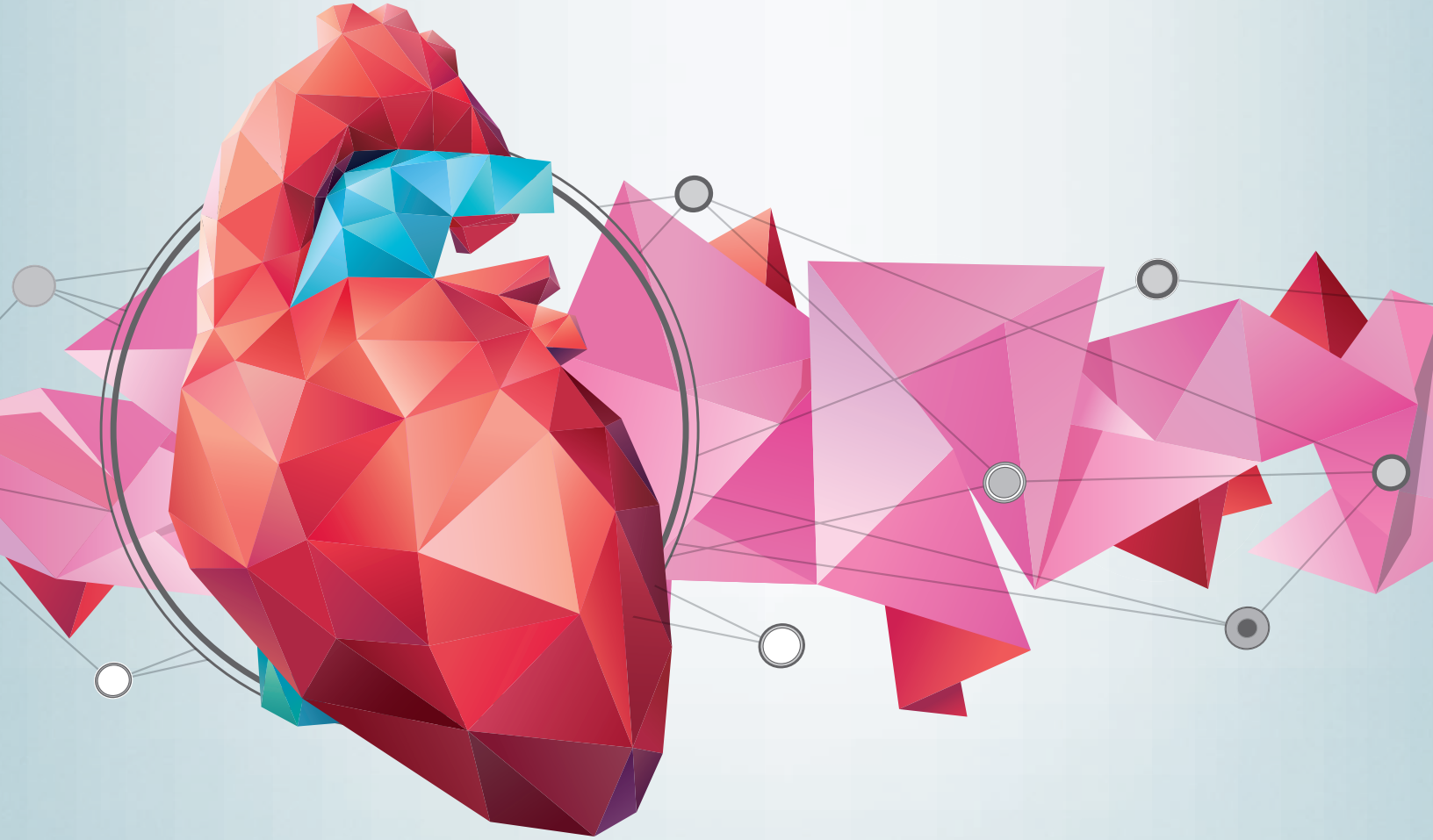
American Heart Association.

END OF NETWORK REPORT

ARRHYTHMIAS AND SUDDEN CARDIAC DEATH



STRATEGICALLY FOCUSED RESEARCH NETWORK

For more than 100 years, the American Heart Association (AHA) has been dedicated to fighting the No. 1 killer worldwide: cardiovascular disease. Research is a core part of its mission. Since 1949, the AHA has invested about $6 billion to spur scientific innovations to help people live longer, healthier lives.

