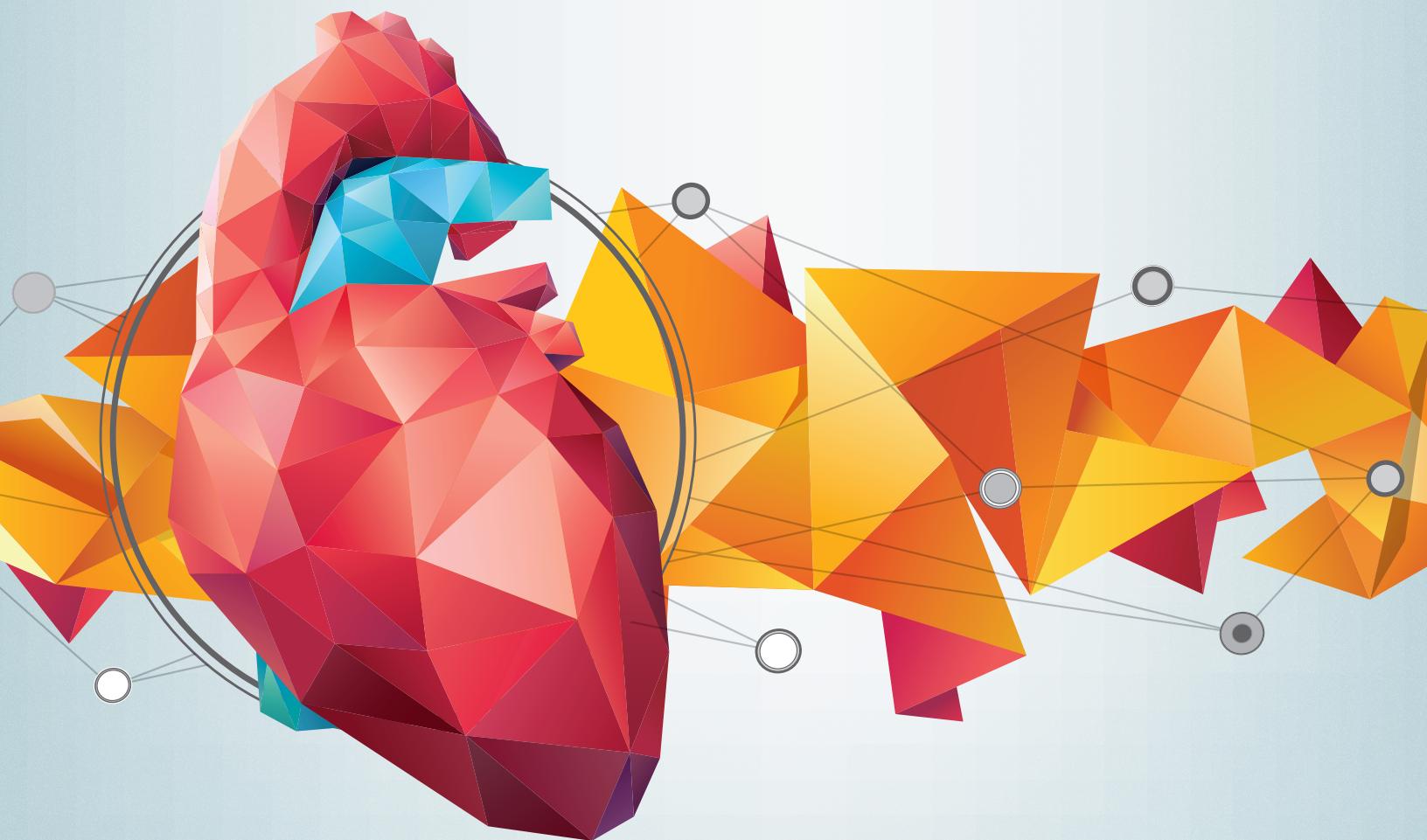




American
Heart
Association.

END OF NETWORK REPORT

HEART FAILURE



STRATEGICALLY FOCUSED RESEARCH NETWORK



Every year, more than six million adults in the U.S. have heart failure and nearly 380,000 die from the condition, which is difficult to treat.

