidelines.

“We evaluate screenings, preventive medications, and behavioral interventions,” Owens says.

Topics include screening for lung, breast, colon, prostate, cervical, skin, and thyroid cancer as well as screening for infectious diseases including HIV, hepatitis C, tuberculosis, and syphilis and other sexually transmitted diseases. Recommendations on preventive medications include statins and aspirin for prevention of cardiovascular disease and colorectal cancer.

“We also make lifestyle and behavioral recommendations,” Owens adds, “which are of course among the most important activities that people can do to stay healthy.”

DOUGLAS K. OWENS, MD, MS

A recent draft task force recommendation, for example, called on seniors to get more exercise to prevent falls, rather than rely on Vitamin D supplements.

“Through his work, Dr. Owens enables Stanford Medicine to advance its mission to precisely predict and prevent disease,” says Stanford School of Medicine Dean Lloyd Minor, MD. “As our country faces an increasingly diverse, aging patient population and rising health care costs, I am thrilled that Dr. Owens will contribute his perspective and expertise to this national task force.”

The task force was created in 1984 and is supported by the Agency for Healthcare Research and Quality (AHRQ) within the US Department of Health and Human Services. All recommendations are published on the task force’s website and/or in a peer-reviewed journal.

“The task force has very rigorous methods for assessing evidence, and we are fortunate to have state-of-the-art evidence reviews provided by AHRQ-funded Evidence-Based Practice Centers,” Owens says.

Each year, the task force makes a report to Congress that identifies critical evidence gaps in research related to clinical prevention services and recommends priority areas that deserve further attention. All their reports and recommendations are made public on the task force website and leave room for public comment.

United by Technology: A New **MEDICATION SAFETY** Program at the VA

Like many other tools, technology can be used for good or ill, to enlarge gaps between people or to bridge them. But for Paul Heidenreich, MD, professor of cardiovascular medicine (and, by courtesy, of health research and policy at the Palo Alto Veterans Affairs Health Care System), technology can be used to create a "community of practice."

Heidenreich serves as vice chair for clinical, quality, and analytics in the Department of Medicine and is currently heading the MedSafe project, sponsored by the VA's Quality Enhancement Research Initiative, which seeks to improve medication safety.

This aspect of medicine needs improvement. In 2011, 12 percent of veterans were prescribed a potentially inappropriate new medication with an incidence of six percent per year. Heidenreich explains that this happens for various reasons: Patients may be inappropriately prescribed a high-risk medication or be on a high-risk medication without appropriate lab monitoring. "Our systems are not such that we can catch that or realize it happened every time," he says.

Interventions to Improve Safety

The VA has initiated programs to improve medication safety. The interventions come in various forms: for example, educating patients about risks, writing draft medication or lab test orders for physicians to sign, or even reaching out to patients. While a variety of these interventions have been implemented, they lacked a way to measure their effectiveness. This is where Heidenreich's project comes in.

"One of our goals was to look at all the interventions the VAs in different states were using, see which sites were most effective and had the best safety records, and then note what were they doing to manage things," he states.

To that end, his group designed MedSafe, which is government-funded and set to run for five years with access to all patient records within the VA system. The VA serves more than 8.9 million veterans at 168 VA Medical Centers and 1,053 outpatient clinics each year. Data about all patients is tracked and can be fed back to the various hospitals and clinics.

The project consists of three subprojects. While Heidenreich's group studies the effectiveness of various interventions, another group is putting the interventions (suggestions, orders, etc.) into the electronic dashboard so physicians and hospital staff can immediately access the information. A third subproject, headed by Mary Goldstein, MD, a professor of medicine at Palo Alto VA Health Care System, focuses on developing "clinical decision support (CDS)" integrated with the dashboard to guide providers through the process of implementing the interventions.

"In addition to updating the knowledge bases to newer evidence and guidelines, we are linking the CDS to a clinical dashboard," Goldstein states. "For example, if a patient with diabetes is out of range for glucose control, our CDS system will generate recommendations for the primary care team."

