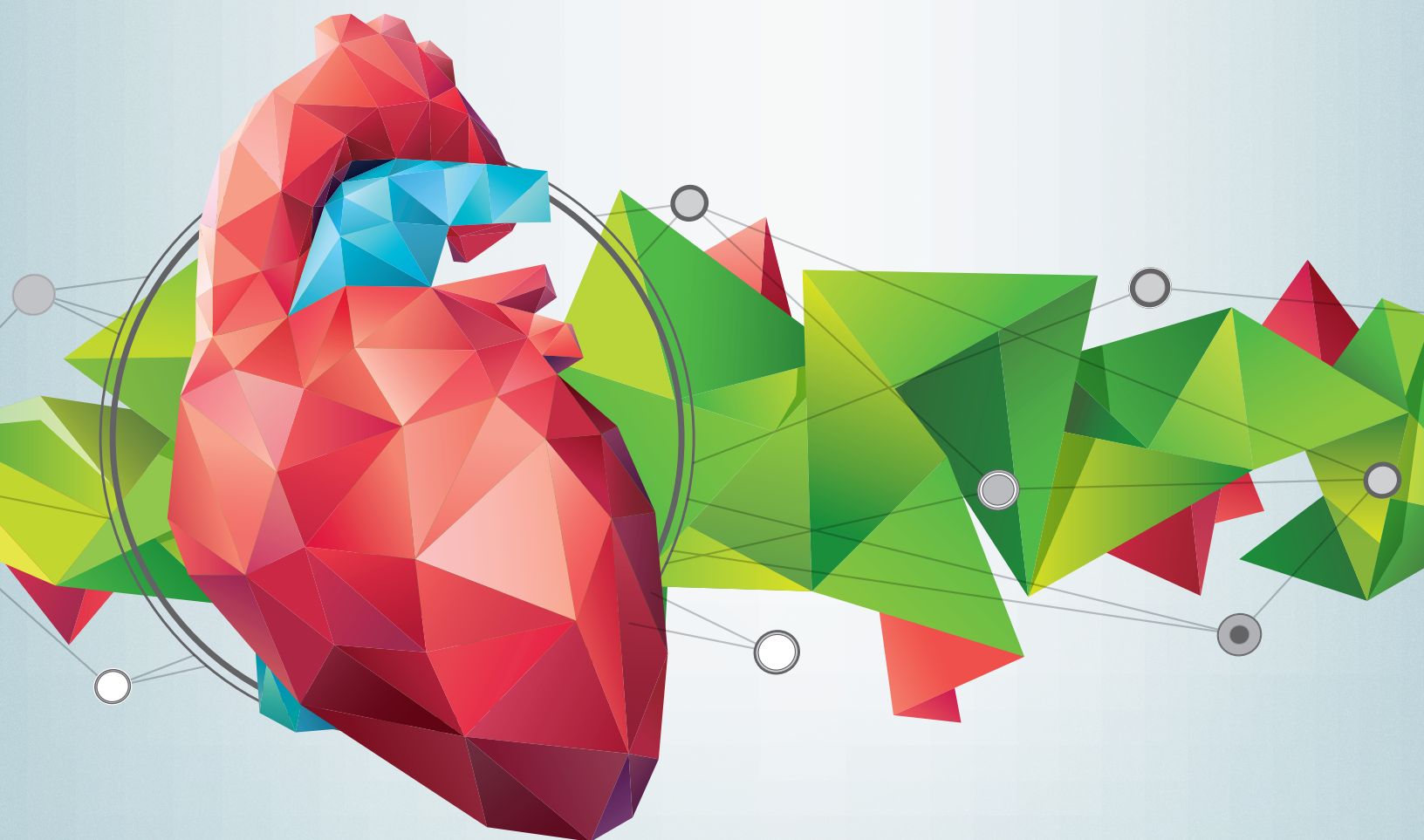


END OF RESEARCH REPORT

PREVENTION



STRATEGICALLY FOCUSED RESEARCH NETWORK

Cardiovascular disease and stroke are the leading killers worldwide. Deaths from these diseases — and risk factors for them — disproportionately impact low-income communities and racial and ethnic minorities. The American Heart Association established the Strategically Focused Research Network (SFRN) in 2014 to fund cardiovascular research that has the potential to improve the lives of women and men throughout the United States and the world.

Researchers routinely look to the AHA for these types of funding opportunities. The organization is the largest not-for-profit funder of cardiovascular disease and stroke research in the United States, investing over \$4.5 billion in research since 1949.