This is why the American Heart Association supported four centers in the Heart Failure Strategically Funded Research Network to identify ways to better diagnose, prevent and treat heart failure in a wide array of patients through basic, clinical and population projects. The four centers are:

- **Duke University, Intersection of Heart Failure and Diabetes**
- **Massachusetts General Hospital, Extracellular RNA Markers and Modulators of Heart Failure**
- **University of Colorado Denver, A Comprehensive Approach to the Treatment of Heart Failure with Reduced Ejection Fraction**
- **University of Utah, Functional, Metabolic, and Patient Centered Determinants of Recovery in Heart Failure**

Researchers and fellows at the four institutions have presented at national and international conferences and published their findings in journals such as the *Journal of the American Medical Association* and *Circulation Heart Failure*.



Dr. David van Wagoner
Oversight Advisory Committee Chairperson

Subjects investigated in the Heart Failure SFRN included:

- The link between diabetes and heart failure patients and possible therapeutic benefits of diabetes drugs for heart failure patients
- The role of RNA, genes that control metabolic pathways and/or “families of genes” in identifying and treating heart failure
- Nutritional impacts — including the efficacy of a ketogenic diet — on recovery for heart failure patients, in addition to exercise and lifestyle changes
- Socioeconomic and racial differences in identifying and treating heart failure, including how health professionals can offer more equal and inclusive care

“Heart failure is more challenging to combat than other heart-health issues,” said Anthony Rosenzweig, M.D., Center Director at Massachusetts General Hospital.

“We’ve gotten very good at getting people through their heart attacks, and we’ve gotten very good at treating high blood pressure,” he said. “The problem is the people who survive these events go on to have other issues such as heart failure, rhythm issues and other cardiovascular problems.

“Unfortunately, we’re less good at treating those. About half the heart failure we see falls into a category that we still don’t have therapies for.”

The Heart Failure SFRN investigated isolated aspects of different heart failure cases while sharing information between departments and centers — bringing together researchers and scientists to train a new generation and find answers to revolutionize care.

Fellows supported by the SFRN are now pursuing independent research and securing tenured positions at some of the most recognized universities across the country.

“We all feel that’s a crucial part of our mission,” Dr. Rosenzweig said. “Training the next generation of people who will replace us and become leaders in the field is so important, and there really aren’t that many mechanisms for supporting it.”

David van Wagoner, PhD, Oversight Advisory Committee Chairperson, and a translational scientist at the Cleveland Clinic specializing in heart failure and arrhythmias, said the Heart Failure SFRN was important because the condition is complex.

Heart failure with preserved ejection fraction tends to be understudied and underdiagnosed. SFRN researchers “tried to tackle questions that have a lot of unresolved issues and, definitely in heart failure, there are still quite a few unresolved issues,” said Dr. van Wagoner.

“So the goal, when you’re reviewing SFRNs, is to try to identify people who are doing outstanding science and ensure the project they propose is feasible — and that it’s going to, in theory, change the course of how you treat people.”

SFRN CENTERS: HEART FAILURE

Duke University

Center Director: Michael Felker, M.D.

The Heart Failure Strategically Focused Research Network Center at Duke University focused on the link between diabetes and heart failure and whether diabetes drugs could treat the latter.

"There has been increasing recognition that there's an interaction between patients with heart failure and the presence or absence of diabetes that affects heart failure patients' outcomes — and also their response to therapy," said **Michael Felker, M.D.**, Center Director at Duke.

Dr. Felker and his team explored how mitochondria and muscle cells interact, use glucose and metabolize similar "substrates," or fuel for the body. Researchers in the basic, clinical and population studies investigated tissue from patients with both conditions, monitoring how physical activity could improve the health of sedentary patients and researching the effects of different patterns of drug therapy.

One class of drugs was "OK" for diabetes, but "an extremely effective heart failure medication, whether or not you have diabetes," Dr. Felker said.

"The link between diabetes and heart failure has gathered momentum within the medical community since Duke began its SFRN — but merits much more attention in light of the prevalence and relatively limited knowledge of heart failure," Dr. Felker said.

Duke University Center



Dr. Michael Felker

"There has been a lot of progress on research into heart failure, but I think it's only going to need to be more and more," he said. "A key thing is: How do we get people using the right treatments in the most effective way consistently?"

"We still know there's a big gap between what we know is out there, best therapy and what's actually happening in the real world." He added that programs and organizations such as the SFRN and AHA are fundamental to fueling research and enhancing scientific developments.

"AHA is both an advocacy organization — funds research, does public health awareness campaigns — and it has physician members, volunteer members, patients," he said. "It really brings together in one organization a lot of the different stakeholders for cardiovascular health."

University of Colorado Denver

Center Director: Peter Buttrick, M.D.

The goals of the SFRN aligned well with the expertise of many scientists at UCD, according to **Peter Buttrick, M.D.**, Center Director.