As science evolves, the organization's research has grown and evolved to keep pace. In 2014, the AHA established the Strategically Focused Research Network (SFRN), a unique venture that brings together scientists from multiple institutions to study a common topic from different perspectives.

SFRN scientists collaborate across disciplines to create new approaches, ideas and knowledge. The AHA Board of Directors selects each SFRN topic, guided by the organization's scientific leadership — including the most recent network to conclude: Arrhythmias and Sudden Cardiac Death.

Dr. Karl Kern
Oversight Advisory Committee Chairperson

Sudden cardiac death (SCD) is a contributing cause of death in about 13% of deaths in the United States. It happens quickly, often without warning, when an electrical failure in the heart causes an irregular heartbeat, or arrhythmia, and the heart stops pumping, leading to sudden death.

Unlike a heart attack, which occurs when blood flow to the heart is blocked, SCD is an electrical problem, not a circulation problem. But SCD isn't limited to older individuals. Young people, even children, die every year from sudden cardiac death. Family members of SCD victims are twice as likely as the general population to experience SCD themselves.

To address the problem, the AHA committed $15 million to establish the Arrhythmias and Sudden Cardiac Death SFRN, giving researchers a critical opportunity to explore complex questions about these issues and develop better ways to prevent and treat them.

The AHA awarded $3.7 million to each of four centers beginning in 2019:

University of Michigan, to develop new resuscitation therapies for out-of-hospital cardiac arrest.

Northwestern University, to study genomic risks of arrhythmias and sudden cardiac death.

University of Washington, to investigate genomics, precision medicine and sex-specific resuscitation strategies in cardiac arrest.

Vanderbilt University, to examine the RyR2 calcium gatekeeper for heart cells and its role in arrhythmias.

"The four centers were quite diverse, conducting a wide variety of genetic-based research and resuscitation science research. The network really ran the gamut in this field," said Oversight Advisory Committee Chairperson **Karl Kern, M.D., FAHA, FACC, FSCAI.**

Arrhythmias and Sudden Cardiac Death SFRN Awardees & Oversight Advisory Committee

Each center was asked to include a basic science, clinical science and population science research component. Each center also designed a two-year postdoctoral research training program for three fellows, who built relationships with faculty across multiple disciplines, within their own institution and throughout the research network.

"Researching ways to prevent sudden cardiac death is at the core of what the AHA is all about," Kern said.

"Out-of-hospital cardiac arrests were once considered a hopeless situation. We've made progress since then, but it's still a major killer in the U.S. today, which is why continued research is so critical. This strategically focused research network will hopefully play a major role in making sure more lives will be saved."

The network's research is also bound to build greater public awareness of a long-misunderstood problem, said University of Michigan Center Director **Robert Neumar, M.D., Ph.D., FAHA**.

"It's very challenging. I've been working in this field for 40 years, and the media still mistakenly interchanges the terms 'heart attack' and 'cardiac arrest.' Research like this is essential not only to improving outcomes, but in helping the public realize how many people are impacted by sudden cardiac death."

SFRN CENTERS: ARRHYTHMIAS AND SUDDEN CARDIAC DEATH

University of Michigan

Center Director: Robert Neumar, M.D., Ph.D., FAHA

When someone's heart suddenly stops beating in a non-hospital setting, CPR and defibrillators are key emergency interventions.

Unfortunately, the outcomes aren't favorable. Fewer than 10% of patients survive with intact neurological function when resuscitation occurs outside the hospital, and the odds worsen with every minute of delay.

That's why the University of Michigan SFRN center aimed to find novel techniques to improve time-sensitive interventions for sudden cardiac arrest.

Scientists integrated basic, clinical and population science projects to focus on the early delivery of neuroprotective therapies, including medications. Center Director **Robert Neumar, M.D., Ph.D., FAHA** compared the approach to the common use of Narcan for opioid overdoses.

University of Michigan Center

Dr. Robert Neumar

"It's the same thing: If someone has a cardiac arrest, laypeople or first responders could quickly and easily give a drug by intranasal spray or by intramuscular autoinjector that would protect the brain and save lives."

Neumar said center scientists are studying the effectiveness of intranasal insulin, a drug that's already shown promise for people with Alzheimer's disease. University of Michigan researchers also developed an intervention that educates lay rescuers, improves response times and helps save lives.

Neumar said the SFRN on arrhythmias and sudden cardiac arrest provided essential research on a problem that's widespread but often misunderstood.

"About one out of every 10 deaths in the United States is a sudden cardiac arrest, but the National Institutes of Health investment for this is dramatically smaller compared to most other diseases with relatively lower number of deaths."