The AHA committed \$15 million to establish the Prevention SFRN, giving researchers a unique opportunity to pursue vexing questions about cardiovascular health. The four centers that received the awards are:

- **Icahn School of Medicine at Mount Sinai**
- **Northwestern University**
- **UT Southwestern Medical Center; and**
- **Vanderbilt University**

Each center's research focus included a basic science, clinical science and population science component. The goal was to bring together researchers from different disciplines to generate and accelerate important, novel ideas for cardiovascular prevention — and it did. The centers were funded from 2014 to 2018.

The funded research areas were unique yet complementary, with opportunities for collaboration that could extend beyond the AHA-funded period. The awards resulted in 170 published research papers.

Researchers:

- Examined if lifestyle education programs with the potential to improve heart health could be targeted to preschool children and their parents and caregivers in under-resourced neighborhoods;
- Explored whether declines in heart-health measures that occur from childhood to middle age could be reversed;

- Investigated how salt causes tissue damage and results in high blood pressure;
- And studied ways to prevent heart failure with preserved ejection fraction. This work has substantially changed how researchers will study the disease

Dr. Alan Go, who chaired the Prevention Strategically Focused Research Network Oversight Advisory Committee, noted how long it takes to get science into clinical practice.

"Part of that is because there aren't systematic conversations by the people doing some of the most innovative science at the basic, clinical and population levels to recognize where those opportunities are to accelerate the translation from the lab to the patient and to the population," he said. "A big part of the mission and the vision of these networks is to do that."



Dr. Alan Go

Each center designed a research postdoctoral fellowship training program. These two-year fellowships allowed three young scientists at each center to build research relationships with faculty across multiple disciplines in their own institution and across all four centers.

"Cross collaboration was promoted at meetings of the four centers and at the AHA's annual Scientific Sessions," Go said. "This was an opportunity to invest in and build the next generation of cardiovascular researchers."

**Prevention SFRN
Awardees and Oversight
Advisory Committee**



SFRN CENTERS: PREVENTION

With basic, clinical and population scientists working together, the Strategically Focused Research Network centers generated pioneering ideas and insights aiming to improve cardiovascular health across the lifespan.

Northwestern University

Center Director: Philip Greenland, M.D.

At Northwestern University in Chicago, researchers studied environmental factors that affect cardiovascular health throughout the lifespan.

"No one before had ever looked at harmonizing the data collected from studies of three different age groups to create a picture of risk factor change across the lifespan," said Center Director Philip Greenland, M.D.

The clinical project enrolled college students in a research study exploring the impact of different types of health education programs on environmental risk factors for cardiovascular disease, such as stress, diet and exercise.

The basic science researchers used blood samples from students in their freshman and senior years for epigenetic analyses. Epigenetics refers to changes in gene functions caused by environmental factors. The scientists will compare the changes in students who maintained or adopted a healthy lifestyle with those who developed risk factors for cardiovascular disease.



Dr. Philip Greenland

The basic science team also analyzed blood samples stored from Northwestern's ongoing Coronary Artery Risk Development in Young Adults study. Their studies showed that people who had more risk factors had more adverse effects on their epigenomes. The study also showed an association between metabolic syndrome — a cluster of conditions that increases risk for cardiovascular disease and stroke — and epigenetic changes associated with accelerated aging. This novel finding was published in *Clinical Epigenetics*.

The population science researchers analyzed data from previous studies that looked at distinct age groups to investigate changes in cardiovascular risk factors from childhood through middle age.

The center's work launched additional basic, clinical and population studies investigating why heart-health measures decline from childhood to middle age, and how to help people maintain ideal heart health or reverse declines. The center's work also led to multiple publications and grant awards, including two additional SFRNs.

Icahn School of Medicine at Mount Sinai

Center Director: Valentin Fuster, M.D., Ph.D.

The Icahn School of Medicine at Mount Sinai in New York City studied the benefits of a community-based heart-health education program in preschools in Harlem. One of the best approaches to preventing disease is to work with children, according to Center Director Valentin Fuster, M.D., Ph.D.

"Children at this age absorb and store in their brains what you tell them," Fuster said. "We are taking advantage of how centers of the brain connect when we teach children this information when they are in preschool."

The population scientists tested a 60-hour heart-health education program, FAMILIA, that was developed for preschool-age children. This work complemented the clinical science research, which investigated whether peer coaching or individual lifestyle coaching could get parents and caregivers to integrate healthier behaviors into family life. The basic scientists studied genetic and genomic data collected from the children and their parents or caregivers to seek clues to cardiovascular disease prevention.