> **IMPROVING** patient safety is also important to operations people

The project is too new to have conclusive data, but Heidenreich expects the "more active, targeted, interruptive interventions" to be the most effective. On a past project they "found that physicians were for the most part very willing to receive a draft order for a diagnostic test," and he believes that the same will hold true for this CDS project, which plans to provide recommendations for medications and lab tests.

The VA, like many governmental institutions spread across states, is both a local and a national organization. This can sometimes cause friction, but Heidenreich sees his project as potentially both a centralized and a localized effort. "I think in the long run there's no reason why it couldn't be centralized," he says. "It's not clear that physicians need to see a recognizable name before they're going to look at the recommendations in the dashboard. The VA system is still fairly decentralized in terms of medical records and care, so our goal would be to see which things are the most effective and then go back to all 100-plus facilities and encourage them to adopt those interventions."

He's optimistic about the adoption. "We don't do these projects just as isolated researchers," he explains. "We do them in partnership with the operations people. The nice thing is that improving patient safety is also important to operations people, and since everything we're doing is improving care, we're all in sync."

Implementing the Interventions

This mutual interest can be drawn on in the next stage, as the project yields results that need to be implemented. Heidenreich's team has ideas for this as well. In the past, he explains, they used what they called "a community of practice."

In one case, they invited the lead pharmacists of all VA facilities to get together and then "we would present data or, even better, we'd have different facilities present things that they'd done. We would then show effects and which things seemed to work well. We were able to link people and also provide them with information like, 'This is how they did it, this is how you can do it, this was the cost to implement it.' To get them all talking to each other is one of the ways we'll be implementing MedSafe."

Goldstein agrees that the project "holds a lot of potential. In working with newer technology, such as dashboards with CDS, it can be helpful for groups to talk with each other to share ideas of what works best," she says. "We know of some clinical groups who are using the dashboard to share information within their teams, and we hope that they will be able to take this a step further by using the recommendations from the CDS. We plan to talk with health professionals from multiple teams to learn about what works for them, and we hope later in this project that the teams will share best practices with each other."

Technology that Unites

Goldstein is a believer in the power of this technology to unite: "I think what drives the community of practice is the shared goal of providing best care for patients. I see the technology as something that, if designed and introduced to the clinical setting in a way that is helpful to the health professionals working there, can be part of an overall approach to providing best care. In my view it's never about the technology per se, but about the technology making it easier for the health professionals, ideally freeing up time from rote work so that they can spend more time interacting with patients—doing the things that humans do well, attending to relationships, emotion, patient goals—and less time with the computer."

It's a sentiment echoed by Heidenreich. The efforts, he says, "give a sense of community to those people, especially some who are at smaller facilities. I think it helps them feel engaged in a larger effort."

The MedSafe project ultimately seeks to do just that: use technology as a tool to create stronger bonds among far-flung hospitals and clinics. This information sharing creates a broad community of practice and practices, funneling research, technology, and real-world knowledge into something that ultimately benefits the individual at the heart of all of this: the patient.

PAUL HEIDENREICH, MD

The Project Baseline Study: Offering a Unique **CONTRIBUTION** to Mankind

The Project Baseline study is no less than an ambitious effort to map human health. It came about as the result of discussions that began in 2013 between Drs. Sanjiv (Sam) Gambhir of Stanford, Robert Califf from Duke, and Andrew Conrad (then from Google X, now the chief executive officer of Verily Life Sciences).

Gambhir provides the background: "Google X was looking to undertake a landmark study in human health. I was initially contacted by Dr. Conrad due to my focus on early cancer detection and the potential for studying large cohorts of individuals at low and high risk for cancer. Dr. Califf was brought into the discussions due to his experience in running large cardiovascular trials at Duke. Over the course of many months and several discussions, the study evolved to what is now referred to as the Project Baseline study."

The Project Baseline study is enrolling approximately 10,000 participants across the United States in an extraordinarily detailed, four-year examination of what it means to be healthy and to identify what happens during a transition to disease.