He thanked the AHA for "bringing institutions together that are like-minded in advancing our scientific understanding and trying to solve this problem. There are so many deaths we can be preventing."

Northwestern University Center

Northwestern University

Center Director: Elizabeth McNally, M.D., Ph.D., FAHA

At Northwestern University, genomic researchers took a novel approach to finding clues in DNA to help prevent sudden cardiac death.

With the AHA's blessing, they deviated from the typical basic/clinical/population research format. In their first segment — a hybrid clinical-population effort — they analyzed the genomes of 1,200 people and, for the first time ever, developed a new method of combining three genomic components to drastically improve risk prediction.

"We're very excited because we think it's a model for how people can look at more complex genetics across every condition, not just arrhythmias," said Center Director **Elizabeth McNally, M.D., Ph.D., FAHA**

Data from that project informed the center's basic research section, where scientists took adult human cells, turned them into induced pluripotent stem cells (iPSCs) in the lab, and created actual beating heart cells. In the end, they came up with dozens of cell lines and a model system to study high genomic risk groups.

"Defining common mechanisms that lead to disease will help develop new drugs and treatment and have a big impact on heart health," McNally said.

The third section was an education project to improve how cardiologists and cardiac nurses order and interpret genetic information – skills that some don't currently have. After asking medical providers which areas they needed most help in learning, researchers designed a series of free educational modules, which are already in high demand through the nonprofit Jackson Laboratory.

Northwestern's risk prediction research will benefit people of all ages and walks of life, with particular value to children and their families.

"Sudden cardiac death and arrhythmia often goes undiagnosed in children, either because it has no symptoms or because people think 'It just can't happen to a child,'" McNally said.

"When an individual does die at a young age, it's one of the worst things that can ever happen to a family. Even worse is if it happens a second time: We want to be very aggressive in testing other family members for genetic risk and treat them appropriately."

Dr. Elizabeth McNally

Vanderbilt University Center

Vanderbilt University

Center Director: Björn Knollmann, M.D., Ph.D., FAHA

Most people associate calcium with strong teeth and bones, but they may not realize it also plays a crucial role in heart health.

Researchers at Vanderbilt University delved deep into the workings of a calcium gatekeeper for heart cells called Ryanodine Receptor 2 (RyR2). When it doesn't process calcium properly, RyR2 can trigger sustained arrhythmias in the lower heart chambers, a condition known as ventricular tachycardia. It can lead to sudden cardiac death, particularly in people with certain types of heart disease.

Vanderbilt scientists set out to find new approaches to treat the problem and potentially save lives.

In their first basic science project, they researched RyR2's role in animals and discovered that dantrolene – an FDA-approved drug for muscle disorders – prevented arrhythmias and sudden cardiac death. For their second basic project, researchers found positive results when dantrolene was used on human hearts that had been donated but rejected for transplants.

Dr. Björn Knollmann

In the clinical project, scientists studied to see if dantrolene helped doctors in cardiac ablation procedures for patients with hard-to-control arrhythmias. Again, the drug had positive results, with no major side effects.

"It's a very exciting new therapeutic target," said Vanderbilt Center Director **Björn Knollman, M.D., Ph.D., FAHA**. "It really provides the basis for a potential new treatment to prevent ventricular arrhythmias and sudden cardiac death." The next step, he said, is more research to improve the drug's safety and effectiveness.

Knollman called the SFRN "an ideal mechanism, because it really brings basic scientists and clinicians together at the same table to share approaches," he said. "For me, as a physician-scientist, it's the perfect platform to accelerate discovery and bring things closer to the clinic."

He thanked the AHA for funding a research network that "would not have existed otherwise. This is such an important project, and we could have never done it without the AHA."

University of Washington

Center Director: Nona Sotoodehnia, M.D., MPH

Behind every case of arrhythmia and sudden cardiac arrest, there's a unique story. At the University of Washington, scientists sought new ways to piece together the narrative while keeping a close eye on gender.

"Currently, the approach to sudden cardiac arrest research and clinical care largely takes a one-size-fits-most approach, treating men and women similarly," said Center Director **Nona Sotoodehnia, M.D., MPH**. "But there are key differences between men and women, highlighting the need for a more individualized approach."

In the basic science project, University of Washington researchers looked for genetic markers in the blood of thousands of patients to find clues about sex-specific risk factors and what happens in the body before sudden cardiac arrest occurs.

For the clinical project, scientists tried to untangle the relationship between sex hormones and arrhythmias by taking a deep look at long QT syndrome, a condition that affects how the heart beats.