Findings were presented at the American Heart Association's Scientific Sessions in Philadelphia in November 2019. The center's research advanced previous work by Fuster and his colleagues on cardiovascular health promotion and disease prevention in children in Colombia and Spain.

"The American Heart Association allowed us to bring this study to the U.S.," Fuster said.

After learning about the research, the children's television show "Sesame Street" created a Muppet named Dr. Ruster who, like Dr. Fuster, teaches children how to make heart-healthy lifestyle choices.

Fuster has received additional funding to follow the 50,000 children taking part in his research worldwide until they're 20. He also has applied for a grant from the National Institutes of Health to extend the work to all five boroughs of New York City.



Dr. Valentin Fuster



Dr. Joseph Hill

UT Southwestern Medical Center

Center Director: Joseph Hill, M.D., Ph.D.

At UT Southwestern Medical Center in Dallas, researchers made significant advances that could lead to new treatments for patients with heart failure with preserved ejection fraction (HFpEF), which is increasing in prevalence worldwide and has no effective treatment.

"Our observations completely turned the field upside down, providing an explanation for why previous clinical trials have failed and opening up new ideas on how to move forward with new treatments," said Center Director Joseph Hill, M.D., Ph.D.

Heart failure is a chronic condition in which the heart can't pump the blood and oxygen cells need. People with HFpEF have a heart that can pump normally but is too stiff to fill properly. Diabetes, high blood pressure, kidney disease and obesity all increase the risk for HFpEF.

Hill was conducting basic science research on HFpEF when he learned about the Prevention SFRN.

"I thought we were uniquely positioned to bring basic, clinical and population science together because of the programs we already had in place," he said. "So we looped in the clinical and population science groups and put together a truly cohesive multidisciplinary program."

The clinical science project studied middle-age patients at high risk for developing HFpEF. It demonstrated that a one-year aerobic exercise program could reverse stiffening in the heart muscle.

This research tied into the population scientists' study on the relationship between physical activity level and heart failure. This study enrolled African American women and men, who have higher rates of heart disease than white women and men. It found that people who already had heart damage and an enlarged left ventricle — the heart's main pumping chamber — had nearly a 40% risk of being diagnosed with heart failure over the next 10 years. This study was also the first to show that people who engage in higher levels of physical activity are less likely to develop HFpEF.

The basic science project developed a new preclinical mouse model of HFpEF. In addition to having HFpEF, these mice had the health issues most often seen in these patients: obesity, diabetes and high blood pressure. Their studies showed that prior mouse models did not accurately represent HFpEF in humans. This work was published in April 2019, in *Nature*.

"Our success came out of our three teams asking the same questions but using different strategies to approach them," Hill said. "Honestly, this is the most important research I have ever done."

Vanderbilt University Medical Center

Center Director: David Harrison, M.D.

At Vanderbilt University, scientists united to investigate how salt damages heart tissue and to identify new approaches to prevent and treat high blood pressure, a leading cause of cardiovascular disease.

The basic science project showed that sodium enters cells that are important in activating the immune system. This, in turn, causes an inflammatory response which activates other immune cells that can damage the heart, blood vessels and kidneys. The basic science researchers also discovered that sodium can activate centers in the brain that get the central nervous system to activate inflammatory processes.

"With the American Heart Association funding we discovered ways that sodium enters cells — in particular, immune cells, which no one suspected are affected by sodium — and the intercellular signals that occur in response," said Center Director David Harrison, M.D.

"Identifying these targets is the first step to developing medications that can intervene in these processes to reduce inflammation and, in turn, bring blood pressure back to normal levels," Harrison said.

The clinical science research, done in collaboration with the center's basic scientists, used sodium magnetic resonance imaging to measure tissue concentrations of salt. These



Dr. David Harrison

studies showed that people with high tissue concentrations of sodium had inflamed immune cells, pinpointing a new mechanism for identifying high-risk patients.

The population research tied together the basic and clinical science studies, investigating how a polypill that contains low doses of three drugs used to treat high blood pressure and one drug used to lower cholesterol affects risk for cardiovascular disease in underserved populations.

The study, published in the *New England Journal of Medicine* in September 2019, showed that the single pill reduced the estimated risk of cardiovascular disease by 25%, a finding that attracted widespread media attention. Currently polypills aren't sold in the U.S., but they're available in other countries.

