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Research Institute

BETTER TOGETHER

HonorHealth Research Institute **Annual Report 2023**

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'Better, Together' connects scientists, physicians, nurses, research professionals, donors, sponsors, patients and their families at the HonorHealth Research Institute

HonorHealth Research Institute adopted the theme "Better, Together" in 2023 – emphasizing collaborations and connections as colleagues partner to advance tomorrow's health innovations, today.

Since 2005, the Institute has evolved into the pre-eminent regional multi-pronged powerhouse of early phase clinical research and care, deploying the promising new drug and medical device innovations – often for the first time in the world – to provide patients with remarkable opportunities for longer, high-quality survival.

The 2023 Annual Report reflects a sampling of the joint work of dedicated professional teams across the Institute; extending to partners, donors, sponsors, HonorHealth system caregivers and administrative partners, patients and their families. Institute investigators initiated 82 new clinical trials in 2023, representing one-third of the Institute's 255 ongoing clinical studies and nearly 2,700 patient visits, to ensure novel innovations are available for personalized applications with patient needs across the Institute, providing new hope for challenging conditions.

The HonorHealth Research institute is fortunate to have the ongoing clinical and scientific leadership of Dr. Michael Gordon as Chief Medical Officer and Dr. Daniel Von Hoff as Chief Scientific Officer Emeritus. As you will see in the pages that follow, they, along with Institute division leaders, established investigators and emerging talents, are leading the way to clinical impact for real life patients right here, right now, across many areas of medicine.

Exciting advances from the Institute in 2023, such as innovations in radiation protection, prevention of ALS, trauma and concussion, cardiac rhythm control, early detection and treatment of cancers from melanoma to pancreatic to brain to women's cancers, GI/Bariatrics, and pulmonary, are making care safer for patients and caregivers, more effective and providing longer, healthier lives locally and globally.

Looking forward, the Institute has plans to accelerate innovation, performance, growth and most importantly impact in our areas of focus that builds on the strong foundation laid together in 2023. The coming year calls on all colleagues at the Institute to continue to develop new capabilities and work together with integrity, initiative, and urgency to achieve our goals of advancing medical innovation that provides hope for patients with challenging illnesses.

In 2024, the Institute will continue to develop and expand programs and facilities to help patients across our community and beyond. Exciting opportunities to expand access to clinical trials in collaboration with our community caregivers across HonorHealth, advances in cell and biologic therapy, innovations in radio imaging and therapeutics, novel approaches to early identification and interception of disease, and development of data systems and technology will complement our ongoing early phase drug and device trials.

Our Institute without walls philosophy will continue to drive productive collaborations with leading scientists and organizations to accelerate impactful innovations that advance science and medicine. The impact of new technologies and advances in science, moving medicine forward, improving patient care, and changing the lives of individuals and their families will be a top priority throughout 2025, marking the Institute's 20th Anniversary.

I am inspired to work with an exceptional team of clinical research professionals, affiliates and supporters. The Institute truly is "Better, Together," and together we are providing hope and changing the fortunes of patients with limited options from standard care.

Mark A. Slater, Ph.D.
Chief Executive Officer
HonorHealth Research Institute

Dr. Daniel Von Hoff

YOUNG GUNS IN RESEARCH

HonorHealth Research Institute pursues excellence by encouraging young talent

Few know the importance of cultivating young medical talent as well as Daniel D. Von Hoff, M.D., the Virginia G. Piper Distinguished Chair for Innovative Cancer Research at HonorHealth Research Institute.

In 2020, Dr. Von Hoff received the inaugural Daniel D. Von Hoff Award for Outstanding Contributions to Education and Training in Cancer Research from the American Association for Cancer Research (AACR). The award recognized Dr. Von Hoff for his groundbreaking accomplishments as a dedicated and inspirational educator, especially for conceptualizing the AACR/ASCO Methods in Clinical Cancer Research Workshop, which has trained thousands of young physicians about how to execute optimally designed clinical research studies.

"Our goal together has always been to make sure patients would only be asked to participate in well-designed clinical trials, which would answer important questions impacting patient care," Dr. Von Hoff said at the time.

With those sentiments in mind, we introduce to you on these pages three up-and-coming clinical trial investigators at HonorHealth Research Institute.

Shashvat Desai, M.D.

With an aging global population, stroke specialist Dr. Shashvat Desai seeks to make universal the quality treatment of stroke victims

Shashvat Desai, M.D., 32, Medical Director of the Institute's Neurovascular Lab, is already realizing his goal of "making an impact" in creating not only better treatments for stroke victims, but also helping make those treatments globally accessible.

Growing up in Mumbai – home to 21 million people, India's largest city – Dr. Desai was bombarded with the inequities of a still-developing nation: "You see vast disparities in everything – in access to health, in the way healthcare is practiced, in the way resources are invested – and you see that full spectrum in the course of one day, every day."

He studied internal medicine at King Edward Memorial Hospital and nearby Seth GS Medical College, founded by Indian doctors, trained in England, who could no longer abide by the ban on training Indian doctors in India during years of British rule.

After just 2 years at the Institute in Scottsdale, he has already been instrumental in three major achievements:

- Simplifying the process of assessing stroke patients by using simpler, and less expensive, imaging techniques, thus getting the patient to treatment sooner before the lack of oxygen kills too many brain cells. This process has been adopted across the U.S. and around the globe.
- Helping establish Mission Thrombectomy (the name of the surgical treatment for stroke) with the goal of creating global access for stroke treatment. The Mission is a group of like-minded individuals from 89 countries who lobby to improve funding for research, improve compensation and insurance for stroke, all leading to improved treatment.
- Finding through clinical experience that most stroke victims – Slow Progressors – are resilient to major brain damage and that patients are affected in vastly different ways because of their age, genetics, overall fitness and how inherently fragile or robust their brains are.

WINNER OF THREE INTERNATIONAL AWARDS

"I hope to leave a mark in the field, not only with new treatments, but also expanding those treatments across the world," said Dr. Desai, who in the past 5 years has won three international young investigator awards – one this past May from the European Stroke Organization Conference (ESOC); and two from the Society of Vascular and Interventional Neurology (SVIN).

"Research satisfies my natural curiosity for understanding and learning, and the side effect is that we can find new ways to treat people, new ways to manage diseases and eventually see that as creating long-lasting human impact," he said.

Dr. Desai said he feels fortunate to enjoy the support of the Research Institute's CEO Mark Slater and that of Angelina Cooper, who oversees the Institute's clinical trials managers. And he is proud of his part in helping establish the Institute's Neurovascular Laboratory, one of only a handful of similar "futuristic" labs worldwide, focused on pre-clinical development, testing and validation of treatment devices for stroke.

> "I hope to leave a mark in the field, not only with new treatments, but also expanding those treatments across the world" – DR. SHASHVAT DESAI

Amar Thosani, M.D

Dr. Amar Thosani brings interventional endoscopy to Scottsdale

Amar Thosani, M.D., completed college at Cornell University followed by medical school at Rutgers University. He then moved to New York City where he furthered his knowledge in internal medicine, gastroenterology, and finally interventional endoscopy. After eight years of training, he was finally ready to showcase his talents.

Flying from New York to Scottsdale to interview at HonorHealth, he was more excited to visit for a weekend of sunshine, with little intention, initially, to settle in the desert.

But on his first interview day at HonorHealth, he knew this is where he wanted to build his career. He quickly saw the vast opportunity to grow an interventional endoscopy program. At the time, there were only five other physicians in the Valley with his caliber of training. He signed a contract the very next day!

In the decade since, Dr. Thosani has strived to build the reputation of HonorHealth as the Valley's preeminent center for endoscopy. Ultimately, he was able to recruit the Valley's top talent in the field of interventional endoscopy from another health care system: Dr. Rawad Mounzer and Dr. Teodor Pitea.

Over the past three years, this trio has worked tirelessly to offer patients throughout the area the most cutting edge procedures in all aspects of endoscopy. They have tripled the endoscopy volume at both Shea and Deer Valley medical centers. Still, their ultimate goal has been to build a world renowned center solely dedicated to interventional endoscopy.

The Center for Interventional Endoscopy is currently being planned on the Shea campus, which will integrate high quality patient care, enhance collaboration with the HonorHealth Research Institute, and champion interventional endoscopy throughout the HonorHealth system. It is set to open on the second floor of the Piper surgery center in 2025.

For more on Dr. Thosani and his pioneering work, please see GI/Bariatrics studies on P. 22.

The Center for Interventional Endoscopy will champion interventional endoscopy throughout the HonorHealth system and enhance collaboration with the HonorHealth Research Institute.

Justin Moser, M.D.

Dr. Justin Moser takes on multiple challenges in rare cancer care

Only 10 years out of medical school, Justin Moser, M.D., is up for the challenge. Whether treating a rare incurable melanoma of the eye or finding ways to resuscitate a patient's own lymphocytes against their cancer, Dr. Moser believes the answers could be as simple as looking inwards at the body's own immune system.

Dr. Moser is an associate clinical investigator in the Cancer Research Division of HonorHealth Research Institute, where he specializes in a rare cancer that starts in the pigment, or coloration, of the eye known as ocular melanoma. He also is playing a key role in building the Research Institute's cellular therapy programs.

"We want to develop better therapies for patients with cancer," he said. "Not only do we want to help develop these new therapies, but we also want to be able to offer those treatments today, via clinical trials."

Uveal melanoma, once spread, has no cure and so far has proved resistant to immune therapy. But Dr. Moser, who has created Arizona's largest clinical trials program against this rare disease, thinks he may be on to something.

