Northern California Institute for Research and Education

DNA

DETAILS NEWS AWARDS

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Focus on Research

Science Team crucial in research to detect and prevent kidney disease

The statistics for chronic kidney disease (CKD) are stark and vexing: 37 million adults—1 in 7 in the U.S.—suffer from the devastating condition, according to the Centers for Disease Control and Prevention.

Sadly, as many as 90 percent of people with CKD will show no symptoms until they need dialysis or even a kidney transplant. The "silent" disease, which is all too common among adults with diabetes and high blood pressure, disproportionately strikes African Americans, Hispanics, and Native Americans.

The economic costs are enormous: Medicare spends more than $70 billion a year for CKD—nearly a quarter of Medicare spending for people over the age of 65, according to the U.S. Renal Data System 2020 Annual Report. Tack on another $49 billion in Medicare spending for end-stage kidney disease.

Such data—and more so, seeing patients who end up in hospitals and dialysis centers because their kidneys have failed—frustrate, but also motivate Michael Shlipak, MD, MPH, NCIRE Board Chair, Associate Chief of Medicine for Research Development at SFVAHCS, and UCSF Professor of Medicine, Epidemiology & Biostatistics.

When Shlipak joined University of California San Francisco (UCSF) and the San Francisco VA Health Care System (SFVAHCS) some 25 years ago, early stages of kidney disease were largely ignored and clinically unrecognized.

Michael Shlipak, MD, MPH
Associate Chief of Medicine for Research Development, SFVAHCS
Scientific Director, Kidney Health Research Collaborative, UCSF
Professor of Medicine, Epidemiology & Biostatistics, UCSF
Chair, NCIRE Board

But kidney disease does not have to reach an advanced or deadly stage, Shlipak maintains. And he has since devoted his research to developing strategies for the early detection and prevention of kidney disease.

Shlipak, a general internist with many questions and ideas about solving the unacceptable rates of advanced kidney disease, needed research partners and specialists with similar passion and motivation to improve kidney

health worldwide.

That first partner was nephrologist Carmen Peralta, MD, MAS, another NCIRE-supported scientist. In 2015 they founded the Kidney Health Research Collaborative (KHRC), based at SFVAHCS and UCSF. Shlipak now serves as its Scientific Director and Peralta is the Senior Advisor.

In 2016, NCIRE-supported researcher Michelle Estrella, MD, MHS, UCSF Professor of Medicine and Renal Section Chief at the SFVAHCS, came on board and now serves as the Executive Director of the KHRC.

Pioneering research

In just eight years, the KHRC has conducted pioneering research. Importantly, KHRC investigators, led by Shlipak, helped establish CKD as a significant cardiovascular disease risk factor. The KHRC is also a leader in using novel markers of kidney health in blood and urine to detect disease at its earliest stages. And researchers are examining the large burden of CKD in vulnerable populations such as racial/ethnic minorities, elders, and HIV-infected persons.

The KHRC has grown to include some 18 research faculty members, a Biomarker Core Facility with state-of-the-art technology, and an expanding network of collaborators from around the country and the world.

Unique and impactful

Some important core values distinguish the KHRC from other kidney disease research programs.

"First, we have always been committed to the prevention of kidney disease and to slowing its progression across stages," he said. "By developing methods for detecting kidney disease at its earliest stages and identifying the causes, we believe that we can make the greatest impact to reduce the global burden of kidney disease.

"In contrast, most kidney research groups have focused on the population with kidney failure or late-stage kidney disease.

"Second, we take our commitment to team science to the highest level; and we share everything—ideas, leadership, finances, space, and credit," said Shlipak. "This makes our group completely inter-dependent and collaborative, which contrasts with the traditional academic model that expects successful investigators to be independent of one another.

"Third, we build mentorship and career development into all of our research projects," he said. "Research training is common, but we invest exceptionally in our students, post-doctoral fellows, and junior faculty with our time and commitment."

Turning passion into ideas

Vasantha Jotwani, MD, an NCIRE researcher and UCSF Assistant Professor of Medicine who joined the KHRC in 2018, typifies those values and spirit.

"One of my greatest and most heartbreaking challenges as a nephrologist is that by the time people come to see us in clinic, the damage is already done," said Jotwani. "There is little that we can do to fully reverse or even halt the process, and I have seen so many people progress to end-stage kidney disease over the years despite our best efforts to keep them healthy.