"We liked the idea of bridging the gap between basic and population science," he said. "We try to think very broadly and translationally, so it was consistent with our general approach to scientific discovery. We were blessed in having experts in heart failure in all three domains."

Researchers looked at cellular mechanisms affecting heart function, drug therapies and genetic links, focusing on whether certain genes or "families of genes" could be manipulated or blocked to prevent heart dysfunction or heart failure.



Dr. Peter Buttrick

Researchers also looked "for small molecules that were novel that would influence expression and binding of these particular domains and would, by extension, influence the expression of families of genes," Dr. Buttrick said.

Like Duke, UCD researched new medications and discovered several drugs that seemed promising in preventing heart failure in animal models.

"We were trying to identify gaps in therapy, which is to say our current therapy's not perfect," Dr. Buttrick said. "We know a lot about how to treat heart failure, but there are a large number of patients who don't do very well. We thought there were biological pathways that could be exploited to develop therapeutic agents."

Massachusetts General Hospital

Center Director: Anthony Rosenzweig, M.D.

Anthony Rosenzweig, M.D., Center Director and Chief of Cardiology of the Corrigan Minehan Heart Center at Massachusetts General Hospital, called heart failure the “cancer of cardiology.”

MGH focused on finding molecular clues for curing it.

Much of the research focused on the role and possible use of RNA molecules. While scientists know those molecules create proteins, MGH also explored the function of RNA that didn’t.

“It turns out RNA does an enormous number of things,” Dr. Rosenzweig said. “They control whole genetic programs. We were focused on studying that kind of molecule and understanding how it might be used in both clinical and basic research to work on heart failure.”

We showed RNA in the blood could be a biomarker for developing heart trouble and identified RNA pathways that could potentially regenerate heart muscle.

MGH studied blood from a diverse group of patients using large-scale sequencing techniques, in addition to looking at patients who had recovered from heart failure and their traits.

Dr. Anthony Rosenzweig



The basic study also focused on molecular effects on the heart in small animal models and “found a couple of molecules that could prevent or even restore function,” said Dr. Rosenzweig, adding the team looked to apply the findings to larger animals and human cells.

Most therapies for heart failure “slow the decline and mitigate the disease but don’t really reverse or repair the damage that’s occurred in the heart — so it’s a huge unmet clinical need,” he said. “What this program did was bring together a lot of people interested and focused on this.”

As a physician scientist, Dr. Rosenzweig said the SFRN provided unique opportunities for medical advancements, teaching and collaboration.

“I think most of us who have a foot in the clinical world and a foot in the research world recognize that for us to come up with new therapies and approaches that improve the kind of care we can deliver for our patients, it takes collaboration across these disciplines from people who do very fundamental discovery to people who do clinical studies and population science,” he said.

“One of the things I think is unique about the SFRN program is this explicit mandate to bring in people who really address each of those areas to work together in a collaborative way within a center in the hope of making transformative discoveries and moving them forward.”

University of Utah

Center Director: Craig Selzman, M.D.

SFRN researchers at the University of Utah focused on discovering “why bad hearts get good,” said **Craig Selzman, M.D.**, Center Director.

“A lot of people spend a lot of time figuring out why a good heart becomes a bad heart,” said Dr. Selzman, noting that his team attempted to do the opposite and looked at why some patients may recover without a transplant.

“When you have a really bad heart, there’s a discreet population of patients, when supported with devices, in which the heart muscle recovers its function and we can actually remove the devices and avoid a heart transplant altogether,” he said. “So, we have been curious for over a decade to study this population.”

The SFRN “really resonated with what we were trying to do locally at the University of Utah,” Dr. Selzman said. “It was a good opportunity for us internally to try to unify our message and our efforts. The bonus was that we were going to get to hang out with a few other centers that were like minded, with the glue being the AHA.”

Dr. Craig Selzman

The Utah team reviewed thousands of patients’ histories in addition to investigating biological and metabolic factors. In mice, researchers studied the impact of genetic deletions and whether manipulations could aid heart recovery. In humans, they also tried to devise a scoring system to indicate heart problems for clinicians that could be widely adopted and almost considered as another “vital sign”.

It helped that other centers worked on related topics.

“Having four centers actually was a nice number; it wasn’t too small, but it wasn’t so big that things got lost,” Dr. Selzman said. “Over the course of the project period, everybody had a good feeling about what the others were doing. And then it allowed the natural integration of ideas.”

“I think it was a brave, courageous move by the American Heart Association, and obviously the concept’s working.”