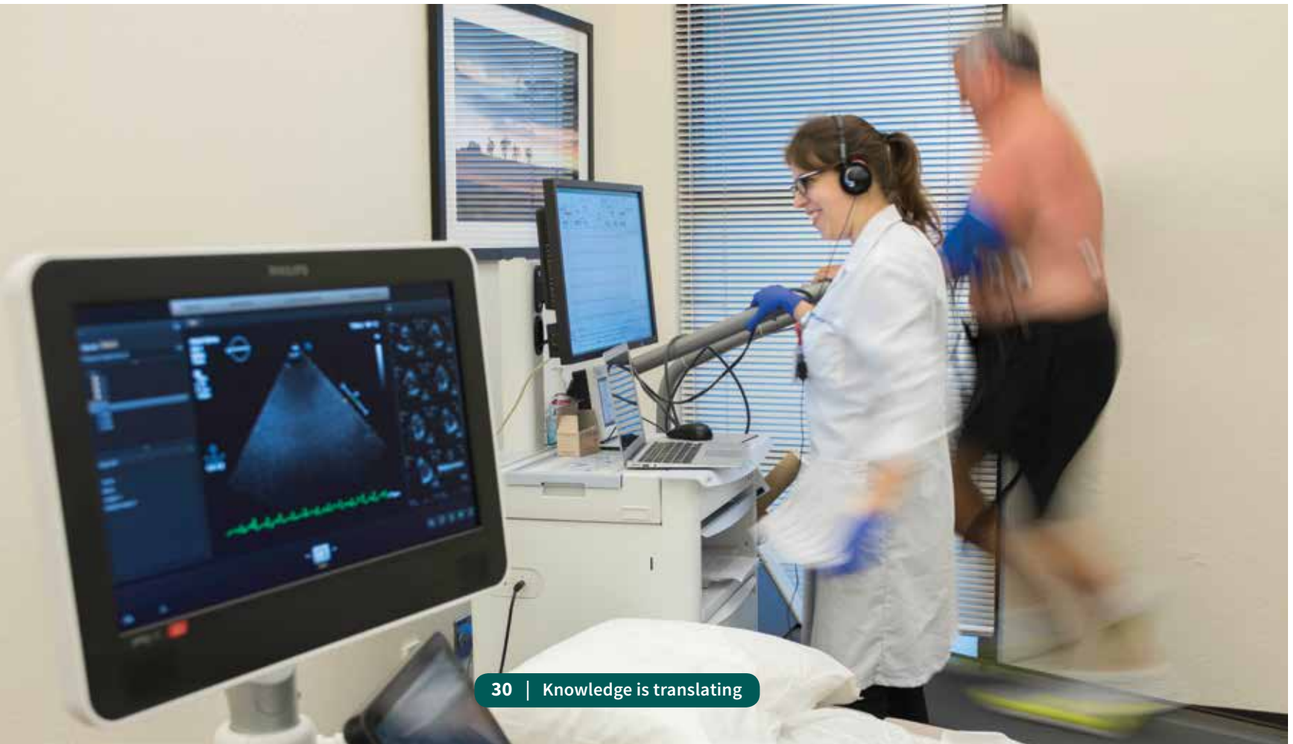
The leadership at Stanford includes Gambhir, MD, PhD, a professor and chairman of radiology; Kenneth Mahaffey, MD, a professor of cardiovascular medicine and director of the Stanford Center for Clinical Research (SCCR); and Rebecca McCue and Susan Spielman, who wear several hats in the School of Medicine.

Volunteers who elect to enroll are in for a comprehensive two days of tests, says McCue, who is the associate director of the SCCR and oversees site-based research in the Department of Medicine. "The staff who work with the enrollees have prioritized ensuring that their experience is positive and treating them as engaged participants. We've focused on that across all the institutions involved since day one as we've designed the workflows and the protocol, because we recognize we're asking the participants to do a lot."

McCue gives a glimpse of the testing participants undergo: "They get an extensive battery of tests: basic medical history and vitals, electrocardiogram, ankle-brachial index, some physical performance testing, cognitive testing, eye exam, echocardiogram and stress echocardiogram, X-ray, coronary artery scan, audiometry. We're trying to get a comprehensive view of each person's health."