"There is growing evidence in the scientific literature that strongly suggests that there is something in the liver that, when cancer spreads to the liver, prevents the cancer from responding to immune therapy," he said, noting that when uveal melanoma spreads to other parts of the body, in 93% of the cases it spreads to the liver. "Knowing uveal melanoma almost exclusively spreads to the liver and has low response rates to immunotherapy, we can use this disease as a model to make immunotherapy work better for all patients with cancer that has spread to the liver."

So, an obvious target for research – working with the Immune Monitoring Lab at the University of Arizona in Tucson – is the immune biology of uveal melanoma.

Another area of his research is radioligand therapy, in which radioactive molecules are given by IV that target cancer cells.

"They selectively radiate cancer from the inside (the body), rather than radiation from the outside," said Dr. Moser, adding that such therapy already is FDA approved for prostate cancer and certain gastro-intestinal cancers. In Arizona's only such clinical trial, he wants to see if such a therapy could be extended to patients with melanoma and sarcoma.

Dr. Moser also is a leader in cellular therapy, especially in the area of Tumor Infiltrating Lymphocytes (TILs).

Find out more about Dr. Moser's work in expanding possibilities for cell therapy, P. 18.

"Not only do we want to help develop these new therapies, but we also want to be able to offer those treatments today, via clinical trials." **– DR. JUSTIN MOSER**

CARDIOVASCULAR RESEARCH

HonorHealth Research Institute is Arizona's first to adopt new radiation protection technology in treatment of heart disease

In 2023, HonorHealth Research Institute became one of the first healthcare providers in the U.S. – and the first in Arizona – to use an advanced radiation protection system as part of the diagnosis and treatment of heart disease.

The results of a clinical study completed at the Research Institute found that the new radiation protection system called Protego™ significantly reduces overall room radiation during cardiac catheterization interventions, and in most cases, eliminates exposure to physicians and nurses.

David G. Rizik, M.D., medical director of the Cardiovascular Research Division at HonorHealth Research Institute, likened the use of radiological equipment without the protection of radiation shields to football teams playing without helmets.

"Since the first college football game in 1869, there have been dramatic equipment improvements to enhance the safety of the game and reduce injury to athletes. Yet, interventional cardiology – one of the most advanced fields of medical science over the last half-century – has made no substantive changes in how to protect physicians and nurses who perform interventional procedures," said Dr. Rizik, who served as the clinical study's principal investigator.

> "This system will especially protect the next generation of physicians and researchers."
>
> **– DR. DAVID G. RIZIK**

RADIATION A BY-PRODUCT OF IMAGING

Modern cardiac catheterization laboratories use multiple X-ray beams from different angles to produce high-quality images of the heart, major arteries and other tissues. These low-level radiation beams enable physicians to guide catheters and other devices during interventional cardiology procedures, which are non-surgical, catheter-based therapies for patients who do not require open-heart surgery.

While generally considered safe, repeated exposure to low-level radiation over time presents a potential cancer and other risks to doctors, nurses and other catheterization laboratory staff. Current standard radiation protection for operating room personnel – a lead apron – offers no protection to the head and face, with suboptimal shielding of the extremities, creating a potential risk of cataracts and certain cancers. In addition, the weight of the lead apron has been associated with orthopedic injury of the spine, hips and knees.

The Institute's findings, published in the *Journal of the Society for Cardiovascular Angiography & Interventions (JSCAI)*, may have a profound impact on reducing radiation exposure to healthcare workers. In nearly 70% of the cases, radiation exposure to the physicians and nurses was so low as to be "undetectable" using real-time dosimetry.

RESEARCH INSTITUTE LEADS THE WAY

Dr. Rizik, lead author of the study published in JSCAI, said, "I am so very proud that HonorHealth is leading the world in this important field of research."

The study by HonorHealth Research Institute – the world's first side-by-side comparison of standard protection compared to the Protego system – also suggests that the radiation reduction may eliminate the need for cardiac catheterization laboratory staff to wear the orthopedically burdensome lead aprons. The new system allows physicians complete freedom of movement, the study said.

The required lead aprons worn in catheterization laboratories can weigh as much as 15 pounds and place up to 300 pounds psi on intra-vertebral disks. According to the Society of Interventional Radiology, 70% of interventional cardiologists experience lower back pain, 40% experience neck pain and 42% experience both.

RISKS TO HEALTHCARE PROFESSIONALS

Studies suggest a link between brain tumors and occupational radiation exposure, and interventional cardiologists have a three-fold higher risk of developing cataracts than the general population. Those working in catheterization laboratories for 20 years or more are estimated to have received the equivalent of more than 10,000 chest x-rays to the head and neck.

Results of HonorHealth Research Institute's clinical trial showed that – of the 25 interventional cases completed using the Protego™ system – 17 recorded undetectable radiation exposure, and 4 cases measured 0.1 millirem (mR) of total exposure, only about 5% of the 2.0 mR/hour maximum considered safe.

Interventional cardiologists specialize in treating coronary artery disease, heart valve disorders, congenital heart disease, and other heart problems. With equipment modifications for specific applications, these findings may confer workplace benefit to other physicians working in specialties exposed to radiation, including rhythm management specialists (electrophysiologists) and radiologists.

"Use of this groundbreaking radiation protection system is a first in Arizona. This system will especially protect the next generation of physicians and researchers," Dr. Rizik said. "It will help protect the lives of those on the front lines of lifesaving cardiovascular therapies and is literally getting the lead off our backs."

HONORHEALTH LEADERSHIP BACKS CHANGES

Dr. John Neil, HonorHealth's executive vice president, chief physician executive and network strategy officer, was a practicing clinical vascular and interventional radiologist for two decades.

"The challenge of radiation exposure to those who work in the interventional lab is an issue that hits very close to home," Dr. Neil said. "I am proud and appreciative of the groundbreaking work done by Dr. Rizik and the team at HonorHealth. Our Mission is to improve the health and well-being of those we serve, and that includes protecting the health and well-being of those who dedicate their professional careers to saving lives and caring for others."

Also contributing to this study from the HonorHealth Research Institute were: Dr. Robert D. Riley; Dr. Robert F. Burke; Sabrina R. Klassen; Ariana M. Nigoghosian; Kevin P. Gosselin, Ph.D.; and Dr. James A. Goldstein. Dr. Goldstein is an equity owner and board member of ECLS Inc., which licenses technology to Image Diagnostics Inc., which makes the Protego shield.

HonorHealth Research Institute clinical trial helps secure FDA approval of revolutionary new pacemaker

World's first dual chamber leadless pacemaker successfully implanted in 22 HonorHealth patients, stimulating two heart chambers without using wires

HonorHealth Research Institute is helping usher in a new era of heart pacemakers for patients with abnormal or slow heart rhythms by helping secure FDA approval of the world's first dual chamber leadless pacemaker.

"What a difference this makes for our patients!" said Rahul Doshi, M.D., an electrophysiologist in the Research Institute's Cardiovascular Research Division, and one of the authors of a study published in June in *The New England Journal of Medicine*, which outlined the benefits of the new pacemaker system. Later that same month, the dual system received FDA approval and is now available commercially at the Research Institute, one of the nation's first to offer it.

"We're able to get this technology that is brand new and that provides real benefit to our patients," said Dr. Doshi, the principal investigator of the clinical trial at HonorHealth Research Institute, which successfully implanted the revolutionary device in 22 patients, including some of the first of the more than 300 clinical trial participants worldwide.

Dr. Rahul Doshi with patient Barbara Giovan

"You can imagine that for these patients it's absolutely life changing," said Dr. Doshi, noting the nearly half-century evolution of pacemakers: from the large, wired devices that once required open-heart surgery, to the sleek new AVEIR DR dual chamber leadless pacemaker system, in which two cylinders, each smaller than an AAA battery, are placed using a catheter through a large leg vein directly into the upper and the lower right chambers of the heart.

Study patient: 'I felt so much better'

Barbara Giovan, a retired hospital laboratories administrator, once had a weak heart with a low heart rate, at times dipping to a mere 40 beats a minute, which often left her short of breath even after the slightest exertion.

Today, the 73-year-old Scottsdale resident plays golf several times a week and is loving life with a heart that beats a vibrant 70 times a minute, thanks to the dual-chamber leadless (wireless) pacemaker implanted by Dr. Doshi in April 2022 at the Research Institute.

"I've never had any problems since. I felt so much better. I have so much more energy," she said. "I play golf 3 or 4 times a week. I exercise. I walk. I feel totally fine. I'm not inhibited in any way, and I'm looking forward to having a good long life."

Because Barbara also had open heart surgery in February 2022 to replace leaky valves, Research Institute physicians determined that she would be a good candidate for the dual chamber leadless pacemaker that was in clinical trials, as opposed to the traditional pacemaker that was implanted on the chest wall and connected to the heart by wires.

"This new system now provides a solution for the vast majority of patients who need pacemakers," said Dr. Doshi, predicting, "Dual chamber leadless pacing is going to revolutionize leadless pacing, and I believe it could actually take over the entire pacing world."

How system makes the heart work

The two Aveir cylinders communicate wirelessly, providing a steady electrical pulse that first stimulates the heart's upper right atrium, which loads blood into the lower right ventricle, and then stimulates the lower right ventricle to pump the blood to the lungs – a process known as "atrioventricular synchrony." (And, in sync with the right-side chambers, the heart's left atrium and powerful left ventricle pump the oxygenated blood from the lungs to the rest of the body.)

Continuing a history of "phenomenal evolution driven by technology," Dr. Doshi said, dual chamber pacemakers with leads have been in use for nearly three decades. But their wire leads were potentially problematic; subject to breakage and able to cause scarring in the veins, heart valves and heart muscle, and create risk of trauma that may cause bleeding in the lungs and heart. Pockets are created under the skin to hold the generator, which can also lead to infections, skin erosion, and unwanted scarring. Plus, the wires are subject to being infected, requiring their removal, which Dr. Doshi described as "a high-risk procedure."