THE FELLOWS: A CLOSER LOOK

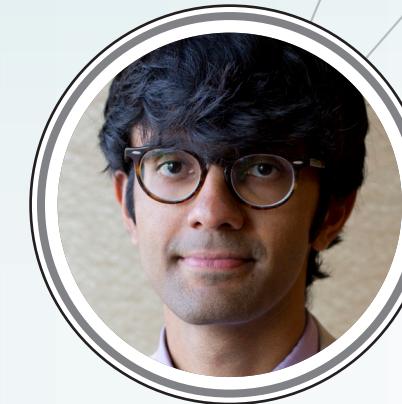
The Fellowship Program

The American Heart Association's Heart Failure SFRN provided essential mentorship and interdisciplinary learning opportunities that will yield valuable discoveries in the future of heart failure research. Collaborating with scientists and mentors, these fellows gained incomparable, varied experience through basic, clinical and population research projects to further knowledge about the global impact of heart failure.

In line with the SFRN's goal of training the next generation of researchers and physician scientists, many of these fellows have chosen to continue their involvement with and investigation of heart failure. They have published multiple papers, received awards from the AHA and other organizations and presented to scientists and clinicians from across the globe.

Each scholar not only garnered experience but brought their own expertise and areas of interest to the projects, allowing for interdisciplinary progress that continues.

The unique, comprehensive and collaborative opportunity has fortified the strong ongoing clinical and research efforts of each fellow, giving new promise to the endeavor of advancing research into heart failure.



Dr. Abhinav Sharma

Here are the stories of four of the fellows:

Abhinav Sharma, M.D.

Duke University

SFRN Heart Failure Fellow, 2016-2017

The high global mortality rate in heart failure patients is alarming to **Abhinav Sharma, MD**.

That's why the American Heart Association Heart Failure Strategically Focused Research Network at Duke University appealed to him. He focuses on diabetes and heart failure patients, and how advances in digital health and technology can improve understanding and therapies.

As a fellow, Dr. Sharma said the SFRN allowed him to lead several projects and to be part of a bigger series of collaborations that extended beyond his time at Duke.

"It certainly has opened up many years of collaboration and many years of opportunities to work with my mentors and to really network amongst a lot of the other sites," said Dr. Sharma, now an assistant professor in the Department of Medicine, Divisions of Cardiology and Experimental Medicine at McGill University in Montreal, Quebec, Canada.

At Duke, Dr. Sharma worked on population and digital health care studies. He helped design the digital program, learned about site management and wrote the methods paper.

Several hundred people recruited from outpatient clinics wore devices and were monitored using an app to gauge physical activity and medication adherence and to prompt them to move more. They were also followed when intervention efforts were withdrawn to see if those behaviors persisted.

The Duke studies also focused on the safety and efficacy of anti-hypoglycemic drugs that many of the patients used.

"My hope was that I would be involved in a project that actually has real-world benefits and real-world applicability — and, certainly, the digital health project has a very specific real-world impact, because if we show that it's beneficial, then it can be scaled and made available to a lot of people," Dr. Sharma said.

Many experiences with the SFRN have translated to his major research interest at McGill: digital health in diabetes and heart failure.

Investing in the future of medicine and training well-rounded researchers is a hallmark of the SFRN system.



Heart Failure SFRN Fellows Drs. Brisa Peña Castellanos and Joshua Travers

"It really gives fellows and early-career researchers an opportunity to take ownership of a project that can build the foundation of their career," he said. "I think there are certainly a lot of avenues to explore. And to conduct a project that's funded, and to see it through from beginning to end, I think that's a really powerful part of the SFRN."

The emphasis on collaboration and mentorship is also key.

"With every AHA meeting, when we would connect around the SFRN and hear what everyone was doing around the different sites, it sparked so much discussion and opportunity for new research and collaboration," said Dr. Sharma, who also won an AHA Get With The Guidelines Award.



Dr. Khadijah Breathett

Khadijah Breathett, M.D.

University of Colorado Denver

SFRN Heart Failure Fellow, 2016-2017

The American Heart Association's Heart Failure Strategically Focused Research Network was a perfect fit for **Khadijah Breathett, MD**.

While a fellow at the University of Colorado Denver Center, Dr. Breathett explored how to improve medication-based therapy for patients with heart failure — matching her interest in racial and ethnic disparities in health care.

As a fellow in the Heart Failure SFRN, she focused on population studies and assessed hospitalization information on thousands of patients across the U.S. She looked at whether race impacted cardiologists' care for patients, particularly among the sickest requiring an ICU stay for heart failure.