In the first two projects, researchers discovered key differences between men and women, including that young pre-menopausal women have better survival chances from SCA than men. They also found a blood protein signature that may predict who is at high risk of sudden cardiac arrest, and identified that certain oral contraceptives can increase the risk in women with long QT syndrome.

Dr. Nona Sotoodehnia

The population project zeroed in on resuscitation efforts for men and women, including using artificial intelligence. After combing through a library of defibrillator recordings taken during cardiac arrest resuscitations, researchers found that AI algorithms could possibly improve the treatment approach in up to half of patients.

Many of the Center's findings hold "great promise" and may lead to new lifesaving interventions, Sotoodehnia said.

"The AHA's funding was instrumental in allowing us to improve risk stratification for sudden cardiac arrest, particularly in high-risk men and women," she said. "It's also allowed us to improve sex-specific resuscitation strategies for cardiac arrest through individualized treatment."

"The future of research into sudden cardiac arrest prevention and treatment is exciting. We're thrilled to build upon resources and collaborations from this SFRN to continue asking important questions and developing new methods."

University of Washington Center

Director **Robert Neumar, M.D., Ph.D., FAHA** "They got to see what works, what doesn't work, and get valuable feedback on their research."

The research would have been unthinkable without the fellows' hard work, said Vanderbilt University Center Director **Björn C. Knollmann, M.D., Ph.D., FAHA** "The ability to have dedicated fellows on our project was huge."

"Each center really did a nice job of involving, training and mentoring the fellows," said Oversight Advisory Committee Chairperson **Karl Kern, M.D., FAHA, FACC, FSCAI**. "With all the unpredictable things going on in academic medicine, training the next generation is such an important part of this research network."

THE FELLOWS: A CLOSER LOOK

The Fellowship Program

The fellowship program is an integral part of the Arrhythmias and Sudden Cardiac Death SFRN. It's also an important step toward the future, as the AHA trained and mentored postdoctoral fellows to be part of an innovative new generation of investigators. Fellows were assigned to specific teams at each SFRN center.

They forged relationships with scientists and mentors inside and outside of their centers as they conducted research on new ways to treat arrhythmias and prevent sudden cardiac death. The fellows also advanced their careers by networking and presenting research at AHA conferences and meetings.

"We tried to give the trainees a unique experience with exposure across the spectrum, from laboratory to clinical to implementation science," said University of Michigan Center

Here are the stories of four of the fellows:

Amanda Missel, Ph.D., RN

University of Michigan

When it comes to saving someone from sudden cardiac death, every moment is critical. With that in mind, University of Michigan fellow **Amanda Missel, Ph.D., RN** searched for new ways to shave off minutes and seconds in resuscitation efforts.

Missel worked on the center's population project to identify the biggest obstacles to shortening bystander and first responder treatment times in out-of-hospital cardiac arrest. She then investigated the most effective strategies for training individuals to respond more quickly in emergency situations.

After reviewing data from 911 phone calls, Missel and her team found the median time for someone to recognize cardiac arrest was 76 seconds, and the median time in starting CPR was more than 3 minutes. Her research uncovered a wide range of stumbling blocks, from delays in recognizing the problem to a caller's hesitation or inability to act.

Dr. Amanda Missel

She and her fellow researchers held dialogue sessions and CPR simulations and then developed HeartSafe Home, an online intervention that helps lay rescuers prepare and practice.

"Out-of-hospital cardiac arrest is a time-sensitive event: The likelihood of survival decreases with each minute delay in treatment," she said. "Our research may be used to optimize the lay rescuer and first responder response, which may improve survival rates."

Missel published her research in several publications, including *Journal of the American Heart Association* and *Resuscitation*. For the latter, she collaborated with **Thomas Rea, M.D., M.P.H.**, from University of Washington's SFRN center.

She said her AHA fellowship paved the way for a second postdoctoral fellowship funded by National Institutes of Health T32 grant, and her hiring as a tenure-track professor at Wayne State University College of Nursing.

She thanked the AHA for enabling her to "meet, learn from and collaborate with researchers who are leaders in their field from around the country. This fellowship provides the opportunity to gain the experience needed to become an independent investigator."

Betty Yang, M.D., MS

University of Washington

Can chilling the blood after sudden cardiac arrest make medication safer?

University of Washington fellow **Betty Yang, M.D., MS** posed that question to learn more about blood-cooling – known as targeted temperature management (TTM), an intervention sometimes used after successful resuscitation to reduce brain injury.