"Without this funding, we wouldn't have been able to do any of these studies," Harrison said.

THE FELLOWS: A CLOSER LOOK

The Fellowship Program

The unique, collaborative environment of the American Heart Association's Strategically Focused Research Network in Prevention mentored, trained and supported 12 fellows to pursue research and/or clinical careers in prevention.

These fellows met with basic, clinical and population scientists across all four centers as they conducted research that furthered the field of cardiovascular disease and stroke prevention. They also had multiple opportunities to advance their careers by networking and presenting research at the AHA Research Leaders Academy and other AHA conferences and meetings that draw scientists and clinicians from across the globe.

The benefits extended far beyond the two years of participation to support career development and independent research. Several of the fellows, including Aseel Alsouqi, M.D., Ana Victoria Soto, M.D., Serpil Muge Deger, M.D. and Yuichiro Yano, M.D., Ph.D., have multiple publications to their name. Others, such as Rodrigo Fernandez-Jimenez, M.D., and Abbi Lane-Cordova, Ph.D., received awards from the AHA and other organizations for their research.

Gabriele Schiattarella, M.D., and Michinari Hieda, M.D. obtained additional fellowships and funding as a result of their scientific contributions during the training period. Jason Foss, Ph.D., is now a scientist in the biotech industry, and many others have moved into tenure-track positions, where they intend to continue their prevention research.

Here are four of their stories:

Victor Wenze Zhong, Ph.D.

Northwestern University

SFRN Prevention Fellow, 2017-2019

Victor Wenze Zhong was a fifth-year Ph.D. student at the University of North Carolina, Chapel Hill when he learned about the Prevention SFRN Fellowship at Northwestern University.

He had already been planning to pursue postdoctoral research, and he saw this fellowship as a unique opportunity to work with multiple mentors in many disciplines.

"The program sounded fascinating to me," said Zhong, who earned a Bachelor of Medicine in preventive medicine from Huazhong University in Wuhan, China. "As an international student, there are fewer opportunities for training grants. It is nonprofits like the AHA that make training like this possible."

Zhong was involved with the population science research carried out by Northwestern's Prevention SFRN. The work complemented and expanded his interest in metabolics (how food is broken down and transformed into energy), genomics and big data analysis. His fellowship research also created opportunities to network with postdocs who were part of the broader Prevention SFRN and to present his research at Scientific Sessions, the AHA's annual conference for cardiovascular professionals around the world.

In 2018, Zhong was awarded both the AHA Council on Lifestyle and Cardiometabolic Health Early Career Investigator Award and the AHA Roger R. Williams Award for Genetic Epidemiology and the Prevention and Treatment of Atherosclerosis. He also was a finalist for the AHA Jeremiah and Rose Stamler Research Award for New Investigators.

Zhong is the first or senior author of 12 peer-reviewed original research articles and is a co-author of seven additional peer-reviewed articles. He's also the first author or co-author on 19 research studies that were presented over the past six years at conferences sponsored by the AHA and other organizations.

In July 2019, Zhong moved to Ithaca, New York, to start a tenure-track assistant professor position in the Division of Nutritional Sciences at Cornell University. There he's pursuing his interest in big data research, using databases with millions of patients as well as metabolic and genomics databases to study how nutrition affects the development of cardiometabolic diseases.

"I would encourage everyone who is looking for some further postdoc training to seize this AHA opportunity," he said.

Jacqueline Latina, M.D.

Icahn School of Medicine at Mount Sinai
SFRN Prevention Fellow, 2014-2016

Jacqueline Latina was a resident in internal medicine at the Icahn School of Medicine at Mount Sinai in New York when she learned that the AHA had awarded the school one of four Prevention SFRN grants.

Latina jumped at the opportunity to take part in a research program that would look at lifestyle intervention to reduce cardiovascular risk among minority children and adults from diverse and socioeconomically disadvantaged communities. She also used her time as an SFRN Fellow to obtain a Masters in Science in biostatistics.

For the SFRN research study, Latina helped recruit 562 children ages 3 to 5, plus parents and caregivers, at Harlem preschools. She was also involved with data collection and analyses. All the children took part in a 40-hour curriculum about heart-healthy behaviors. Parents and caregivers were randomly assigned to a control group, a peer support group or individual counseling.

Initial findings, published in the April 30, 2019, *Journal of the American College of Cardiology*, showed the intervention raised the children's awareness of healthy behaviors. Those who benefitted most received more than 75% of the curriculum. A paper on the program's impact on the parents and caregivers was recently accepted for publication.