It doesn't end after two days. Participants will return to their site of enrollment for a visit each year for four years. Some participants will be asked to return quarterly. All participants will receive tools to use, including an investigational study watch designed by Verily that tracks things like heart rate and activity level as well as a bed sensor that reports on quality of sleep. They will also have access via a mobile app to a portal where they will be able to respond to surveys and enter data of their own.

A PROJECT BASELINE STUDY PARTICIPANT UNDERGOES AN EXERCISE STRESS TEST.



Every effort is being made to enroll a participant population that reflects the US population by age, ethnicity, health status, and other demographic variables, according to Spielman, director of strategic initiatives for radiology. She was involved in project discussions among the three principals from the beginning and currently co-leads Stanford's strategy and development plans for the Project Baseline study with McCue.

She describes how the enrollment cohort came to be defined: "There's a broad definition of who we're targeting, so it allows for an easier recruitment process that is more inclusive and more realistic. Collecting information from a diverse group of people with different health histories is critical to the success of the study. Because it's so difficult to recruit and retain in research, by redefining the cohort structures we're able to bring in a bigger range of people more easily and enroll the diversity of the population that we need to be successful."

Recruitment began in June 2017, and Stanford continues to enroll several new participants every day.

Most sponsors of clinical research studies provide the funding and are otherwise mostly silent partners. In the case of the Project Baseline study, it is the true partnership between academia and industry that makes the study possible, as Spielman explains:

"The mission of the study was developed collaboratively among Stanford, Verily, and Duke. Verily is developing many tools that are enabling us to perform the study as envisioned. As we are doing all these assessments to collect the data at each site, they are creating the necessary infrastructure that allows people to consent and enroll, developing the electronic data capture system for all the data to be entered, and implementing the software platforms for robust multi-dimensional data analyses at a later time."

The intention is to make data available to anyone with an institutional review board-approved research study in accordance with guidelines established by a committee set up to handle such requests. It will be a tremendous resource for the whole global community.

Both Spielman and McCue express excitement about how well the study is going so far. Spielman recalls that "there were a lot of people who thought the scope was so big and the depth of the data being collected was so comprehensive that there would be many roadblocks. So the fact that we've been able to get started and are gaining momentum in enrollment is thrilling."

> It will be a tremendous resource for the whole global **COMMUNITY.**

McCue concurs, saying, "It's remarkable how much effort has gone into this study from all sides. It took many years for the collaboration and the study protocol to come to fruition, through the efforts of a lot of dedicated individuals from Verily and Stanford and Duke. I've been really impressed by the intensity with which the faculty and everybody across the board have been engaged. What excites me most is seeing how motivated the teams are and how much people believe in the study and want to make something really good come of it."

Sites at Stanford Medicine, the Duke University School of Medicine, and the California Health and Longevity Institute are currently enrolling. Additional sites may be added over time. Sometime in the coming years, when all approximately 10,000 participants have completed four years of tests and surveys and measurements, a vast treasure trove of data will have been amassed. It will be uniquely capable of answering questions about health and disease that have never been able to even be asked before.

Reflections on a Lifetime of **DISEASE PREVENTION**

The year 1927 was certainly noteworthy! In that year, nine decades ago, Werner Heisenberg described his uncertainty principle. Philo Farnsworth transmitted the first image from a television camera tube. Charles Lindbergh made the first solo non-stop trans-Atlantic flight. The success of *The Jazz Singer* marked the end of the silent film era. António Egas Moniz developed cerebral angiography.

It was also the year that a pioneer in preventive medicine, John W. (Jack) Farquhar, MD, was born. Among myriad accomplishments, Farquhar (with Nathan Maccoby) co-founded the Stanford Heart Disease Prevention Program to activate communities to change their lifestyle, preventing disease and improving health. As the scope of the organization widened to include multiple aspects of disease prevention and health promotion, its name changed to the Stanford Center for Research in Disease Prevention and later to the Stanford Prevention Research Center (SPRC).