"We found that, unfortunately, it did," she said, along with other factors such as hospital size and location and comorbidities.

"Consistently, there was the same finding where, if you were a black patient, you were less likely to receive care by a cardiologist than if you were a white patient. If you were a black male patient, you were the least likely of all the different groups to receive care by a cardiologist", she said.

Dr. Breathett, who participated in weekly Colorado Cardiovascular Outcomes meetings, said her role in the Center and the information shared with colleagues across the Network helped develop her career. She is an advanced heart failure and transplant cardiologist, physician scientist and assistant professor of medicine at the University of Arizona College of Medicine – Tucson.

She has received an NHLBI grant, known as a K Award, to explore the best ways to address racial disparities in health care. And in 2019, the National Minority Quality Forum selected Breathett as one of the 40 Under 40 Leaders in Minority Health.

Dr. Breathett is also an AHA Oversight Advisory Committee member, giving her insight into the benefits of SFRNs and similar projects from multiple sides.

She said the AHA welcomed her, providing focus areas — disparities and equity in cardiovascular care — that she cared about. "They provided the opportunity to serve and lead in ways that can change clinical care and lead to better health care delivery."

"And I'd say, as a long-term member, I am happy to see how the AHA has continued to stand behind its mission to seek cardiovascular health equity for all groups."

Haobo Li, Ph.D.

Massachusetts General Hospital

SFRN Heart Failure Fellow, 2017-2019

Dr. Haobo Li was completing his Ph.D. in Hong Kong when he heard about the American Heart Association Heart Failure Strategically Focused Research Network.

He jumped at the chance to participate because of its unique and exciting three-part configuration.

His first postdoctoral fellowship in the U.S. would allow him to collaborate with researchers from basic, clinical, and population science disciplines.

In the basic science study at Massachusetts General Hospital, Dr. Li and his colleagues focused on animal models to investigate the role of micro-RNA in cardiac hypertrophy, the thickening of the cardiac muscle.

The aim was to determine how long non-coding RNAs factor into both cardiac hypertrophy in response to exercise and disease. Physiological cardiac hypertrophy is a healthy response to exercise and can protect against stress. Pathological hypertrophy occurs in disease and often precedes heart failure.



Dr. Haobo Li

Dr. Li and his colleagues explored why different types of hypertrophies can affect the heart and how each is influenced by different molecules and micro-RNAs.

Sharing clinical sample data with the University of Colorado Center in Denver and others helped him and his colleagues look for similarities or trends between basic and clinical studies.

"It's good to collaborate with different centers to increase the number and diversity of samples you can have, which can strengthen your findings and make them more generalizable," he said.

"We can share information to not only give us the chance to learn from different people, but it can also provide the opportunity to expand your network."

Dr. Li, now an instructor in medicine at the Cardiovascular Research Center, Massachusetts General Hospital/Harvard Medical School, said his current work is an extension of his research with the Heart Failure SFRN.

"We're looking in more detail at this long noncoding RNA that we identified from the SFRN project that we would like to explore further for cardiovascular disease and heart failure," said Dr. Li, who also received an AHA Career Development Award based on his research and an AHA Abstract Travel Award in 2019.

Yuan Zhang, Ph.D.

University of Utah

SFRN Heart Failure Fellow, 2017-2019

Dr. Yuan Zhang's interest in cardiovascular research was piqued at an early age. She was about 12 years old when both her grandparents in China died of heart attacks, but their doctors couldn't give concrete answers for the causes. She turned that interest to her undergraduate studies at the University of Beijing and Ph.D. work at Peking Medical College, where she focused on the intricacies of heart disease and cardiovascular disease related to mitochondrial dysfunction. Heart failure is particularly important to research, given the high cost, lack of effective treatments and high death rates, says Dr. Zhang.

As soon as she heard about the Heart Failure Strategically Focused Research Network at the University of Utah Center, she was interested in the SFRN fellowship.

"The networking and the collaboration are impressive not only because we have the collaborations in the same institution, but also we exchange the studies' progress and we got some suggestions" from other centers, Dr. Zhang said.

She said it was helpful to meet with other fellows and field their questions. "Some questions might be tough, but at least, for this network, discussing questions in small groups" helped her "understand it better and find my future direction."

In the University of Utah's basic science project, Dr. Zhang investigated how glucose and pyruvate, a byproduct of glucose metabolism, affects heart failure in mice and how an altered diet could prevent or reverse negative effects.