Latina said she was impressed with the array of programs the AHA created for the SFRN fellows. For example, the two-day invitation-only AHA Research Leaders Academy gave her significant opportunities to network and practice her research presentation skills.

"I met other fellows in the program, who were all amazing and inspiring, and I now have a large network of connections," Latina said.

In July 2017, Latina started a cardiology fellowship at Johns Hopkins Hospital in Baltimore. There she plans to pursue her interest in preventive cardiology and non-invasive cardiovascular imaging, and continue to contribute to data analyses with her Mount Sinai SFRN Prevention colleagues.

She credits the SFRN Fellowship with helping her get the position and for bolstering her ability to work on clinical research.

"As a resident, you are enthusiastic, but you don't understand all the logistics of actually running a clinical trial, the funding mechanisms, how long things take or the challenges you might face," Latina said. "Now I feel that I have the skills, technical abilities and understanding to effectively work on a clinical trial and, one day, be a primary investigator."

Ambarish Pandey, MBBS

UT Southwestern Medical Center
SFRN Prevention Fellow, 2014-2016

Ambarish Pandey said his experience as an SFRN Prevention Fellow was one of the best training opportunities of his short academic career.

Pandey, who was born in India, moved to the United States in 2010 to begin a fellowship in nanomedicine at Brigham and Women's Hospital in Boston. The following year he started a residency in internal medicine at UT Southwestern Medical Center in Dallas. He completed the residency in June 2014 and started his SFRN Fellowship the following month. In 2018, he accepted a position as an assistant professor of cardiology at UT Southwestern.

"The fellowship couldn't have arrived at a better time in my career," Pandey said. "We had done a lot of work in the clinic on heart failure, and the SFRN was about heart failure with preserved ejection fraction, so it gave me a perfect opportunity to build on my interest, to learn the skills necessary for population science research and to take it to the next level."

Since 2013, Pandey has received 10 awards from the AHA. These include the Jay D. Coffman Early

Career Investigator Award and the Award for Excellence in Addressing Cardiovascular Health Equity. In 2017, he received the Northwestern Cardiovascular Young Investigator Award. UT Southwestern honored him with the Outstanding Research Mentor Award in 2018.

Pandey said the SFRN's multidisciplinary, multi-institutional framework offered significant opportunities to work with clinical researchers at UT Southwestern and collaborate with population scientists at Northwestern. These collaborations also furthered his standing as a physician-researcher; in the last four years he has been the first author of 47 papers stemming from the Prevention SFRN.

Now, he's heading up his own research program as a principal investigator. In 2018, he received a \$750,000 grant from UT Southwestern to study novel approaches to prevent heart failure.

"The fellowship is just an incredible opportunity to study what interests you and to meet people from all different backgrounds," Pandey said.

"I can't emphasize enough how much I have benefited from being in this program. It has encouraged me to strive for more."



Aseel Alsouqi, M.D.

Vanderbilt University

SFRN Prevention Fellow, 2016-2018

Dr. Aseel Alsouqi was intrigued when she learned about Vanderbilt University's Prevention SFRN fellowship.

"It was something new, it wasn't common and it looked very promising," said Alsouqi, who was at the university for an away rotation during her last year of medical school.

When the away rotation ended, Alsouqi returned to the University of Jordan Medical School in her hometown of Amman. After earning her degree, she returned to Vanderbilt to start her SFRN Prevention fellowship.

For two years, Alsouqi was part of the SFRN's clinical research team. She recruited patients for their sodium MRI studies, collected and analyzed data, and composed posters for presentations. Currently, she is preparing a paper for publication.

If the clinical studies continue to show a relationship between decreased salt in body tissue and improved cardiovascular health, the research could lead to new medications to treat high blood pressure, she said.

Now a resident in internal medicine at Vanderbilt, Alsouqi believes her experience as a fellow will help her attain a position as a clinical researcher and continue her research on high blood pressure.

"Being part of that network, working on such good projects and making lots of connections at the AHA and in other departments at Vanderbilt was crucial," she said. "It's a great program. You learn a lot, meet a lot of people, do a lot of science and it opens doors for you."

By creating these opportunities, the program also benefits other researchers working to prevent heart disease.

"The information our research provided will help guide further studies on hypertension," she said.

COLLABORATIONS

The synergy among the four SFRN centers sparked important research collaborations that enabled 12 fellows to do critical work with scientists in and out of their fields.