At 90, Farquhar, the C.F. Rehnborg Professor in Disease Prevention, emeritus, and professor of medicine and health research and policy, emeritus, attributes his longevity in part to practicing what he's been preaching—paying attention to lifestyles that are relevant to successful aging. In a recent interview, he discussed how the SPRC got started, some of its seminal achievements, and where he'd like to see the SPRC in the future.

What brought you to Stanford originally?

Well, let's see… I was at the Rockefeller Institute (now Rockefeller University) with Hal Holman, who was invited to Stanford to become its youngest ever chair of the Department of Medicine. At the time, there was a desire to bring what they hoped was a youthful figure into a rather elderly faculty, and he was part of that revolution. In 1962 he asked me to come here with several other eager young faculty who were research oriented rather than clinically oriented.

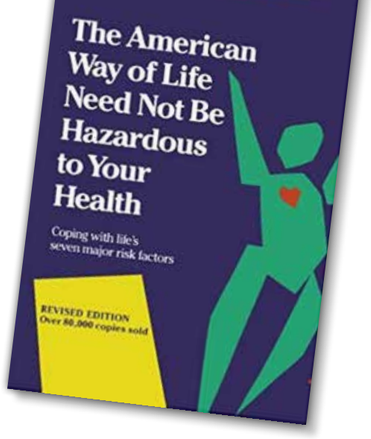
JOHN W. FARQUHAR, MD

> "The advent of the total **COMMUNITY** approach to prevention was really our invention.

What led you to start the SPRC?

As an intern I had a patient in his 40s who died, and I had to comfort his widow. That led me to think of the potential for prevention because we were in the middle of an epidemic of post–World War II expansion of smoking, and of poor diet, and the beginning of a decrease in physical activity due to automation. After World War II we were the richest nation in the world, and the returning veterans were all feeling this post-war irrational exuberance. But smoking rates went up, and there was a return to an expansion of dietary intake of saturated fat from meat and dairy products with a disregard for some of the foundations of atherosclerosis.

There was a combination of increased smoking rates and cholesterol levels from diet along with decreased physical activity. We entered into an epidemic of preventable coronary disease, and I was a pioneer in that from my exposure to it during my residency training. It led me to write the book *The American Way of Life Need Not Be Hazardous to Your Health*.



It was a new way of thinking, but it was gaining momentum internationally. Within the United States, our colleagues at the University of Minnesota in particular were similarly inclined. We formed policy groups and became a pressure group to influence the National Institutes of Health to pay attention to the prevention side of cardiovascular disease.

There was a lot of attention on techniques like heart transplants, but I was convinced that saving people one by one was not the most effective way to address the problem. I realized the need to make permanent lifestyle changes to prevent cardiovascular disease by reaching people in the community where it was needed the most. That led me, with Henry Breitrose and Nathan Maccoby in the Stanford Department of Communication, to create a multimedia campaign to motivate and educate communities to undertake major lifestyle changes. That was really the beginning of the "total community" approach.

Can you name some achievements that came out of the SPRC?

The advent of the total community approach to prevention was really our invention. It was the idea that you could mobilize a community through a campaign using newspapers, radio, television, and medical authorities to provide information and training that people needed in order to change their lifestyle toward a healthier one that would prevent cardiovascular disease.

Peter Wood, Bill Haskell, and I were involved in showing that exercise increased the HDL fraction of blood lipoproteins. That particular discovery then was taken up throughout the world, and hundreds of papers came out about the role of HDL as the protective fraction and LDL as the harmful fraction of blood lipids.

Another area of achievement was some of the methods for smoking cessation. The use of nicotine replacement was a new thing, and we were one of the first groups working on that. Later, a few of our people, including Tom Robinson, who happens to be a pediatrician, developed the methods for educating high school students on risk factors associated with smoking, poor diet, and lack of exercise. That was quite an important chapter, which I would call adolescent or youth education.

We took up the battle over obesity, too. The theme that runs through all this is prevention of disease through lifestyle issues. The whole lifestyle category would include smoking, exercise, and diet. And you could toss in stress management.

Today's SPRC includes the WELL for Life initiative that is aimed at changing the global well-being landscape. There's also a new master's degree program in community health and prevention research.

Where would you like to see the center in the future?