The new system's devices are fully contained, Dr. Doshi explained, including the ability to sense and coordinate the cardiac rhythm, delivering a pacing impulse directly to the myocardium, the heart muscle, in step with the body's needs.

HonorHealth Research Institute implants first state-of-the-art modified pacemaker system in an Arizona patient

Two-device system is designed to detect and treat ventricular fibrillation, providing heart patients with a better way to keep their heart in rhythm

Dr. Thomas Mattioni with patient Adam Boas

The last thing Adam Boas remembered was going about his regular business as an information technology employee in Scottsdale. When he woke up in HonorHealth's Scottsdale Osborn Medical Center, he learned he had suffered a sudden cardiac arrest.

After an initial stay of nearly three weeks, doctors from HonorHealth Research Institute implanted into his heart a Modular Pacing System (MPS) pacemaker. It's a small power pack and electrode, the size of a AAA battery, which is designed to deliver an anti-tachycardia pacing (ATP) therapy that would shock his heart back into rhythm if he ever suffered ventricular fibrillation – when the heart starts beating wildly out of control.

Thus, Adam became the first patient in Arizona to be implanted with this new, potentially life-saving device designed to painlessly reset the heart's rhythm.

Pacemakers continue to improve over time

Biomedical science has been improving heart implants – pacemakers – since 1958 to keep the heart beating regularly and maintain proper blood circulation.

Over the past two years, many HonorHealth Research Institute patients have been implanted with the Subcutaneous Implantable Cardioverter Defibrillator (S-ICD) System, a proven treatment option for patients at risk of sudden cardiac arrest that leaves the heart and vasculature untouched, thus eliminating many of the complications associated with conventional transvenous implantable cardioverter-defibrillator (TV-ICD) which uses leads, or wires.

However, patients don't always need a full electrical shock to reset their heartbeats, and patients have expressed concern about the potential surprise and pain that might be associated with a full electric shock.

Now, HonorHealth Research Institute doctors are implanting a second device, the MPS, into the heart's right ventricle, the chamber of the heart that pumps blood to the lungs where it becomes oxygenated. This MPS device, the size of a AAA battery, delivers anti-tachycardia pacing (ATP) – a therapy designed to terminate potentially deadly episodes of fast, abnormal heart rates. It delivers ATP through several low energy electrical pulses designed to stimulate the heart and return the heartbeat to a stable rhythm.

The MPS implant communicates wirelessly with the S-ICD to form the mCRM™ Modular Therapy System. If MPS fails in using ATP to restore a proper heartbeat, the S-ICD is activated to deliver a full electrical shock.

Device takes worry out of resetting rhythm

"Having the new (MPS) pacemaker takes a lot of anxiety away from me. It would work to get my heart back to a normal pacing without having the threat of a shock," Adam said.

"I was so lucky to have been brought into HonorHealth," said Adam, which he described as, "so generous with my care."

If his heart ever falls out of rhythm, he said, "I might feel light-headed, but I probably won't even know it's happening. It takes a huge weight off my shoulders, knowing that it would be much less traumatic, not only for me but probably for the people around me, if the (MPS) pace therapy activates."

Dr. Thomas Mattioni is a Cardiac Electrophysiologist who implanted the MPS device into Adam's heart at HonorHealth Research Institute.

"While a shock can be painful, ATP delivery through a pacemaker is not painful and usually is not felt at all," said Dr. Mattioni, an Investigator on the ongoing MODULAR ATP clinical trial to test the safety and effectiveness of the two coordinated devices.

Dr. Rahul N. Doshi, head of HonorHealth's Electrophysiology Research Program and Principal Investigator for the clinical trial, said, "This coordinated system is different from having only an S-ICD or a conventional pacemaker implanted, as it uses the communication between the S-ICD and MPS devices to determine how best to treat rapid heartbeats."

NEUROSCIENCE RESEARCH

Dr. Todd Levine being interviewed by ABC15

HonorHealth Research Institute tests first potentially effective treatment for Lou Gehrig's Disease

First-ever clinical study aimed at preventing muscle-debilitating and deadly amyotrophic lateral sclerosis (ALS)

Dr. Todd Levine

Who was Lou Gehrig, anyway?

Lou Gehrig started playing First Base for the New York Yankees 100 years ago. He was by any era's standard a physical specimen, eventually playing in what then was a record 2,130 consecutive ball games, earning the nickname "Iron Horse."

Capping his baseball career with his iconic 1939 "Luckiest Man on the Face of the Earth" speech at Yankee Stadium, even Gehrig could not stop the physical ravages brought on by amyotrophic lateral sclerosis (ALS), since then known as Lou Gehrig's Disease, a chronic and always fatal motor neuron disease in which patients progressively lose control of their voluntary muscles.

And now, as then, there is nothing anyone can do to stop it.

But at HonorHealth Research Institute, there is hope!

Like other neuro-degenerative conditions such as Alzheimer's disease, by the time ALS patients are clinically diagnosed, it is very difficult to reverse the damage. The brain cells have already begun to deteriorate, explains Dr. Todd Levine, the Principal Investigator for the HonorHealth Research Institute's ALS clinical trial, the first in the world aimed at preventing ALS.

"Once nerves are lost, all we can do is try to stop the remaining nerves from dying," said Dr. Levine, who also is HonorHealth's medical director of Neurology, and medical director of the Research Institute's Neuroscience Division. "Our best option to 'cure' these diseases is really to prevent them."

FIRST ALS PREVENTION STUDY

HonorHealth Research Institute is one of just 30 sites worldwide participating in this first ALS prevention study, sponsored by Biogen. The focus of the study is to identify individuals who are genetically predisposed to developing ALS, specifically those who carry the SOD1 gene but who don't yet show any symptoms.

This study, called ATLAS, aims to determine whether pre-symptomatic intervention with a drug called tofersen (BIIB067) can delay clinical onset, or at least slow the progression of disease.

PARTICIPANT'S MOTHER HAD ALS GENE

One of the participants in the clinical trial is Charlie Hargett, who heads a business consulting firm in Denver. Charlie agreed to participate in the trial after he found out he has a mutation in the SOD1 gene associated with ALS, the same gene mutation carried by his mother, Debra "Dee" Hargett, who passed away from ALS in 2018.

"After mom died, I really felt like I wanted, and needed, to do something to contribute to awareness of this disease. My hope is to help find treatments and perhaps a cure," said Charlie, who so far has no ALS symptoms. "I'm really hoping that this study is successful and proves that this drug can keep the SOD1 gene from producing proteins, and block the progression of ALS."

The study includes a sub-set of adult participants who carry certain rapidly progressive SOD1 gene mutations.

"These are people who have a genetic mutation that causes ALS. Many of them have already watched multiple family members die of the disease," said Dr. Levine. "They know what they are facing. They know what's In their DNA."

Previous drug trials have shown little clinical benefit in patients with neuro-degenerative conditions, Dr. Levine explained. "That's because we're identifying the patients after they already have lots of nerves that are lost. We want to identify who's likely going to get ALS before they get it, and then potentially prevent them from getting the disease."

Neuroscience Research patient Charlie Hargett with his late mother, Debra "Dee" Hargett

For more information on referring patients to this study and other neuroscience studies please call HonorHealth Research Institute's Neuroscience Research Team at 602-258-2863 or email neuroscienceresearch@honorhealth.com.

Dr. John Kepros (L) interviewed on Arizona Horizon

TRAUMA

HonorHealth Research Institute potentially part of 8,000-patient global clinical trial to test drug that might prevent severe bleeding

HonorHealth Research Institute is pursuing a local trauma research study to investigate a blood clotting agent as a treatment for trauma patients who are bleeding to death.

Bleeding out is the most common cause of preventable death after injury. The Research Institute is participating in an international study to see if a blood clotting drug, given soon after arrival in the emergency room, can improve survival.

Kcentra® (or 4-factor Prothrombin Complex Concentrate, PCC) is an FDA-approved drug and is currently used to reverse the effects of medications given to "thin" the blood, for patients who experience bleeding and/or require surgery.

The Trauma and Prothrombin Complex Concentrate, or TAP Trial, will evaluate the effectiveness of the drug, in addition to all standard care, in injured patients predicted to require a large volume blood transfusion.

"There is evidence that the drug may reduce the chance of dying in injured patients who are not on blood-thinning medications," explains John Kepros, M.D., medical director of trauma services at HonorHealth Scottsdale Osborn Medical Center and the principal investigator for the TAP Trial for HonorHealth Research Institute.

"The standard treatment of injured patients who are bleeding involves the transfusion of different types of blood products, as well as the use of medications to help the blood clot better, along with surgery to stop the bleeding. But even with these treatments up to 30% of patients suffering from a serious traumatic injury die," said Dr. Kepros. "Finding a way to improve that survival rate is our highest priority here at HonorHealth Research Institute."

Patients in this study will have suffered a serious and potentially life-threatening injury that caused significant blood loss, requiring immediate lifesaving interventions. These types of injuries occur unexpectedly, and it will not be possible for most people to sign up to participate ahead of time. Most patients will be unconscious, unable to speak or hear, and too sick to consent to immediate treatment or participation in the study.

If feasible, doctors will consent patients who fit the study criteria. If consent is not feasible, patients who fit the criteria will be automatically enrolled without their individual consent if they are not wearing an opt-out bracelet.

The TAP Trial will be conducted at about 120 leading trauma centers in several countries and will include 8,000 patients, making it the second-largest trauma trial ever conducted. The trial began in 2023 and will last until 2026, and is funded by CSL Behring, which makes PCC.