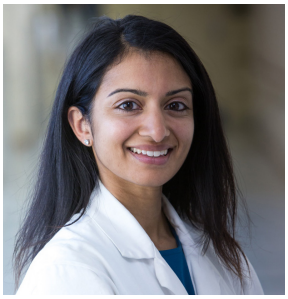
"If I can create knowledge that leads to the development of better diagnostics of treatments for kidney disease, that is what fuels my passion for research," she said.

Jotwani began her research career as a resident and nephrology fellow at UCSF. She met Shlipak during that residency and started studying urine biomarkers as indicators of kidney toxicity from medications in people living with HIV.

Vasantha Jotwani, MD
Associate Professor of Medicine, UCSF

Principal Investigator, Staff Physician in Nephrology, SFVAHCS

Site Director, Nephrology Fellowship Program, SFVAHCS



"One of the drugs I was studying at the time damages the kidney tubules by targeting mitochondria, which are the structures within cells that drive aerobic respiration," she said. "As I began to learn more about mitochondria and their importance for kidney health, I realized there was a huge untapped opportunity for research. While there had been many studies using animal models, there were hardly any data linking mitochondria with the risk of kidney disease in humans. I believed that if we could figure out a way to study this in people, that we will one day develop mitochondria targeted interventions to improve kidney health."

She and Shlipak assembled a multidisciplinary team from across the country, which now includes epidemiologists, nephrologists, geneticists, mitochondrial biologists, aging experts, and statisticians. Their goal is to understand the role of mitochondria in acute and chronic kidney diseases.

"So far, we've learned that having more mitochondria

is associated with lower risk of acute kidney injury after a stressor; that inherited variation in mitochondrial DNA can impact a person's kidney function; and that structural changes to mitochondria that can be seen in kidney tissue correlate with kidney function and other signs of damage and scarring (fibrosis) within the kidneys.

"We've submitted these data for publication and we're actively building the next stage of these projects," she said.

"I believe the best research comes through collaboration and a cross-pollination of ideas," said Jotwani. "Brainstorming with other scientists is one of the most enjoyable parts of my job. There is also a certain magic and fun in creating with other people and being able to do this through KHRC has added so much meaning and joy to the work I do."

Jotwani said she has benefited from partnerships, mentoring and seminars led by other experts in the KHRC, particularly Rebecca Scherzer, PhD, Director of Biostatistics at KHRC, who has guided analytics required for her studies.

Scherzer does statistical analyses to model associations of biomarkers with kidney disease. The goal of these analyses is usually to figure out which biomarkers are best for early detection or for monitoring drug safety.

She also mentors the younger researchers on statistical methods. Currently, Scherzer collaborates with

Rebecca Scherzer, PhD

Director of Biostatistics, Kidney Health Research Collaborative, UCSF

a UC San Diego epidemiologist studying cognitive impairment in adults living with chronic kidney disease. She also mentors a UC Davis physician studying ways to personalize clinical decision-making for cardiovascular disease prevention, in particular, how to weigh the harms and benefits from intensive blood pressure lowering in different populations.

These mentoring activities are in addition to being the Biostatistical Advisor for the entire local KHRC team. "Rebecca deserves an enormous amount of credit for the career growth of all of our faculty, from our research fellows and junior faculty, up to Dr. Estrella and me," said Shlipak. "Her abilities, ranging from scientific writing to cutting-edge statistical analyses, are among the best among nephrology-oriented biostatisticians in the United States."

"I have always taken mentoring to be an essential part of our research and an obvious good, as we have a responsibility to give the next generation the tools they need to build on our work," said Scherzer.

Tide turning? Cystatin C finally getting deserved play

For nearly 100 years, doctors have relied on a test for kidney function which measures creatinine in the blood.

In 2005, Dr. Michael Shlipak, co-founder and Science Director of the Kidney Health Research Collaborative, published a landmark study that found a test of kidney function that measures blood levels of cystatin C—a protein produced by most cells in the body—is a far more accurate predictor of mortality risk in elderly people than the creatinine test.

Still, in the last 18 years, most health systems and hospitals have continued to use the creatinine test. Few offered the cystatin C to patients, to the dismay of many researchers and some kidney health advocacy organizations.