I'd like the center to continue to grow in importance to the department and the university as a source of knowledge for methods to promote healthy living. And to have the School of Medicine and the university play an important part in the restoration of what should have been present 30 or 40 years ago—attention to the prevention side of the equation. In the last five years there has been increased attention to prevention within the medical school and the university.

I hope that the center remains important in developing methods of influencing policy and/or of educating society and people in positions of authority. I'd like to see a change in our training system so that people with higher degrees are cognizant of the principles of ecology, economics, and political science such that they can be participants in health policy change.

I want education to remain accepted as part of the equation to have optimal public health. Who you are educating and how they will influence public policy is all part of the dream to produce people who are smart, knowledgeable, and trained to tackle these problems.

At Last, **MEDICAL EVIDENCE** for a 'Psychological Disease'

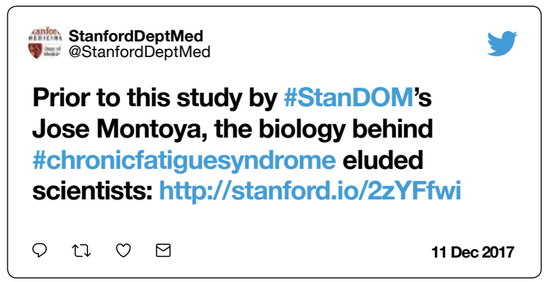
Every now and then the publication of a scientific study makes a patient community go wild with enthusiasm. For patients with chronic fatigue syndrome, a recent study led by Jose Montoya, MD, professor of infectious diseases, was their eureka moment.

More than 1 million people in the United States suffer from chronic fatigue syndrome, also known as myalgic encephalomyelitis, or ME/CFS.

Many patients with ME/CFS experience flulike symptoms common in inflammation-driven diseases. But because the symptoms of this disease are so diffuse and heterogeneous—sometimes manifesting as heart problems, sometimes as mental impairment nicknamed "brain fog," other times as indigestion, diarrhea, constipation, muscle pain, tender lymph nodes, and so forth—it often goes undiagnosed, even among patients who've visited a half-dozen or more different specialists to determine what's wrong with them.

Montoya believes that in around 80 percent of the ME/CFS patients he treats, the condition developed as a result of infection. But because few of them get to see a specialist until they have been ill for many years or even decades, the bacteria or viruses responsible have long gone into hiding inside the body's cells, meaning that many standard blood tests show nothing wrong.

"This is one major reason why so many doctors have dismissed this as psychological in the past," he says.



Supporting Evidence

Previously, there has been little or no correlation between science and patient complaints, but the findings from Montoya's study provide evidence that inflammation is a powerful driver of this mysterious condition, whose underpinnings have eluded researchers for 35 years.

The research found that people with ME/CFS had abnormal levels of 17 cytokines, substances from the immune system, in their blood. The higher the levels of certain pro-inflammatory cytokines, the more severe the symptoms of chronic fatigue syndrome, which led Montoya and his colleagues to suggest a link between excess inflammation and the disease.

Another significant finding concerned one cytokine that has been implicated in development and promotion of lymphoma. ME/CFS patients have a higher predisposition to develop lymphoma, and that finding may lead to the biological link between ME/CFS and lymphoma.

Previous efforts to identify immunological abnormalities behind the disease have met with conflicting and confusing results, says Montoya, who oversees the Stanford ME/CFS Initiative.

That's what spurred him to undertake a systematic study to see if the inflammation that's been a will-o'-the-wisp in those previous searches could be definitively pinned down. The study findings, published August 22, 2017, in the *Proceedings of the National Academy of Sciences*, could lead to further understanding of this condition and be used to improve the diagnosis and treatment of the disorder.

ME/CFS is a disease with no known cure or even reliably effective treatments. It characteristically arises in two major waves: among adolescents between 15 and 20, and in adults between 30 and 35. The condition typically persists for decades.

Three of every four ME/CFS patients are women, for reasons that are not understood. However, Montoya's study found that leptin, one of the 17 cytokines correlating with severity and produced at higher levels in women, may explain why ME/CFS is more common in females.