Early on, the centers at Northwestern University and Vanderbilt University applied for additional funding to build on their shared research interests. The centers received a National Institutes of Health grant to bring sodium MRI to Northwestern, which is now using it in research studies.

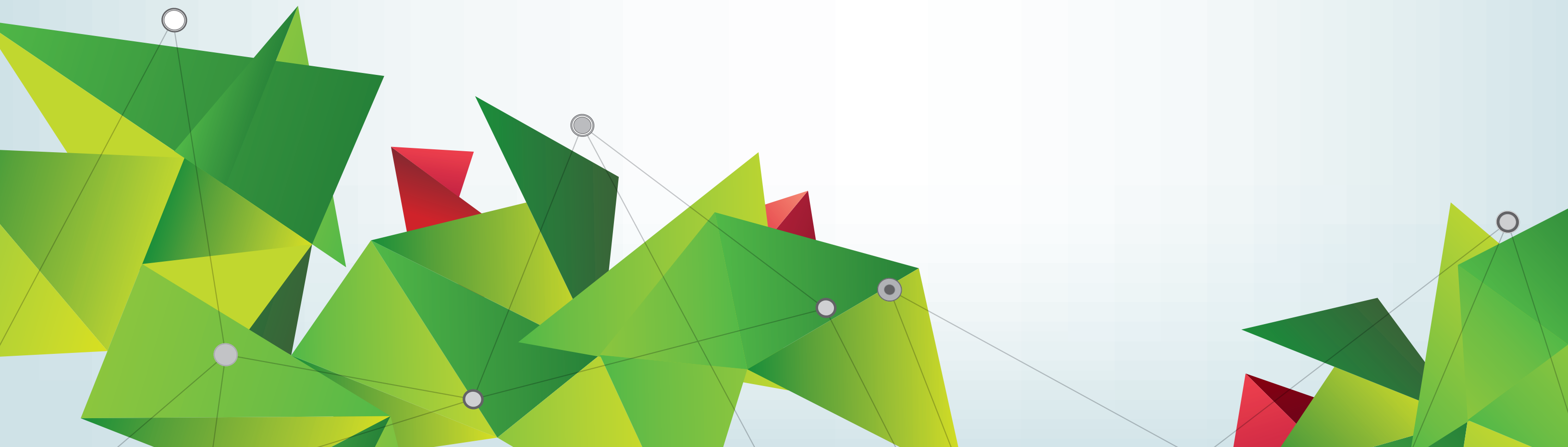
"Their ability to expand the work that was supported by the AHA was one of the tremendous successes of this network," said Dr. Alan Go, chair of the Prevention SFRN Oversight Advisory Committee.

At UT Southwestern Medical Center, the SFRN collaboration "enlivened and broadened" how scientists thought about studying HFpEF, Hill said. Research started under the SFRN has continued under an NIH Program Project Grant focused on identifying mechanisms of exercise intolerance in people with HFpEF and exercise programs that can improve heart function.

Ambarish Pandey, MBBS, a fellow at UT Southwestern Medical Center from 2014 to 2016, seized the opportunity to work with scientists outside his institution. He connected his interest in HFpEF to Northwestern University center's research on lifestyle factors that impact heart failure. This work resulted in multiple cross-center publications. Pandey was awarded Northwestern's 2017 Cardiovascular Young Investigator Award.

Northwestern Center Director Dr. Philip Greenland credited the SFRN with creating a unique opportunity for his group to explore topics of interest from multiple angles.

"With these centers, you can look at a theme area in broader detail than you can with a single grant focus," Greenland said. "Each individual project will have an output, but what you hope is that one plus one plus one is greater than three."



CONCLUSION

Bringing together basic, clinical and population scientists from across four institutions can advance cardiovascular prevention research and train a new generation of cardiovascular scientists in ways that multiply what one center or one field can do alone.

Since the first SFRN in 2014, the AHA has created 10 more. They focus on Hypertension, Disparities, Heart Disease in Women, Heart Failure, Obesity, Children, Vascular Disease, Atrial Fibrillation, Arrhythmias & Sudden

Cardiac Death, and Cardiometabolic Health with a focus on Type 2 Diabetes.

Dr. Alan Go said the centers provide opportunities to build on the AHA's support, further extend their work and improve patient outcomes.

"What we learned from our experience with the Prevention SFRN has been used to expand training and cross collaboration in the SFRNs that came after it," Go added. "The AHA should be credited for launching this funding model to answer really important research questions."





American Heart Association
7272 Greenville Avenue
Dallas TX 75231