"A major reason is the global familiarity with the blood creatinine test," said Shlipak. "With so much inertia by tradition, it takes substantial force to change practice habits. I think the nephrology community, outside of the San Francisco VA Health Care System, has not prioritized alternative tests like cystatin C because their patients are referred so late in the disease course.

"Sadly, we have been waiting too long for cystatin C to become part of routine care to maximize kidney disease detection and treatment," said Shlipak.

But there may be hope and a major trend change.

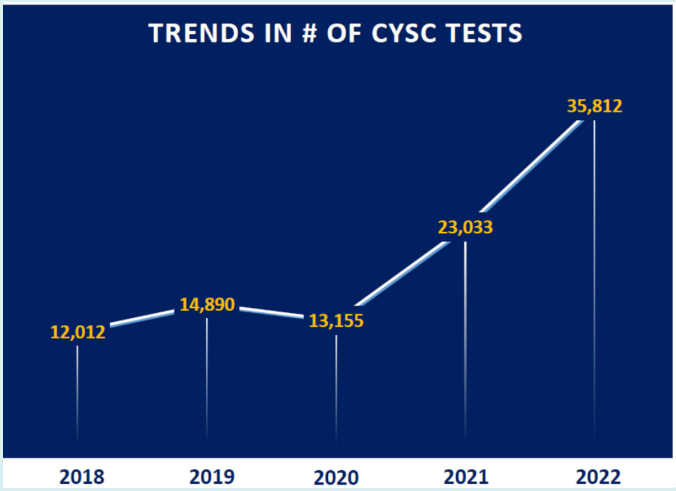
Shlipak said by the fall of 2023, all Veterans should have access to a cystatin C measurement based upon a recent

national mandate.

"This is enormous news," he said. "The requirement is for each of the 22 regions in the national VA system to have at least one major laboratory that measures cystatin C. This lab would then be the referral system for facilities within the region that do not have cystatin C available. In addition, guidance has been provided to primary care clinicians on which Veterans should have cystatin C measurements."

This includes groups of patients who either are at high risk for kidney disease (e.g. diabetes, hypertension), or patients in whom creatinine is unlikely to be accurate, such as those with spinal cord injuries or amputations.

"With this directive, the VA is clearly leading U.S. healthcare for accurate CKD diagnosis," said Shlipak.



In the years following Dr. Shlipak's 2005 landmark study, *Cystatin C and the risk of death and cardiovascular events among elderly persons,* the amount of Cystatin C (cysc) tests conducted by the VA nationwide to determine kidney health has grown rapidly, as seen in the table to the left.

Read more about the study here: https://pubmed.ncbi.nlm.nih.gov/15901858/.

Graphic provided by Dr. Michelle Estrella.

Dr. Michael Shlipak: New NCIRE Board Chair

Michael Shlipak, MD, MPH, Scientific Director of the Kidney Health Research Collaborative, was appointed NCIRE Board Chair in January 2023.

Shlipak, who is also the Associate Chief of Medicine for Research Development at SFVAHCS and Professor of Medicine, Epidemiology & Biostatistics at UCSF, commented about his new appointment:

"This is clearly an honor to follow the prior outstanding NCIRE Board Chairs, including Drs. Theodora Mauro and Raymond Swanson. NCIRE has been a tremendous catalyst to my career; and it has supported my research continuously since 2001.

"The organization is so investigator-oriented that it gives our faculty an advantage in scientific productivity in comparison with larger institutions. The leadership of NCIRE are very professional and competent that my primary objective is to avoid interfering.

"I do believe that NCIRE has a critical role in ensuring the future of research at the SFVAHCS, and the most important component is the development of junior investigators. My priority will be to expand the number of new investigators who are applying and receiving research funding.

"In the internal medicine service at SFVAHCS, we have a Medical Research Council that cultivates and supports early investigators. Other services have also developed programs to develop research faculty. I believe that NCIRE can help facilitate grant writing and career development across the campus, and this will be critical for building our next wave of successful investigators."

Q and A: An Interview with Dr. Jennifer Mitchell

Q: Your neurosciences research has focused on novel therapies for drug and alcohol abuse, PTSD, stress, depression, and other disorders. How did you become interested in pursuing this research?

A: I've long been interested in the treatment of mental health disorders—such as trauma, anxiety, and depression—and in the individual differences (environmental, genetic, psychological, etc.) that contribute to these disorders.