"The results of this study have the potential to change the way trauma patients are treated," Dr. Kepros said. "If we can determine that the drug is safe and effective for trauma patients, we can transform the standard of care for bleeding trauma patients and save thousands of lives."

> "The results of this study have the potential to change the way trauma patients are treated."
>
> **– DR. JOHN KEPROS**

CONCUSSION

Portable EEG would provide instant evaluation of head injuries or nervous system illnesses

Dr. Yazan Al-Hasan

Hand-held electroencephalogram will be tested on college football and soccer athletes to help analyze concussions

Yazan Al-Hasan, M.D., Ph.D., often wishes he had a portable EEG machine as he does his rounds, checking on patients at HonorHealth's Osborn, Thompson Peak and Shea medical centers in Scottsdale.

An EEG, or electroencephalogram, is a device that uses electrodes placed on the scalp to measure the brain's electrical activity. In use for nearly a century, EEG wave patterns are so well known that a trained neurologist can instantly tell if something is amiss.

"Oftentimes, in the clinic, I wish I could get a really quick EEG from the patient as part of my initial physical exam," said Dr. Al-Hasan, a board-certified neurologist who focuses on the treatment of epilepsy, spells of impaired consciousness, headaches, dizziness and cognitive conditions.

So, it was a no-brainer for Todd Levine, M.D., medical director of the Neuroscience Research Division at the HonorHealth Research Institute, to assign Dr. Al-Hasan to work with Ayushi Patel, CEO of Scottsdale-based telehealth company CenSyn,* when she came looking for a partner to help develop the type of device that Dr. Al-Hasan always wished he had.

"The goal is to help health systems expedite diagnosis of conditions such as seizures, strokes and concussions from hours to minutes. This will help save patient lives and reduce treatment costs for healthcare providers," Patel said a year ago when an HonorHealth-CenSyn partnership was announced.

After all, CenSyn is right across the street from where Dr. Al-Hasan works at HonorHealth's Bob Bove' Neuroscience Institute on the Osborn campus. And it didn't hurt that HonorHealth received a $250,000 National Science Foundation grant to help develop a portable EEG.

Developing an EEG stethoscope

"The project is to design what is essentially an EEG stethoscope," said Dr. Al-Hasan, adding that evaluation can take hours to set up a standard EEG.

"We feel there is room for improvement," he added, especially when trying to quickly evaluate the condition of critically ill patients in an emergency room or intensive care unit.

The partnership has already designed a portable voltmeter connected to a smartphone to measure electrical brain activity based on already known standard wave patterns at various points across the cranium.

"We came up with a paradigm for how we could quickly interrogate the scalp within a matter of a few minutes and get a pretty good idea of what we are dealing with," said Dr. Al-Hasan, who is in his third year at HonorHealth after graduating medical school at Texas Tech University and earning an undergraduate degree in Molecular Biology and a Ph.D. in Neuroscience at the University of Texas.

Proof of concept using college athletes

Dr. Al-Hasan hopes to begin a clinical study of college football and soccer players, and even cheer squads, using his experimental EEG to quicky analyze athletes for concussions. Because concussion patterns are also well known, such a test could quickly diagnose players on the sidelines and help determine if they should stop playing or if they are ready to get back in the game.

"We think this is a good population to start off with," said Dr. Al-Hasan, since college athletes would not have the many variable conditions, including age, sex, source of injury, that present in emergency rooms. "The use of our device with athletes would be a good proof of concept."

A portable EEG would be especially important in evaluating minor head injuries, he said, since often the signs of concussion go unnoticed, and it is subsequent secondary concussions that can cause more severe brain damage.

Dr. Al-Hasan is already working on a newer version of his portable EEG.

"This is exactly the kind of thing I wanted to be involved with," he said. "I think it would be nice to incorporate this into routine physical exams. It would be very useful."

**HonorHealth has a small ownership interest in CenSyn.*

Dr. Joseph Mikhael

BLOOD CANCER

HonorHealth Research Institute's Dr. Joseph Mikhael is on the forefront of advanced therapies for multiple myeloma

While there still is no cure, chronic myeloma patients are living longer and with better quality of life

Joseph Mikhael, M.D., director of Myeloma Research and Consultant Hematologist at HonorHealth Research Institute, is excited about the advances taking place and new myeloma treatments available through the Institute's Cancer Research Division.

"There's tremendous progress being made," said Dr. Mikhael, who, as Chief Medical Officer for the International Myeloma Foundation, casts a long shadow across the globe as a leader in treating this often devastating disease.

While there still is no cure for myeloma, people are living longer with this chronic condition.

"Arguably, myeloma may have had the greatest progress of any malignancy over the last decade, where we've doubled and tripled the average survival of patients," he said. "That's been a function of many of these novel therapies that have been introduced, and HonorHealth Research Institute is right in the center of it."

The median survival of those newly diagnosed with myeloma is now more than 5 years; and as much as 10 years in patients who are otherwise fit and with few other medical problems.

Significant progress is underway at HonorHealth's Scottsdale Shea Medical Center campus, including first-in-the-world treatments using technology, two decades in the making, that relies heavily on prompting the body's own immune system to beat back the cancer.

"This is like Star Trek-ian science," Dr. Mikhael said.

THE MAGIC BEHIND CAR T CELL THERAPY

CAR (chimeric antigen receptor) T cell therapy is a novel approach that engages a patient's own soldier cells (T cells). They are removed from patients and engineered to recognize their tumor through a receptor placed on the surface of the T cell. Dr. Mikhael calls these "Rambo-like soldiers just chompin' at the bit to go after myeloma."

Though it is a tremendously complex process, the idea behind CAR T cell therapy is relatively simple. About a pint of blood is taken from the patient. Hundreds of thousands of T cells are removed from the blood and the rest of the blood is given back to the patient. The T cells are then re-manufactured in a laboratory where they are attached with CAR and then multiplied, resulting in hundreds of millions of CAR T cells that are then infused back into the patient.

"We've seen unprecedented response rates exceeding 90 and 95 percent, unheard of previously in myeloma," Dr. Mikhael said.

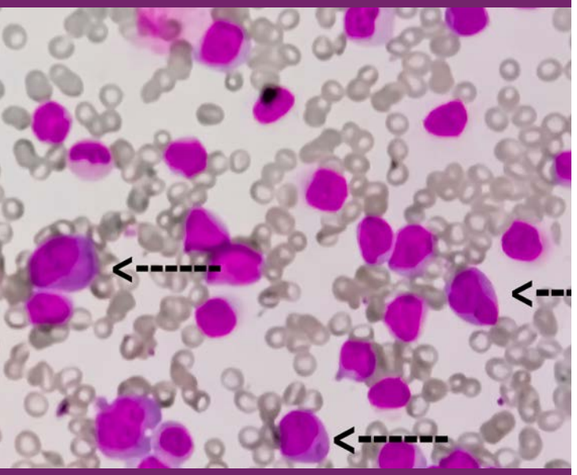
WHAT IS MULTIPLE MYELOMA

Multiple myeloma, or myeloma, is one of three major types of blood cancers, along with Leukemias and Lymphomas.

Myeloma is a cancer of the plasma cells in the bone marrow – the cells that make our antibodies. It is characterized by a set of symptoms known as CRAB: Calcium elevation, Renal insufficiency, Anemia and Bone disease.

In 2023, there was an estimated 35,000 new cases, and more than 12,000 deaths.

The risk factors include: age, 65 and older; sex, it is more common in men; race, it is more than twice as common among African American patients than White patients; family history; weight; and exposure to radiation, chemicals and pesticides.



Dr. Joseph Mikhael

One recently opened clinical trial called PHE885 is now providing CAR T cell therapy as a first line of defense for newly diagnosed myeloma patients. Current approval of CAR T requires patients to receive at least 4 lines of therapy before they can receive CAR T.

"This molecule that we are using, not only are we using it front line, but we sometimes jokingly refer to it as a 'fast' CAR," he said, because it only takes 10 days to manufacture, instead of the usual 4-8 weeks.

"This is especially important for patients who have heavy-burden disease in which waiting 4-8 weeks can really be a challenge," Dr. Mikhael said.

OVERCOMING POTENTIAL PROBLEMS WITH CAR T

One drawback to CAR T is that each therapy is unique, and expensive. The T cells are removed from an individual patient, re-manufactured with CAR, multiplied, and then infused back into that very same patient. The advantage is that the patient's immune system is more likely to accept, rather than reject, the CAR T cells because they originally came from that same person.

To make the process more efficient, another clinical study on the horizon involves collecting T cells from a variety of healthy donors, instead of just one individual patient. These donor T cells could then be manufactured to become CAR T cells and then infused into the patient. These "off the shelf" CAR Ts could save weeks for patients by not requiring T cell collection and manufacturing.

Another potential barrier to CAR T therapy is called Cytokine Release Syndrome (CRS). This is when the immune system reacts to the infusion of CAR T cells and can result in fevers and a multitude of other symptoms that can require hospitalization and highly specialized care.

Researchers at the Institute are responding with another wave of immune therapy involving something called "bispecifics," which are molecules infused into the patient with two antibody arms: one grabs a T cell and the other grabs a cancer cell and pulls them together. Also known as "engagers," bispecifics flip a switch in the T cells: "Here's the enemy right next to you."

"That's a beautiful way of using someone's immune system," Dr. Mikhael said. "You don't have to collect cells. They don't have to be processed in a big, specialized manufacturing center. This could be done out in Payson or Sedona or Yuma or wherever else."