'The Suffering of These Patients'

What got Montoya interested in ME/CFS was "purely the suffering of these patients," he says.

He recalls seeing a young, 35-year-old female patient in 2004 who had been experiencing debilitating symptoms for eight years without a compelling explanation from any medical expert.

"Her circumstances convinced me that there was no reason for her to fake her symptoms, and because one of the major reasons I became a doctor was to empathize with patients and ease their suffering, I just couldn't walk away from a case like that, even though that's what many of my colleagues were doing.

"I couldn't believe that the causes for their symptoms were psychological; there had to be some biological reason why these patients were so sick," he adds.

JOSE MONTOYA, MD

Montoya observes that physicians, lacking proper tools or knowledge at the time, have discounted other diseases that we now understand. During the 19th century people were dying by the thousands in London, and the cause was thought to be bad air or even a punishment from God. Only after the invention of the microscope and the foundation of certain principles of epidemiology did scientists realize the cause was a bacterium we now know as cholera.

For decades patients with ME/CFS were describing symptoms that suggest inflammation, but doctors tended to ignore that.

The medical community has blood tests, imaging studies, and many other methods to determine why somebody is sick. In the case of ME/CFS they were unable to come up with any technique that was applicable.

"Because CFS is complex, falls between specialties, and doesn't fit into a diagnosis, doctors thought it must be something that the patient was inventing. They didn't want to think we weren't smart enough to understand it or that we weren't applying the right technology," Montoya explains.

A Group Effort

He began working with experts in several other disciplines, notably Mark Davis, PhD, professor of immunology and microbiology and director of Stanford's Institute for Immunity, Transplantation and Infection.

"This was a group effort, and the major piece was that the correlation between 17 cytokines and severity of symptoms was something that was not appreciated before. The importance of that is that this disease has been viewed as a psychological disease, something that lived in the patient's imagination, and through that they have been humiliated and ostracized," Montoya explains.

"Now, for the first time, the findings from this study fit very well with what patients have been telling us all along. Finally, these patients have a biological reason for their suffering, and the beauty is that it correlates nicely. The more severe their symptoms, the higher the cytokines are," says Montoya.

For patients, this research is validation. They can now say: "My symptoms correlate with biological measures in my blood, so I'm not crazy!"

The Future

Another benefit of the study is the patient cohort. The research community now has blood that was collected from this patient population that can be used for other studies.

Having "hit the jackpot" with the results from this patient population, Montoya explains that they now can view this population from many different angles.

This initial study focused on the immune system. In the same patients, scientists can study their genes, for example, with the expectation of making equally astounding findings.

"What we've done is put together a group of about 30 people at Stanford. These are faculty and staff of various disciplines who are looking at these data and this patient cohort. So, we will have, within a year, results of other assays, where we apply other technologies to this same patient population where we found this initial amazing correlation," says Montoya.

Why Being Overweight Makes (SOME) People Sick

Not everyone who gains weight develops insulin resistance and metabolic disease. Can research reveal why?

Most Americans today have a body mass index (BMI) that, by definition, puts them somewhere in the range of overweight to obese. But those on the upper end of the BMI spectrum aren't always the least healthy, even when it comes to diseases linked to weight. Someone whose BMI is barely in the "overweight" range may be plagued with diabetes, heart disease, fatty liver, and high blood pressure, while an obese individual may be metabolically healthy. It's a conundrum that's puzzled doctors in recent decades, even as the waistline of the average American has grown.

"We still don't know what causes some people to get insulin resistance when they gain weight, while others seem to be protected," says Tracey McLaughlin, MD, an associate professor in the Division of Endocrinology. But McLaughlin is on the hunt to find out.

She and Michael Snyder, PhD, a professor of genetics, received a $3.2 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD). Their plan is to survey the molecular signatures of blood and fat cells in overweight and obese individuals in whom insulin resistance will be induced and then reversed by, respectively, dietary weight gain and loss.