As a child, I was exposed to a very diverse cross-section of people—many of whom had experienced major trauma—and always found it fascinating that some of these individuals would emerge unscathed while others were irreparably damaged. I thought that, if we could understand these individual differences, we could help those who were most vulnerable.

Additionally, as a native San Franciscan who hung out with a progressive group of kids, I witnessed a fair amount of psychedelic substance use and thought it was fascinating that these compounds could open the mind and re-enable a more childlike state of exploration and learning—sometimes good and sometimes bad—but typically powerful and often life-changing.

Q: Currently, you are studying psychedelic therapeutics, including MDMA, 3,4-methylenedioxy-methamphetamine (also known as ecstasy or molly) for PTSD and psilocybin (often called "magic mushrooms") for demoralization. These are serious disorders within our Veterans population and in the general population, too. What have you and other scientists learned about these potential therapies?

A: When administered in conjunction with therapy and in a well-managed

Jennifer Mitchell, PhD

Associate Chief of Staff for Research and Development, SFVAHCS

Professor, Departments of Neurology and Psychiatry and Behavioral Sciences, Weill Institute for Neurosciences, UCSF

Faculty, Neuroscape, UCSF

Board Member, NCIRE Board

environment, these medicines can significantly attenuate a number of conditions, including PTSD, depression, demoralization, social anxiety, alcohol consumption, and certain aspects of obsessive-compulsive disorder.

We've also learned that the clinical efficacy of psychedelics appears to be durable. While further data are still needed, long-term follow-up data suggest that, when administered in conjunction with therapy, even a single administration of a psychedelic compound can mitigate certain mental health conditions for months to years.

Q: How does this therapeutic treatment work?

A: Because the effects of psychedelics are dependent on the environment in which they are administered, great care needs to be taken to ensure that the therapeutic setting is just right and that the care team is well-trained and brings in the proper mindset and level of expertise.

We also couple psychedelic administration with therapy, which is extremely important in maximizing the positive therapeutic benefit of psychedelic compounds. Our participants typically undergo both preparatory therapy sessions, to ready themselves for a psychedelic experience, and integrative therapy sessions, to really unpack and process everything that the psychedelic treatment brings up.

On a neurological level, we know that psychedelics induce a number of effects across brain regions and brain circuits and that the serotonergic system plays a major role in the efficacy of many classic psychedelics. We also know that the neuromodulator oxytocin is likely contributing to the therapeutic efficacy of MDMA by enabling self-compassion and strengthening the therapeutic alliance (the bond between the participant and the care team).

Q: Not too long ago, psychedelic medicine/research was considered too controversial, unfundable or just a dream. When/what was the tipping point?

A: I don't know that we've actually hit the tipping point yet, though I'd like to think that we are close. We still need to enable federal funding for psychedelic research and to initiate a federal system for rescheduling psychedelic compounds. As an example, to date, the entire phase 3 program for MDMA has been funded by a non-profit sponsor, Multidisciplinary Association for Psychedelic Studies (MAPS), which has itself relied completely on crowdfunding and philanthropic donations to make phase 2/3 clinical trials happen.

Although MAPS is planning to submit a new drug application (NDA) to the FDA this fall, there still isn't a mechanism in place to reschedule MDMA through the DEA, which considers psychedelics to be highly addictive and to hold no medical use.

All this said, I think that there has been a remarkable change in the zeitgeist

surrounding psychedelics over these last five years. This likely started with Michael Pollan's book, *How to Change Your Mind*, which I believe was incredibly effective in getting a certain slice of our population to rethink their stance on psychedelics. And then there was the pandemic, which fostered conversations about mental health and equitable access to treatment.

Lastly, within the U.S., over these past few years we've been confronted by an ever-growing group of Veterans who have been vocal about their need for novel therapeutics for the mental health conditions they've acquired as a result of defending the rest of us.

Q: We're seeing some benefits in clinical phase 3 trials. What are some of the potential risks that need to be studied?

A: We are monitoring a series of Adverse Events of Special Interest for the FDA. These include QT prolongation to assess cardiac risk and changes in suicidal ideation and behavior. In addition, it's important to note that the phase 2/3 data acquired to date using psychedelic agents has not included individuals with personality disorders, schizophrenia, or certain major illnesses; so we will need to collect further data in order to determine which subject populations respond best to psychedelics and for how long.

Q: What's in the future for this research? What are some hurdles?