THE BEAUTY OF NATURAL KILLER CELLS

In another first-in-the world study at the Institute, a new kind of bi-specific therapy eliminates the use of T cells and instead pulls cancer cells together with a different type of immune system weapon known as NK, or Natural Killer, cells. In theory, by engaging NK cells against myeloma, the risk of a CRS reaction is diminished, reducing the likelihood of patients having to be kept in the hospital overnight for monitoring.

This has potential worldwide implications, Dr. Mikhael said, because the NK cell therapy could be rolled out to rural areas, even possibly to developing and third-world countries: "We want to be able to give these kinds of therapies without the risk of some kind of reaction that would require hospitalization and very specialized care."

One of the huge benefits of cellular therapies is that they only need to be given once.

"Most of our myeloma patients are on chronic chemotherapy for years at a time," he said. "But when we give CAR T, we give that one big blast of T cells, and then the patients receive no immediate further treatment. And patients love it. For the first time, for many, they don't have chemo brain. They say, 'I feel normal. I can do the things that I usually do.' This provides hope to patients not only to extend their lives, but to improve their quality of life."

Dr. Mikhael's Special Myeloma Projects

Not only does Dr. Joseph Mikhael supervise myeloma clinical trials at HonorHealth Research Institute, but he also consults community cancer doctors about their myeloma patients, and he heads a project devoted to overcoming the racial disparities in this disease.

"We're a hub of myeloma consultancy throughout the Valley to all patients, providers and practices," he said of the Research Institute. "One of the blessings of being here is that we have this academic center nested within a community hospital. What we do reverberates throughout the whole Valley to all of our HonorHealth oncology locations and beyond. It allows us to multiply the effect of what we do."

HonorHealth Research Institute's work in myeloma is an extension of HonorHealth's other Hematologic Malignancy Programs at HonorHealth's Cancer Transplant Institute, led by Dr. Adrienne Briggs.

Addressing disparities in cancer care

Also, myeloma is nearly twice as common among individuals of African descent, and Black men and women with myeloma only live half as long as White men and women with this disease.

"The disparity is massive," said Dr. Mikhael, who has created a program called M-Power (Myeloma Power), designed to help reduce myeloma's disparity through community engagement, educating primary care physicians to identify the disease earlier, and enhancing the care given by community providers.

"Health disparities are dramatic in cancer, and we can argue that myeloma is the most disparate cancer within the African American community," he said. "We are committed to reducing that disparity and finding ways to improve outcomes in all patients, especially those who have historically been marginalized."

Dr. Justin Moser

TILS THERAPY

Tumor Infiltrating Lymphocytes used for first time at HonorHealth

For the first time at HonorHealth Research Institute, a patient was treated this past April with Tumor Infiltrating Lymphocytes, or TILs, one of the Institute's expanding uses of cellular therapy.

The patient received TILs for a diagnosis of refractory melanoma skin cancer; refractory meaning their cancer has always been resistant to treatment or became resistant during previous treatment.

TILs are immune cells imbedded in a tumor that are fighting a losing battle. They are few in number and essentially exhausted, allowing the cancer to progress.

But because these immune cells can at least recognize the tumor, they still have value.

Dr. Justin Moser, an associate clinical investigator specializing in melanoma at the Research Institute, explained the relatively elaborate process of using TILs to fight cancer.

A melanoma tumor of at least 1.5 cm is surgically removed and sent to a laboratory where it is broken down into individual cells. The TILs are removed and over six weeks are enhanced and multiplied, resulting in billions of energized immune cells, which are then given by IV back to the patient.

Prior to the reintroduction of the TILs, the patient is treated with a combination chemotherapy of fludarabine and Cytoxan for 5-7 days. After the TILs are re-introduced, the patient receives a three-day boost of interleukin 2.

HonorHealth Research Institute was among a handful of sites nationwide given permission to use TILs in advance of FDA approval through an Expanded Access Protocol. Dr. Moser is hopeful that the therapy is soon approved by the FDA and that the Institute will be one of the first sites in the nation to offer this unique therapy commercially.

For patients with refractory melanoma, clinical trials have shown that TIL therapy produces a nearly 30% response rate, or more than triple the rate of the current standard-of-care chemotherapy, ipilimumab, which has an average response rate of 8.6%. In addition, past studies have shown that, for roughly half of patients who respond to TIL therapy, they continue to have a response for at least 2 years, following this one-time treatment.

"The data suggests that this is likely the best option for patients with refractory melanoma, and that it can provide long-time, durable disease control in some patients," said Dr. Moser, who also is a clinical assistant professor at the University of Arizona College of Medicine-Phoenix, and an adjunct faculty member at the Translational Genomic Research Institute (TGen).

Dr. Michael Gordon, Chief Medical Officer of the HonorHealth Research Institute, said the initiation of TILs therapy at HonorHealth holds the promise of better outcomes for a variety of patients.

"This represents a major step forward in providing access to a novel therapy, not just for melanoma, but hopefully in other diseases," said Dr. Gordon. "It uses immunotherapy in a way that potentially creates another avenue for durable responses."

As an Institute without walls, collaboration is key. L-R: Dr. Syed Rahmanuddin of City of Hope; Dr. Erkut Borazanci of HonorHealth Research Institute; Dr. Derek Cridebring of TGen; and Dr. Daniel Von Hoff of HonorHealth Research Institute and TGen

PANCREATIC CANCER

HonorHealth Research Institute makes progress against pancreatic cancer

New tests, new dollars, new imaging mark advances by Cancer Research Division

Erkut Borazanci, M.D., M.S., medical director of the Cancer Research Division at HonorHealth Research Institute, oversaw significant progress over the past year in the study and treatment of pancreatic cancer, one of the most aggressive of all malignancies.

In a potential breakthrough that could extend patient survival, Dr. Borazanci was part of an international team of researchers – led in part by HonorHealth Research Institute – who devised an investigational blood test that might one day help doctors detect pancreatic cancer earlier.

Researchers from the U.S., China, South Korea and Japan created a biomarker panel that detects small amounts of RNA genetic material that circulates in the bloodstream when someone has cancer.

More than 50,500 Americans will die this year from pancreatic cancer, making it the third leading cause of cancer-related death behind lung and colon cancers. Only about 11% of those diagnosed with this type of cancer survive more than 5 years. One of the primary reasons for the dismal survival rates in pancreatic cancer is that most patients are usually diagnosed in late stages when the disease has already spread to other parts of the body.

"When pancreatic cancer is caught early, the chance of survival is so much greater than when diagnosed in the advanced stage. Therefore, there is a great need to develop novel ways to detect pancreatic cancer," Dr. Borazanci said.

RESEARCH INSTITUTE SHARES $4.5 MILLION NCI GRANT

As part of a related effort, the Cancer Research Division shared a $4.5 million National Cancer Institute (NCI) grant to advance a blood-based test for early detection of pancreatic cancer.

In addition, the Research Institute will be one of 10 clinical sites that will use a blood-based "liquid biopsy" test to look for exosomal microRNAs that serve as a genetic biomarker fingerprint for detection of disease or the recurrence of disease.

Co-principal investigators are Ajay Goel, Ph.D., M.S., AGAF, chair of the Department of Molecular Diagnostics and Experimental Therapeutics at Beckman Research Institute of City of Hope cancer center, and Daniel D. Von Hoff, M.D., distinguished professor in the Molecular Medicine Division at Translational Genomics Research Institute (TGen), part of City of Hope, and also the Virginia G. Piper Distinguished Chair for Innovative Cancer Research at HonorHealth Research Institute.

The high mortality rate of pancreatic cancer is due, in part, to the general absence of symptoms and a lack of reliable methods for diagnosing it at an early stage when the disease is most easily treated, especially through surgical resection.

DECIDING BEST CANDIDATES FOR SURGERY

Together, this collaboration of HonorHealth Research Institute, City of Hope and TGen developed a more precise method that may help determine when it is best to surgically remove pancreatic cancer tumors.

Surgical removal of the tumor can be a key step in helping extend the survival of patients with pancreatic cancer. Currently, surgery – or surgery plus chemotherapy – are the only curative treatments for pancreatic cancer.

Because of the intricate web of critical organs and major arteries and veins surrounding the pancreas, located just below the stomach, surgery involving the pancreas is very challenging.

To take some of the guess work out of when it is safer, and more effective, to surgically remove pancreas tumors, the three research centers developed a precision method of scoring tumors based on an innovative 3D imaging technology, according to the findings of a clinical trial study published March 29 in the scientific journal Frontiers in Imaging.

WOMEN'S CANCER

New head of gynecological cancer research excited to increase patient awareness of clinical trials

Lyndsay Willmott, M.D., cannot recall a time when she didn't want to be a doctor. Even as a toddler, she used her plastic toy stethoscope to pretend checkups with her little brother, Ryan.

"There was never a moment in my life that I didn't think that I wanted to be a doctor, and I never swayed from that," said Dr. Willmott, a self-described nerd who always loved science and math, loved reading, loved working with her hands and playing the flute. "I love the merging of science and art, and critical thinking."

Now, her brother is conducting his own medical residency in Buffalo, N.Y., training to be an anesthesiologist, and Dr. Willmott is the recently appointed head of gynecologic cancer research for HonorHealth Research Institute.

Dr. Willmott received her medical degree at the State University New York (SUNY) at Buffalo, School of Medicine. It was during her subsequent residency training at University of Rochester where during rotations she was drawn to working with patients with gynecological cancers. "I felt like, this is my home."

She served her post-doctoral fellowship in oncology at University of California-Irvine, including two years training in research and two years of clinical practice. It was there that she met her mentor, Dr. Bradley Monk, who would later become head of gynecological cancer research at HonorHealth Research Institute.