Specifically, she wanted to find out if it also might lessen the harmful effects of epinephrine, a drug used by emergency medical workers to help restart the heart. When used in higher doses, epinephrine is thought to cause irreversible brain damage.

Working in the Center's clinical project, Yang and her colleagues analyzed scores of data and found the benefits of TTM went up as levels of epinephrine increased. These findings suggest body cooling may attenuate the adverse effects of higher-dose epinephrine and might be tailored to specific patients who receive higher doses, she said.

In a separate project, Yang studied the interaction between age and sex in resuscitation and how it affects outcomes.

She published her findings in *JAMA Network Open* and *Resuscitation*. During the SFRN, she received the NIH Loan Repayment Program Award. Afterward, Yang received an institutional early career award and the AHA Career Development Award.

"This fellowship has been fundamental to starting my career," said Yang, now an assistant professor in emergency medicine at UT Southwestern Medical Center. "It was instrumental to my understanding of what I would need to develop further as a physician-scientist. It gave me a clearer idea of what I might need to be successful."

She thanked several mentors, including Clinical Project PI **Thomas Rea, M.D., MPH**, and Co-Training Director **Michael Sayre, M.D.**, for "their instruction and leadership and for helping me focus my career goals."

"I'm grateful for the opportunities from the AHA and their support in helping me learn fundamental skills in research. I learned the nuts and bolts of working with a team, advancing each stage of the project, from conceptualization to the end publication and presentation. The fellowship has been key to my commitment and success."

Dr. Betty Yang

Dr. Majd El-Harasis

Majd El-Harasis, M.B.B.S.

Vanderbilt University

All **Majd El-Harasis, M.B.B.S.** needed was a nudge.

When a professor "highly encouraged" him to take part in the AHA's SFRN and told him that past Vanderbilt fellows benefited from SFRNs, El-Harasis decided to apply. Today, he's thrilled he did.

"It's been a wonderful, insightful experience," he said. "It's a great opportunity to learn all the different aspects, behind the scenes, of how electrophysiology trials are done."

El-Harasis was part of a team of clinical researchers studying the link between calcium, the Ryanodine Receptor 2 (RyR2), and a type of arrhythmia known as ventricular tachycardia.

"Ventricular tachycardia affects a lot of people and can be life threatening, but there haven't been any new antiarrhythmic medications to suppress it for over 20 years," he said. El-Harasis' team found promising results with dantrolene, a drug that stops calcium from leaking in the RyR2. "By preventing this leakiness of calcium, it prevents the dangerous rhythm from happening," he said.

The findings could benefit a wide range of clinicians and researchers. "We were able to gather a lot of information on the effects of this medication, not just on fast heart rhythm, but on blood pressure, heart rate and lung and muscle function. Our results are going to be quite useful," he said.

El-Harasis and his colleagues planned to present the findings in April 2025 at Heart Rhythm Society's annual conference, where it was short-listed for the Young Investigator Award. He's currently completing another clinical electrophysiology fellowship at Vanderbilt and hopes to work in the future at an academic medical center, caring for patients and teaching trainees.

He thanked the AHA and his colleagues **Benjamin Shoemaker, M.D.**, **William Stevenson, M.D., FAHA** and **Björn Knollman, M.D., Ph.D., FAHA** "for all of the time and energy they invested in mentoring and teaching me. The knowledge I gained from this fellowship has been really amazing. It's something I will take forward with me as I embark on an academic career in electrophysiology," he said.

Dr. Tanner Monroe

Tanner Monroe, Ph.D.
Northwestern University

As **Tanner Monroe, Ph.D.** explains it, small details can have a huge impact.

As part of the AHA's Arrhythmias and Sudden Cardiac Death SFRN, Monroe studied how tiny differences in a person's DNA can affect how their heart works and increase their risk of heart disease.

Those miniscule details are the key to improving personalized medicine "by helping clinicians precisely target their treatments directly to the genetic pathology," he said.

Monroe and his colleagues at Northwestern University built a nationwide network of cardiologists, medical coroners and genetic counselors to find the best study subjects. After gathering genetic material, they examined it with powerful supercomputers and analyzed the data to identify arrhythmia risk and predict outcomes.

"We found that both low- and high-effect risk variants can add up to contribute to overall risk. This contrasts with most current approaches, which typically examine risk variants in isolation, without considering the broader genomic context unique to each individual," he said.