A: There are many, many regulatory steps that still need to be completed before psychedelics could ever be made available to the public as approved therapeutics. One particularly onerous hurdle lies in convincing health care providers and insurance companies to help underwrite the cost of treatment. But if MDMA therapy for PTSD is approved by the FDA next year (which is what the sponsor hopes will happen), this will then open the door to further opportunities; and hopefully federal funding and scientific innovation will follow.

Q: You were recently appointed Associate Chief of Staff for Research and Development, SFVAHCS. What are your plans or goals in this role?

A: My biggest short-term goal is to tackle some of the space and facility hurdles that we are currently facing on campus; and to secure better research space and equipment to facilitate our study teams and improve the experiences of our participants. I am also hoping that we can expand our SFVAHCS research range to include a greater number of National Centers for Excellence and Innovation. Lastly, I'd like to continue the fostering of our young investigators and early career scientists to ensure that our VA has a strong research program and pipeline for years to come.

In the Helix

Alison Myoraku, MS
NCIRE Staff Research Associate II

Q: If you could eliminate one thing from your daily routine, what would it be and why?

A: If I could eliminate one thing from my daily routine, it would be meal planning. I don't necessarily do this every day, but I find it so difficult to find new recipes and decide what I want to cook for the week!

Q: If you had to teach a class on one thing, what would you teach?

A: If I was to teach a class on something, it would be about Japanese customs and culture. My Japanese heritage is a very important part of my identity and I love to share it with those who are willing to listen and learn.

Clara Tong
NCIRE Accounts Payable Specialist

Q: If you could eliminate one thing from your daily routine, what would it be and why?

A: I would try to eliminate scooping our eighteen-year-old cat's smelly litter. Yet, to be able to scoop it daily means our cat is having a healthy life.

Q: If you had to teach a class on one thing, what would you teach?

A: I would teach gardening. Gardening teaches me how to be patient, respect nature, and appreciate the growth of each stage. Gardening brings me challenge, joy, frustration, and happiness.

If you or someone you know is an NCIRE employee and would like to be featuered in *In the Helix*, contact us at dna@ncire.org.

Eclipse Study Success!

Congratulations to Kendrick Shunk, MD, PhD, Joseph Yang, MD, Jeffrey Zimmet, MD and Nurse Coordinator Cynthia Huynh, RN for successfully enrolling 60 subjects into the ECLIPSE Trial (Evaluation of Treatment Strategies for Severe CaLcIfic Arteries: Orbital Atherectomy vs. Conventional Angioplasty Technique Prior to Implantation of Drug-Eluting StEnts). The ECLIPSE Study recently reached its enrollment goal of 2,005 subjects; Dr. Shunk's team consented over 459 research subjects over the past 5 years to successfully enroll 60 eligible research subjects. The San Francisco VA ranked 7th among the top 20 enrolling sites and 1st for all VA Hospitals.

New Federal Funding Awards

Congratulations to the following Principal Investigators for your recently funded awards!

Linda Chao, PhD
Project Title: Examining the Reproductive Health of Gulf War Veterans and the Subsequent Health and Development of Their Children
Sponsor: Army Medical Research and Material Command via subcontract from Boston University
Activation Date: 2/23/2023

Karen Seal, MD
Project Title: HEAL Data2Action Research Adoption Support Center (RASC)
Sponsor: NIH via subcontract from Stanford University
Activation Date: 3/16/2023

Carolyn Gibson, PhD
Project Title: Assessing the feasibility of Courage Group therapy for women Veterans who have experienced military sexual trauma
Sponsor: International Society for the Study of Women's Sexual Health
Activation Date: 3/22/2023

Amy Byers, PhD, MPH
Project Title: Alzheimer's Disease and Related Dementias in The Most Incarcerated Generation: An Understudied Population with Health Disparities
Sponsor: NIH/NIA
Activation Date: 3/23/2023

Amy Byers, PhD, MPH
Project Title: Long-term Neuropsychiatric Sequelae of SARS-CoV-2 Infection in Late Life
Sponsor: NIH/NIA
Activation Date: 3/28/2023

Daniel Mathalon, MD, PhD
Project Title: Identification of Distinct Biotypes in Clinical High Risk for Psychosis State Using Objective Brain-Based Biomarkers
Sponsor: NIH via subcontract from Beth Israel Deaconess Medical Center
Activation Date: 4/6/2023