After completing her fellowship in 2012, Dr. Willmott followed Dr. Monk to Arizona where she worked at various practices before starting to collaborate with HonorHealth two years ago. In December, she replaced Dr. Monk, who recently left HonorHealth after helping develop a new therapy for endometrial cancer. Dr. Monk's pioneering work in endometrial cancer clinical trials was published in March in the prestigious New England Journal of Medicine.

"How far we've come in gynecological cancer care is just tremendous," said Dr. Willmott, who is excited to make cancer care breakthroughs through the nearly 20 clinical trials now underway in ovarian, uterine and cervical cancers. "It's a huge area of active research to find new medications that can be more effective in these patients, and help them live longer, and with good quality of life."

Her biggest challenge is to increase patient awareness of clinical trials and to remind providers that clinical trials provide options; access to experimental drugs that may perform better than the current standard of care.

In this effort, she has her own personal example. While Dr. Willmott was attending medical school, her father, Robin, had a recurrence of a gastro-intestinal cancer after being treated with surgery and chemotherapy. He was told that he didn't have long to live. However, her father found a clinical trial in Boston that offered hope with a new experimental drug. He lived for more than a decade before succumbing to non-cancer causes.

"It was a very motivational event for me; understanding that not all doctors are aware of all the research that is going on, and that research can change lives," Dr. Willmott said. "It changed my life. It changed my dad's life. And it is changing my own patients' lives."

Dr. Lyndsay Willmott

Dr. Bradley Monk

BRAIN CANCER

GammaTiles help eliminate last vestige of brain cancer in HonorHealth Research Institute clinical trial

Radiation micro-sponges line the areas resected during brain cancer surgery, providing immediate therapy to guard against recurrence of malignancy

Dr. Steven Sckolnik

Surgeons walk a fine line when resecting tumors from the brain: How do you remove as much of the cancer, while at the same time removing as little healthy brain tissue as possible?

"It's a delicate balance. You want to remove as much of the cancer as possible so that the tumor doesn't grow back. But you don't want to remove so much of the brain that, while the tumor might not grow back, it gives the patient a functional deficit," said Steven Sckolnik, M.D., a radiation oncologist who specializes in brain tumors and clinical trials for the HonorHealth Research Institute.

Often there are small pockets of cancer that go undetected during surgery. They remain in the brain, often resulting in a recurrence of cancer.

To prevent recurrence, radiation is applied from outside the cranium 3-6 weeks following surgery. The downside of this is that the radiation may damage healthy brain tissue. And, waiting several weeks can give the remaining bits of tumor the chance to re-establish themselves.

Instead, clinical trials through HonorHealth Research Institute are taking a different approach. Immediately following surgery, while the patient's brain is still exposed, small pieces of radioactive material are placed around the perimeter of the resection with a goal of killing any remaining cancer cells .

"Rather than have the surgeon close the incision on the patient, and apply radiation from the outside afterwards, we are instead placing tiny radioactive seeds, or particles, that give a very high dose of immediate pin-point radiation to the area of the brain that is at risk for the cancer coming back. We're treating them immediately," said Dr. Sckolnik, co-investigator for the Surgically Targeted Radiation Therapy (STaRT) clinical trials at the Research Institute.

These GammaTiles are being used in cases of primary tumors, those that originate in the brain, as well as metastatic tumors, those that arise elsewhere – from a lung or breast cancer, for example – and then migrate, or spread, to the brain.

INSIDE THE OPERATING ROOM

When the neurosurgeon is done resecting the tumor as best as possible, the radiation oncologist's team steps in to apply 2-12 radioactive tiles, which look like small white sponges about the size of a thumbnail. The number of sponges depends on what is needed to expose radiation to the area at risk for the cancer returning. The neurosurgeon then returns and closes the incision. The radioactive tiles stay inside the brain, remaining radioactive for about 90 days before becoming inert. Patients awake and breathe on their own within 30-60 minutes following surgery. Typically, these patients are discharged from the hospital in 1 to 4 days.

The first clinical trials using radioactive tiles through the Research Institute started nearly 3 years ago, followed by a second that started in October, and a third that started in November, said Dr. Sckolnik. "What has proven most successful is reducing the side effects; reducing the number of cognitive deficits, skin irritations, swelling, pain. It's a significant improvement."

So far, nearly 40 patients have been enrolled for surgeries taking place at HonorHealth Scottsdale Osborn Medical Center under the administration of the Bob Bove' Neuroscience Institute and the HonorHealth Research Institute. It is the only such clinical site in the Valley. There are about 40 sites elsewhere, including Tucson.

HONORHEALTH RESEARCH INSTITUTE IS IN GOOD COMPANY

"Our center has a relatively small footprint, but we are treating patients on these clinical trials along with MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center," Dr. Sckolnik said. "It's kind of exciting to be enrolling and treating patients with the latest and greatest technology and have it in the patient's own backyard so they don't need to leave Arizona and go someplace else. They can just have this right here."

Dr. Sckolnik said the clinical trials are working: "It's been going really well. We're finding that patients are tolerating the treatment well, and that many are not having recurrences down the road. It does really change the outcome significantly for these patients."

Dr. Amar Thosani

Research initiatives in Gastroenterology, Bariatrics and Endoscopy hold the promise of living longer and healthier

While the brain, lungs and heart are marvels of evolutionary efficiency, it could be argued that the most intricately interlaced trellis of large veins and arteries, multi-purpose organs and connecting tubes is the complicated set of bodily functions known as the gastrointestinal system.

The gastrointestinal system is a relatively simple idea: a long tube through the abdomen, starting at the mouth, where food is absorbed. Multiple organs, such as the liver and the pancreas, add tremendous complexity to the system. Movement of the organs, called peristalsis, combined with digestive enzymes, help to break foods into simple building blocks that are easily absorbed across the intestines. However, this complex system can fail at times leading to blockages, inflammatory process, and cancers.

Gastroenterology and endoscopy seek a diagnosis for many of these problems, and often offer relatively simple solutions that may treat even major gastrointestinal issues. Using endoscopy, or a tube with a light source that is able to illuminate the inside of the GI tract in precise detail, we are able to not only diagnose disease but provide therapy through this small tube in a minimally invasive manner.

By definition, Endoscopy is the use of a light source to see inside an organ. Besides a light, the Endoscopy tool uses a camera for observation and a micro tool for therapy. Coupled with endoscopic ultrasound, the tool can also manipulate organs adjacent to the GI tract, including the pancreas, liver and bile duct. The tool can be used to remove small stones and insert stents. If the cancer is caught early, Endoscopy can be used to resect small tumors from throughout the digestive system.

PLANNING FOR THE FUTURE

The HonorHealth Interventional Endoscopy group is on the cutting edge of endoscopic procedures to provide the highest level of care to the community. The ultimate goal is to establish the *Center for Interventional Endoscopy,* expected to open in 2025 on the campus of HonorHealth Scottsdale Shea Medical Center. This center will focus on clinical care, education, and research to advance the field of interventional endoscopy in Phoenix and Scottsdale.

Dr. Amar Thosani, a board certified interventional gastroenterologist, said the idea of the center was a collaboration between Honor Health and Interventional Endoscopy Associates, led by Drs. Teodor Pitea and Rawad Mounzer.

"One day, we came together and started talking about the things that we want to do professionally in a place that we want to build and work at for the rest of our careers," said Dr. Thosani, whose medical focus is the management of endobariatrics, hepatobiliary and pancreatic diseases, GERD, and the endosurgical treatment of complex gastrointestinal conditions.

> Significant new clinical trials include one that will focus on creating a blood test for pre-cancerous colon growths, and another that will treat the lining of the upper intestine to reduce calorie absorption and reduce blood-sugar levels.

Just as Barrow Neurological Institute has built a reputation for advanced brain care, the three doctors foresee the *Center for Interventional Endoscopy* becoming the go-to facility for specialty endoscopic care.

"Our goal for this center is to make it the premier destination in the southwest for patients seeking the highest level of interventional endoscopy; a place in the Valley patients can identify with when they seek out this care," Dr. Thosani said.

Building on the foundations established by Dr. James Swain, medical director of GI/Bariatrics Research Division at HonorHealth Research Institute, Dr. Thosani said the center will be the cornerstone of a gastroenterology research initiative, partnering with industry to advance the field of endoscopy. With the large patient volume and endoscopic talent, this center will be at the forefront of innovation in collaboration with the Honor Health Research Institute.

TWO MAJOR STUDIES ON THE HORIZON

One of two major clinical trials that will start this year includes one colossal study that hopes to enroll nearly 500 patients. Researchers want to create a blood test that could identify biomarkers associated with large polyps – called advanced adenomas – in the colon. Often during routine colonoscopies, these pre-cancerous growths require a second procedure to be removed. Better screening could eliminate multiple procedures.

Known as the Fractyl trial, another study of as many as 50 enrollees could help patients with type 2 diabetes by using a catheter to steam-burn the lining of the upper intestine in an effort to both reduce absorption of calories and to change the production of hormones to reduce blood-sugar levels. This procedure will only be offered initially in Arizona at HonorHealth Research Institute.

MULTISPECIALTY RESEARCH

New tool assists surgeons in reducing the amount of normal tissue removed during breast conservation surgery

Fluorescent imaging helps enable breast surgeons to delineate whether normal breast tissue is free of tumors

Surgical removal of breast cancer can be done in two ways: mastectomy or breast conserving therapy.

A Mastectomy removes all the breast tissue but can potentially come with physical and psychological complications. Therefore, many women elect to pursue breast conservation.

Breast conservation involves removing the cancer and a small margin of normal tissue surrounding the tumor. The challenge in breast conservation surgery is that it is extremely difficult to know if all the cancer has been removed at the time of the surgery. Assessing these margins at the edge of the tumor is performed by a pathologist, following surgery. If the margins of the resection have tumor at the edge, then a subsequent surgery is required. Nearly 25% of breast cancer surgeries result in a second surgery.