The project involved deleting MPC, or the mitochondrial pyruvate carrier, in adult mice and embryos. When researchers deleted the protein, the heart failed — a finding with possible serious implications for heart failure in people.



Dr. Yuan Zhang

Dr. Zhang was shocked at how effective — and fast — dietary changes were in mice who had already exhibited enlarged and failing hearts.

"MPC is important for the heart to continue beating and using glucose efficiently," she said. "We tried to rescue the failing heart by providing it another substrate. So, we tried to feed the mice with a ketogenic diet."

Success, even at late stages of heart failure, was "pretty dramatic" and "outside of my expectations," she said. Some mice model hearts returned to normal within two months.

"From the beginning, I felt like there might be some beneficial effect," Dr. Zhang said. "The mice may live longer on this because we are providing it with other substrates it can use. But I was surprised to see, wow, they just came back to normal."

Further research must be conducted to delve deeper into the phenomenon and the translatable consequences for human patients.

Dr. Zhang is already doing that at the University of Iowa, where she is an instructor in the Roy J. and Lucille A. Carver College of Medicine. She has also applied for an AHA Career Development Award.

Her findings and experience in the SFRN have further fueled her determination to learn more about heart failure, especially the roles of other "interesting molecules" identified in the basic study.

"There are more questions coming out, so it's not like the end," she said. "It's a milestone to keep working on."

COLLABORATIONS

Throughout the SFRN award, researchers and fellows at the four centers provided information and samples from their respective projects and interacted with each other across disciplines.

For example, Dr. Felker's team needed more myocardial samples from patients with and without diabetes and heart failure. The center at UCD offered its "huge, robust tissue bank," he said. "That project never could've happened successfully without that collaboration."

The myriad of collaborations between centers was also instrumental in developing fellows' experiences and enhancing a more promising future for research.

Heart Failure OAC Member, Mark Kindy, PhD and Go Red For Women Fellow, Vanessa Assibey-Mensah, PhD, MPH.



"There's a lot of concern in the field about the pipeline of young investigators coming into research, because there are a lot of pressures," Dr. Felker said. "A mechanism such as the SFRN provides fellows with the opportunity to be involved in high-quality research, didactic training, a chance to interact with scientists and fellows not just at their institution, but across all four institutions. This is valuable in terms of scientific growth and career trajectory."

Dr. Rosenzweig said the SFRN gave researchers at MGH "the opportunity to not only interact with their colleagues, but to really reach outside their center and find synergy with other groups that are focused on the same problem."

CONCLUSION

The American Heart Association Heart Failure Strategically Focused Research Network led to promising discoveries in diagnosis, prevention and therapy — with researchers identifying several medications that could be more effective at treating and ways doctors can show patients how to avoid heart failure.

Projects at the four centers have not only motivated fellows to continue research into heart failure, but also led to further funding from organizations including the AHA and NIH. The funds are integral to investigating a medical issue that, while slowly becoming better understood, remains a challenge.

"It's a disease of older people and the population is aging," said Michael Felker, M.D., Center Director at Duke. "Things that used to kill you, like heart attacks, now people are surviving, which is great, but they are left with long-term heart issues, of which heart failure is kind of the final common pathway."

"People with heart failure are actually living longer, so the number of people out there with heart failure is greater. All those things make heart failure one of the most rapidly growing cardiovascular problems or medical problems of any kind. I think there has been a lot more progress on research in heart failure, but I think it's only going to need to be more and more."

"Collaborative efforts such as the SFRN are important for ensuring future medical strides," said Khadijah Breathett, MD, a UCD fellow

who now serves on another AHA Oversight Advisory Committee.

"If an individual is interested in developing a career as a physician scientist, this is a worthwhile endeavor," she said. "It's incredibly important to develop a foundation of research to be successful and competitive in our current research world."

To discover new treatments for and revelations about heart failure, "it helps that we have national meetings that we can share ideas," said David van Wagoner, PhD, Oversight Advisory Committee Chairperson. "But sometimes those connections are superficial, and when you get to the nuts and bolts of what you do day-to-day to manage the care or investigate the problem, it really helps to take things to a deeper level."

"SFRNs provide opportunities for different centers to work together at that deeper level so there can be a sharing of specimens and data at the raw data level. You can get new insights into the data you've collected if you're sharing it with somebody who has a different perspective. In addition, you can often pool data, so that any one center may have collected data on several hundred or several thousand patients. But if you combine three or four centers -- which is what the SFRNs do -- you can increase the sample size exponentially."





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