Thomas Neylan, MD
Project Title: Discovering DIagnostics, SubtypEs, and NaTurAl history of truamatic brain iNjury (TBI) vs. non-TBI Recovery to Gain MiLitary advantagE - the D2ISENTANGLE Focused Program Award
Sponsor: USA MED RESEARCH ACQ ACTIVITY, via subcontract from UNC Chapel Hill
Activation Date: 4/10/2023

Michael Shlipak, MD, MPH
Project Title: Dimensions of Kidney Tubule Health and Atherosclerotic Cardiovascular Disease and Heart Failure in Middle-Aged and Older Adults
Sponsor: NIH via subcontract from Tufts Medical Center
Activation Date: 4/26/2023

Duygu Tosun-Turgut, PhD
Project Title: Characterizing Cognitive Decline in Late Life Depression: The ADNI-D Project
Sponsor: NIH via subcontract from UCSF
Activation Date: 5/4/2023

Michelle Estrella, MD
Project Title: Non-SteroidAI Impact on Kidney Disease Study (NSAIDS)
Sponsor: NIH/National Institute of Diabetes and Digestive and Kidney Diseases
Activation Date: 5/4/2023

Scott Bauer, MD, MS
Project Title: Prescription exercise for Older men with Urinary Disease (PROUD) pilot study
Sponsor: NIH
Activation Date: 5/10/2023

Sunny Wang, MD
Project Title: Oral microbiome and inflammatory status in antimicrobially-treated oral cancer patients
Sponsor: NIH via subcontract from UCLA
Activation Date: 5/12/2023

Michael Steinman, MD
Project Title: Adapting the ShedMEDS Deprescribing Intervention to Dementia Care in Assisted Living
Sponsor: NIH
Activation Date: 6/1/2023

Daniel Bikle, MD, PhD
Project Title: Vitamin D control of calorie allocation to muscle
Sponsor: NIH via subcontract from Children's Hospital of Philadelphia
Activation Date: 6/6/2023

Message from the Chief Executive Officer

Summer is right around the corner, and I am looking forward to the warm, long summer evenings in the Bay Area!

Many thanks to the wonderful contributors of the Summer 2023 Newsletter: Michael Shlipak, MD, Vasantha Jotwani, MD, Rebecca Scherzer, PhD, Michelle Estrella, MD, MHS, and Jennifer Mitchell, PhD. The synergy and dedication to research by all of the contributors are appreciated.

On May 9th I attended the VA Research Week kick-off ceremonial event with Secretary Denis McDonough at the VA Headquarters in Washington, D.C. The ceremony recognized 6 extraordinary VA Researchers.

NCIRE CEO Rebecca Rosales attending the VA Research Week kick-off ceremonial event, pictured with (L-R) National Association of Veterans' Research and Education Foundations (NAVREF) Interim CEO and COO Hawk Tran, VA Secretary Denis McDonough, and NAVREF Board Members Ronald W. Hakes and US Army Veteran Matthew Collier.

The third annual NCIRE Principal Investigator and Research Community 2023 Survey was recently sent out. The goal this year is to achieve 50% participation. Every voice matters as we are planning, and your feedback will translate into data to be used as we strategize and plan NCIRE resources. Use this link to participate in the survey: https://www.surveymonkey.com/r/S6N9FVK. The survey will close on June 23, 2023. As we have done previously, the results will be widely shared with the Research Community and NCIRE Board of Directors.

I would like to recognize the promotion of Shannon Ellis to Senior Manager, Procurement and Logistics, effective June 1, 2023. Shannon has been with NCIRE since 2006 and is an integral member of the NCIRE Leadership Team. She successfully led the NCIRE move from Building 14 in June 2022. Please join me in congratulating her.

Thank you for taking time to read our Summer 2023 Newsletter. Please let me know if you have any questions or comments.

Rebecca Rosales, MBA, CRA
Chief Executive Officer

About NCIRE

NCIRE - The Northern California Institute for Research and Education has one mission and one goal: Advancing Veterans Health. We sustain a scientific community of clinicians and researchers and support nearly 200 researchers who have joint faculty appointments at the University of California, San Francisco (UCSF) and the San Francisco VA Health Care System (SFVAHCS) and are working to foster innovation through leadership in the field of Veterans health research. Our broad portfolio of projects receives generous support from the National Institutes of Health, the Department of Defense, and individual donors, making us the largest nonprofit research institute devoted to Veterans health in the US.

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