"It is not a precise science," said S. Brenda Moorthy, D.O., HonorHealth's Medical Director for Breast Surgery. " 'Positive margins' in the context of cancer surgery are considered unfavorable because it indicates that there may be remaining cancer cells in the surrounding tissue, increasing the risk of cancer returning. Breast surgeons are always seeking out methods to reduce positive margins. Several devices and technologies have been developed with the goal of reducing positive margin rates, but to date, none of them have been sufficiently accurate."

In addition to the physical toll that a second surgery takes, there are also psychological and financial impacts.

To address this challenge, an upcoming phase I trial at HonorHealth will use substances that fluoresce under certain light wavelengths and can help differentiate normal tissue versus cancerous tissue. As part of the HonorHealth Research Institute's Multispecialty Research Division, Dr. Moorthy is the principal investigator of the Integro Theranostics breast cancer clinical trial, in which she will use a specialized imaging tool to detect breast cancer tissue that has been dyed with a fluorescent imaging agent known as LS301. The Research Institute is the first to offer this clinical trial in Arizona.

If effective, the imaging tool along with the fluorescent imaging agents and associated medical devices may enable surgeons to readily see and remove cancerous tissue. Such a tool could assist in the accurate, real-time visualization of cancer tissue which could facilitate a more complete removal of cancer during surgery.

LS301 consists of a small peptide and a dye that emits near-infrared light (NIR). This peptide binds to the activated form of its target protein in cancer cells, aggregating the NIR emitting dye within diseased tissues and cancer-positive lymph nodes. The small molecular size enables LS301 to quickly reach cancer cells. Prior use of LS301 has demonstrated safety in humans.

The fluorescent dye is injected a couple of hours before surgery so the patient can be monitored for any potential side effects.

Dr. Moorthy then uses SPY-PHY, a hand-held advanced imaging system, that detects the tagged fluorescent dye, distinguishing the abnormal from the normal breast tissue.

This technology provides real-time guidance during surgery, empowering surgeons to make more informed decisions, and potentially reducing the need for additional procedures.

Dr. Moorthy has worked with HonorHealth for 18 years and helped establish HonorHealth's system of breast cancer care.

Dr. S. Brenda Moorthy with imaging device

Pulmonary hypertension is focus of aggressive HonorHealth Research Institute study

Meth use is often the cause of high blood pressure in the lungs, leading to heart failure; clinical trial looks to remodel heart and lungs

Therese Sargent

Pulmonary hypertension is a condition of high blood pressure in the lungs brought on by pulmonary vascular disease, which causes the arteries in the lungs to narrow.

It is a progressive, life-threatening condition in which the right side of the heart, which pumps blood to the lungs for oxygenation, is overworked as it tries to push blood through constricted blood vessels.

It is an underdiagnosed and undertreated condition that often is not recognized until its advanced stages, when it can lead to hospitalization in the intensive care unit, requiring continuous intravenous medication, and eventually heart failure and death.

Among the causes of pulmonary hypertension are: genetic predisposition, auto-immune diseases, a thickening of the lung tissue brought on by HIV and COVID, and severe liver disease, including hepatitis C and porto-pulmonary hypertension, in which the liver's portal veins get clogged, increasing blood pressure in the liver and lungs.

Whatever the cause, patients are not being diagnosed quickly enough.

"These patients have often gone to two, three, four specialists before they get a diagnosis, because nobody is really looking for this," said Therese Sargent, N.P., who heads the HonorHealth Pulmonary Hypertension Clinic at John C. Lincoln Medical Center in north-central Phoenix's Sunnyslope district. "We are the only clinic dedicated to pulmonary hypertension in Arizona."

Sargent noted that half of the patients die within 3-5 years of the onset of symptoms; and live only 2.7 years following diagnosis: "We're not getting these patients identified because people don't know to look for it. We're getting these patients when they are really quite sick."

3,300 PATIENTS SEEN SINCE CLINIC OPENED

Her clinic treats 12-15 new patients each month, currently has 300 patients on therapy and has seen 3,300 individuals during 23,000 patient encounters since the clinic opened four years ago.

One of the most common causes of pulmonary hypertension is the use and abuse of methamphetamines, accounting for nearly 1 in 3 patients at Sargent's clinic.

While meth conjures up images of those on the margins of society, Sargent said a surprising number of meth users are actually high-functioning individuals. They aren't addicted and use meth for a variety of reasons – everything from trying to maintain two or three jobs to make ends meet for their families, to those with mental health issues like ADD (attention deficit disorder) and ADHD (attention deficit hyperactivity disorder) who found it difficult to get their medications during the COVID pandemic and started using meth as a substitute.

"They're using methamphetamine to self-medicate," said Sargent, who brought pulmonary hypertension studies and treatment to HonorHealth. "It's amazing how many patients aren't addicted; they are using it for something else."

Meanwhile, there is a lack of resources for addiction counseling and treatment, many are declined for in-patient detoxification programs because their heart is too sick, and typically addicts are not eligible for clinical trials.

ARTISAN CLINICAL TRIAL PROVIDES HOPE

Sargent says there is hope for many patients through her clinic's ARTISAN trial, administered under the umbrella of the HonorHealth Research Institute. The trial is an in-patient study in which pulmonary hypertension patients are aggressively treated with rapidly increasing doses of a prostacyclin treatment called Remodulin, also known as treprostinil.

The hope is that the medication will lessen the severity of the disease, slow its progression, stop inflammatory responses and open up tiny blood vessels in the lungs. Once the blood pressure is reduced and the heart's right ventricle is remodeled, patients could be sent home with a medication pump, eventually transitioning to an oral medication, adding years to their lives with increased productivity and higher quality of life.

"My hopes are that we shed light on early aggressive treatment to slow down this process that has such a high mortality rate," Sargent said.

IMAGING

New AI assisted ultrasound device tested for the first time at HonorHealth Research Institute

Device potentially saves lives by making faster assessments of the heart's condition and quickly measuring all of the heart's components

Dr. Robert Burke

Successful cardiac treatments begin with a cardiologist's ability to see through the body and into the heart.

HonorHealth Research Institute is the first in the nation to use a new ultrasound imaging technology enhanced by Artificial Intelligence.

It's an advantage that could mean the difference of life or death.

"When somebody hits the emergency room, they'll get an electrocardiogram that tells us if they are having a heart attack, or not," said Robert Burke, M.D., a Mayo Clinic-trained cardiologist with 20 years' experience, and HonorHealth's Director of Non-Invasive Cardio Diagnostics.

"Then we need to look at the heart and be able to directly visualize what is going on inside. What's the heart's size? How is it functioning? What do the valves look like? How are they functioning? All of that needs to be assessed immediately, and we do that with ultrasound technology," said Dr. Burke, adding: "It's not invasive. There's no radiation. And everything is done in real time."

Since the 1960s, medicine has been perfecting ways to send ultrasonic waves through the body. Like a submarine's sonar, ultrasound creates images based on how those waves bounce back.

Augmented by AI, advanced ultrasound imaging can more quickly discern the heart and lock on to all its components – atria, ventricles, valves, the aorta – almost instantly assessing size and conducting measurements needed to treat the patient.

KEY CLINICAL TRIAL CONDUCTED AT RESEARCH INSTITUTE

Dr. Burke is the principal investigator for the ACUSON clinical trial, in which he is testing the Siemens Origin imaging device against other imaging devices currently in use.

The device is a premium ultrasound imaging console based on next generation acoustic technologies that enable never-before-seen detail during examinations. The system's AI software uses advanced algorithms and an expert database of real clinical cases to recognize anatomical patterns and perform automated measurements.

"With the Research Institute, we have the ability to initiate research programs like this that allow us to get new technology for our patients prior to it being commercially available," said Dr. Burke, who already is predicting that the device will supplant existing imaging technologies. "It allows us to remain on the cutting-edge of science and technology within cardiology, which is a great perk for our patients."

Dr. Burke demonstrated the technology in September during a meeting of the European Society of Cardiology. It received FDA approval in November and is now commercially available, following the original trial conducted at HonorHealth.

Previous imaging technology was slower, with many manual steps needed to acquire an image, identify its components and take measurements.

"It was more time consuming and more repetitive. It was more wear and tear on the sonographers, the technicians who conduct ultrasounds," he said. "The primary reason we lose sonographers is because of overuse (repetitive motion syndrome) injuries."

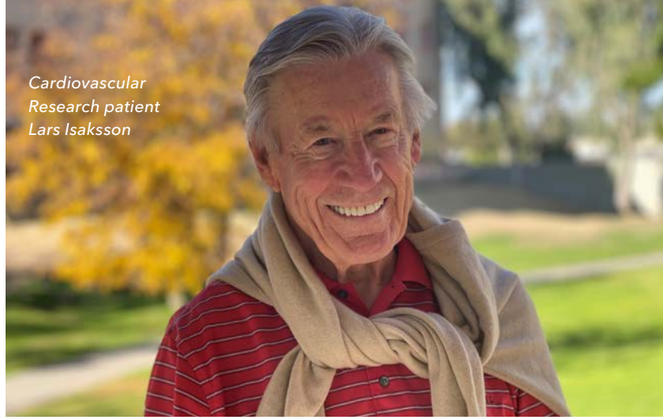
With the addition of AI, Dr. Burke said, the new technology "minimizes the number of touches (and) it's smart enough to know not only what you are looking at, but then will automatically give the baseline measurements. It's infinitely quicker than what we currently have. It is definitely the next step forward in doing cardiac imaging. This technology will replace the current technology that is out there."