Researchers know that, in general, insulin resistance—the first sign that the body isn't processing blood glucose correctly—is linked to weight gain. In turn, insulin resistance can lead to prediabetes and type 2 diabetes, as well as high triglycerides, hypertension, heart disease, stroke, fatty liver disease, and many cancers. Weight loss, in most cases, reverses insulin resistance and prevents the development of metabolic syndrome and associated clinical morbidities.

During the past 10 years McLaughlin has been working out some of the details that make some overweight people more prone to insulin resistance than others. "It has to do more with the qualitative aspects of fat than the quantitative aspects," she says.

McLaughlin has completed both metabolic phenotyping and radiologic measures of where fat is stored. She has also performed fat biopsies on over 600 human subjects. And she performed further research with Samuel W. Cushman, PhD, of the NIDDKD.

Based on that work, McLaughlin and Snyder now want to do even more in-depth studies of fat and blood from overweight and obese individuals who are subjected to a weight-challenge intervention. One goal is to find a biomolecular signature that can help tell clinicians which people are insulin resistant and at risk of developing metabolic syndrome; another goal is to find molecular pathways that link excess body fat to insulin resistance.

"Not all overweight and obese people are metabolically unhealthy. Only about half of them have insulin resistance, and the obesity-related health consequences are concentrated in this group," says McLaughlin. "So it's important to try to figure out who's at risk for those diseases and focus resources on keeping them from gaining weight."

Furthermore, she says, identifying the molecular pathways that link weight gain and insulin resistance may lead to new drugs.

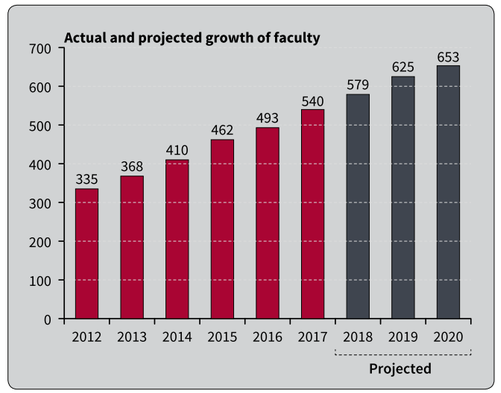
As part of their studies, the researchers are taking blood, fat, and stool samples as participants gain and lose weight to study how levels of different molecules—from RNA to proteins, along with immune cells and the microbiome—change during weight perturbations. They've already collected data on 66 people and are recruiting more individuals toward their goal of 100 people for the study.

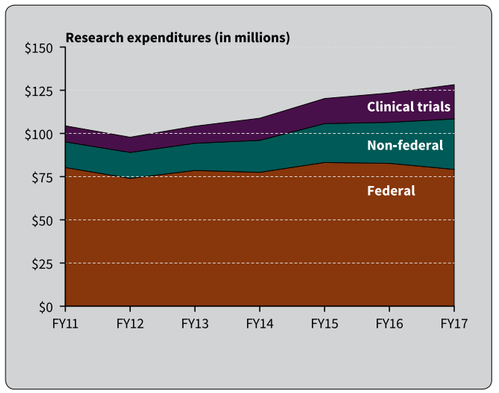
"Once we can identify people in this very early disease state, the first intervention is very easy and cost effective—it's lifestyle changes," McLaughlin points out.

TRACEY MCLAUGHLIN, MD

Department of Medicine in Numbers

15	Divisions
540	Faculty *(103 University Tenured and Nontenured Line, 109 Medical Center Line, 305 Clinical Educators, 23 Instructors)*
30	Endowed Professors
879	Staff & Research Associates *(540 Staff, 100 Research Associates, 239 Temporary Staff)*
494	Trainees *(135 Residents, 135 MD Fellows, 224 Post-docs)*
$128.2M	Sponsored Research *($79.2 million in federal grants, $29.2 million in non-federal grants, $19.8 million in clinical grants)*
523	Grants *(3 Program Projects, 58 R-01s, 31 Ks, 21 Us, 12 Training, 37 other Federal Awards, 361 Non-Fed & Clinical Trials)*





Gaining **KNOWLEDGE** is the first step to wisdom.

Sharing it is the first step to **HUMANITY**.

UNKNOWN

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