"The findings will help scientists build patients' complete genetic profiles, custom design treatments, and rely less on symptoms alone when it comes to diagnosis and treatment," he said.

Monroe called the fellowship "an extraordinary opportunity to train in high performance computing and data analysis and lead a project of this scale." He praised the SFRN's "wide range of mentorship," including Northwestern Center director **Elizabeth McNally, M.D., Ph.D.**, and **Megan Puckelwartz, Ph.D.**

"Most projects of this magnitude require large consortia or federal-level operations, but thanks to (Puckelwartz's) experience and that of another assistant professor in our group, Lorenzo Pesce Ph.D., we managed to conduct all computational analyses with a team of just four people," he said.

Monroe hopes to establish his own genomic research laboratory in the near future.

"This fellowship played a crucial role in rounding out my training, giving me the confidence to oversee my own research program. It also helped me secure NIH funding to launch my independent career."

COLLABORATIONS

Collaboration was instrumental in the Arrhythmias and Sudden Cardiac Death SFRN. The network operated as a strong partnership, with scientists of different disciplines working together inside and outside the four centers to share best methods, models and approaches for studying arrhythmias and sudden cardiac death.

"Scientists get excited when they meet and listen to each other. They begin to think, 'Maybe we could do something with our model in the same way,'" said Oversight Advisory Committee Chairperson **Karl Kern, M.D., FAHA, FACC, FSCAI**.

"The strength of the SFRN model is the way it's enabled us to collaborate across centers. It's been critical to the success of our project," said University of Washington Center Director **Nona Sotoodehnia, M.D., MPH**. She said Washington researchers collaborated with Northwestern scientists on the genetics of sudden cardiac arrest, and with Michigan colleagues on the relationship between CPR and ECG bio signal processing during cardiac arrest resuscitation.

"The format was really helpful in terms of creating collaborations across different specialties and subspecialties," said University of Michigan Center Director **Robert Neumar, M.D., Ph.D., FAHA**. Michigan scientists traveled to Washington state to see how their EMS teams work, he said.

"The University of Washington team has profound strengths in clinical research in treatment of cardiac arrest, while our strength was mainly laboratory research. By bringing those research teams together, we shared data and expertise and answered some important questions." Led by postdoctoral fellow Dr. Amanda Missel from the University of Michigan, their research team discovered that bystander physical limitations can delay CPR and impact patient outcomes, using advanced ECG analysis to reveal how early bystander CPR improves survival. Their findings were published in *Resuscitation* and the *Journal of the American Heart Association*.

Northwestern University Center Director **Elizabeth McNally, M.D., Ph.D., FAHA**, said her team had robust partnerships with both Vanderbilt and University of Washington.

"We had a lot of great meetings and collaborations, especially around the genetics angle," she said. "Each center took very different approaches, but they were complementary. We found a lot of common ground." As an example, researchers from Northwestern and Vanderbilt, in collaboration with the Children's SFRN at the University of Utah, co-authored a publication in *Genome Medicine* to advance the understanding of genetic variation and the impact of epilepsy on sudden death among young individuals.

CONCLUSION

Sudden cardiac death, often driven by undetected arrhythmias, has long been one of the deadliest forms of heart disease — accounting for nearly half of all cardiovascular-related mortalities. And the rate has remained stubbornly high for decades.

Yet for a variety of reasons, research on the problem has not been well-funded, said Oversight Advisory Committee Chairperson **Karl Kern, M.D. FAHA, FACC, FSCAI.**

"Historically, it's been near the bottom in research monies in terms of major killers. But with networks like this one, the American Heart Association continues to lead the way in making progress and finding exciting new approaches to prevent sudden cardiac death," he said.

"The American Heart Association is helping to convince people that this is a problem that deserves attention, that lives can be saved. Their ongoing support will have a profound impact."

Since the first SFRN launched in 2014, the American Heart Association has created 17 strategically focused research networks.

In addition to Arrhythmias and Sudden Cardiac Death, other networks have focused on Prevention, Hypertension, Disparities in CVD & Stroke, Go Red For Women, Heart Failure, Obesity, Children's Health, Vascular Disease, Atrial Fibrillation, Cardiometabolic Health & Type 2 Diabetes, Health Technologies & Innovation, Cardio-Oncology, Science of Diversity in Clinical Trials, Biological Impact of Chronic Psychosocial Stress, Role of Inflammation in Cardiovascular Health, and Cardiovascular Kidney Metabolic Syndrome: Heterogeneity in Women.

American Heart Association
7272 Greenville Avenue
Dallas TX 75231