AI ULTRASOUND WILL NOT REPLACE SKILLED TECHS

Still, it will not replace the skilled sonographers who are trained to know what they are looking at, he said: "It will get rid of some of their manual labor, and hopefully make them more efficient and keep them safer and provide for a more consistent assessment of what is going on with the heart."

Ultrasound is not as expensive, cumbersome or time consuming as MRI or CT scans. It does not require radiation or contrast dye, which can cause kidney problems, kidney failure and produce an allergic reaction, he said. Plus, ultrasound devices are portable; they can be taken to the patient's bedside.

Dr. Burke used the device in June during a cardiac catheterization procedure, in which the advanced ultrasound helped guide the placement of an aortic valve. Known as TAVR (transcatheter aortic valve replacement), the procedure involves the cardiologist threading a catheter through a large artery in the groin and up into the heart, without the need of opening up the patient's chest, as in open-heart surgery.



Cardiovascular Research patient Lars Isaksson

Scottsdale man is first to undergo heart procedure assisted by Artificial Intelligence-guided ultrasound

Heart valve replacement similar to one performed on iconic Rolling Stones front man Mick Jagger

In June, patient Lars Isaksson became the first person in the nation to receive an artificial heart valve in a procedure using ultrasound imaging enhanced by Artificial Intelligence.

Lars underwent a procedure known as a transcatheter aortic valve replacement, or TAVR, which is the replacement of the valve governing the flow of blood from the heart to the aorta, the large artery that funnels blood to the body.

Lars, an 81-year-old Scottsdale resident, had open-heart surgery a decade earlier to replace this same valve, but it eventually failed, resulting in shortness of breath and an inability to get around and do what he wanted: "I felt lousy. I was very tired," Lars said.

This time, a non-surgical, catheter-based procedure was used in which the valve is placed through a large leg vein up into the heart.

To guide the placement of the new artificial valve, Dr. Robert Burke, HonorHealth's Director of Non-Invasive Cardio Diagnostics, used a new type of ultrasound that uses AI to lock onto images of the heart and its internal components. Dr. Burke did this by placing the ultrasound device down the esophagus, or throat, viewing the backside of the heart to better see any aortic valve problems.

"Using this new echo, we were able to go in and guide the replacement with the new valve," Dr. Burke said. "The valve functioned great. There was no leak. He (Lars) had a significant clinical improvement over night. He did wonderfully and he's doing great."

"I feel great," echoed Lars, six months after the procedure.

Though unassisted by AI, a similar TAVR procedure was used in 2019 when Rolling Stones lead singer Mick Jagger had to temporarily stop the band's tour because the 75-year-old front man needed a new aortic heart valve. Jagger's replacement was no less successful. Four months later, the Stones' concert tour resumed along with Jagger's seemingly unstoppable voice and dance moves.

Second Annual HonorHealth Research Institute Symposium features informative and inspirational talks by faculty and patients

HonorHealth Research Institute, a world-class destination for advanced biomedical research and patient care, conducted its second annual Symposium in August with the theme "Better, Together."

The symposium was attended by more than 230 Research Institute colleagues, and included presentations by Institute leadership, the research division directors of the Institute's five Research Divisions, grateful patient stories, the impact of philanthropy, staff projects, employee milestones, research rockstar awards and keynote speaker Gunnar Esiason, the son of NFL quarterback Boomer Esiason, who once played for the Arizona Cardinals. Gunnar shared his journey with cystic fibrosis and passion for early-stage drug development and patient empowerment.

Advancing tomorrow's health innovations today, HonorHealth Research Institute offers unique new treatments through the rigors of clinical trials. The institute's more than 250 active clinical studies are based on the latest laboratory discoveries, and often represent the first time in the world patients are eligible to receive these new treatments.

Accomplishing THE Incredible

HonorHealth Research Institute By The Numbers

In 2023, the HonorHealth Research Institute impacted the value and quality of patient care by accelerating innovation, while seamlessly integrating the best science.

NUMBER OF RESEARCH PARTICIPANTS WITHIN THE LAST FIVE YEARS

4,742

NUMBER OF CLINICAL TRIALS IN 2023

255

82

NEW CLINICAL TRIALS INITIATED IN 2023

2,696

RESEARCH INSTITUTE CLINIC PATIENT VISITS IN 2023

FIVE

FDA NOVEL THERAPY APPROVALS IN 2023

NUMBER OF ACTIVE INVESTIGATORS IN 2023

180

172

NUMBER OF PUBLICATIONS IN 2023

CARDIOVASCULAR RESEARCH

Clinical Trials | **51**

New Clinical Trials Initiated | **20**

HRI Clinic Patient Visits | **256**

FDA Novel Therapy Approvals | **3**

Active Investigators | **59**

Publications | **35**

Research Participants Within The Last Five Years | **311**

MULTISPECIALTY RESEARCH

Clinical Trials | **6**

New Clinical Trials Initiated | **4**

HRI Clinic Patient Visits | **227**

FDA Novel Therapy Approvals | **1**

Active Investigators | **20**

Research Participants Within The Last Five Years | **1,678**

CANCER RESEARCH

Clinical Trials | **138**

New Clinical Trials Initiated | **28**

HRI Clinic Patient Visits | **879**

Active Investigators | **23**

Publications | **90**

Research Participants Within The Last Five Years | **2,262**

NEUROSCIENCE RESEARCH

Clinical Trials | **53**

New Clinical Trials Initiated | **27**

HRI Clinic Patient Visits | **258**

FDA Novel Therapy Approvals | **1**

Active Investigators | **65**

Publications | **47**

Research Participants Within The Last Five Years | **369**

GI/BARIATRICS RESEARCH

Clinical Trials | **7**

New Clinical Trials Initiated | **3**

HRI Clinic Patient Visits | **1,076**

Active Investigators | **13**

Research Participants Within The Last Five Years | **122**

A VISION OF
THE FUTURE FROM

Dr. Michael Gordon, HonorHealth Research Institute Chief Medical Officer

Like wildfire, the medical disciplines embraced by the HonorHealth Research Institute have grown and expanded since its founding in 2005. We are now comprised of five research divisions: Cancer, Cardiovascular, GI/Bariatrics, Neuroscience and Multispecialty.

While most of our divisions have established well-defined programs, our Multispecialty Research Division provides a type of catch-all for emerging areas of research as it builds relationships with groups of investigators who are entering into the research domain.

As we approach our 20th anniversary in 2025, we are expanding the value of research across the entire HonorHealth system. The Research Institute's commitment has been to not only continue to support and uphold the infrastructure for our major programs, but also to be on the lookout for new opportunities.

In 2022, we added research into pulmonary care and in 2023, we expanded to include studies in rheumatology. Through the advancement of these new opportunities, we can ultimately expand the number of divisions within the Institute as evidence by the GI/Bariatrics division's emergence from the Multispecialty Division previously.

As each of our divisions increase in size, their ability to influence direct patient care becomes of greater value to our community. Our work engages and enthralls individuals who see the benefit in our ability to deliver the best high-quality care. We see HonorHealth Research Institute's influence on the quality of care delivered to the patients we serve across the Valley, and around the world, encouraging patients to choose HonorHealth.

The goal for the coming two years is for each of the divisions to develop thematically defined research objectives, and then to find the points of interface between the different divisions where themes are concurrent or complementary.

Young Guns: Up and coming researchers

One of the Institute's prime goals is to support career development of both seasoned veterans and new investigators. In doing so, we provide them with not only the resources to conduct research, but also the connections to optimize their research interests and the infrastructure to be able to move forward with novel investigator-initiated clinical trials.

Our hope is that emerging new investigators will represent a core element in continuing to make research a critical component of the delivery of care to our patients.

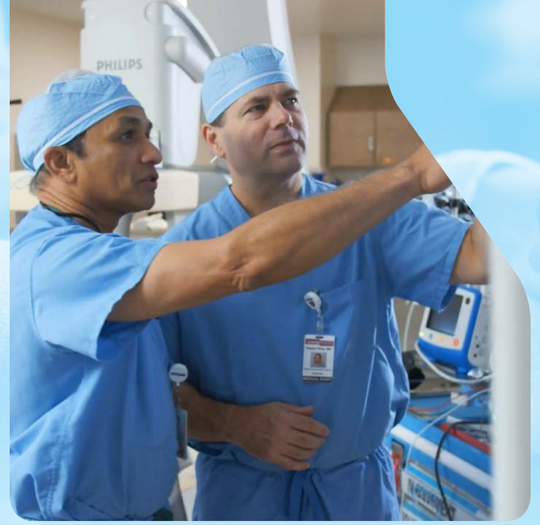
The Future: Growth of personnel

As our research activities increase and our infrastructure expands, we are committed to reinforcing our capacity to conduct research by bringing in the best and brightest colleagues in nursing, IT, research infrastructure and compliance, so that we can create a longitudinally successful program that will stand strong as HonorHealth itself expands.

Foundation: Providing needed resources

The HonorHealth Foundation continues to be the backbone of the Research Institute's activities. We've continued to benefit from the Foundation's ability to familiarize the community with research as a critical component to optimizing the delivery of care. And in so doing, secure the resources that allow us to diversify and expand the breadth of our endeavors.

Michael Gordon, M.D.
Chief Medical Officer
HonorHealth Research Institute



Discovery and innovation are made possible through the generosity of HonorHealth supporters

You can help accelerate breakthrough treatments and discoveries that improve life for patients here and around the world with a gift through HonorHealth Foundation.

Designate your charitable contribution to support the HonorHealth Research Institute and 100% goes to the program you choose.

Help us expand scientific knowledge and improve lives for generations to come.

For more information, or to make your gift today, please visit HonorHealthFoundation.org/HRI or contact HonorHealth Foundation at 480-587-5000.

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