HONORHEALTH®
Research Institute

Elevating Research

Annual Report 2024

ELEVATING **RESEARCH**

Innovative advances provide immediate impact and hope for patients

James Swain, M.D.

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ELEVATING **RESEARCH**

Our overarching goal as HonorHealth Research Institute nears its 20th anniversary and looks toward the future

During our first two decades, HonorHealth Research Institute has excelled, becoming a national and international hub of precision medicine, where compassionate patient care merges with state-of-the-art science to produce the highest levels of patient outcomes.

Examples of this great work appear on every page of this *2024 Annual Report*, from new techniques to fight cancer, to protecting our healthcare workers from radiation, to finding new ways to prevent stroke, recurrent brain tumors, childhood diabetes and more.

We reached these heights by *Elevating Research* on every level and in every medical discipline in which we engage. Throughout this report, you will see examples of new treatments, new devices, new technologies; all designed to make a substantial difference in the lives of our patients.

These efforts have laid the groundwork for further achievements, extending and elevating our scientific research, from basic science to translational and clinical pursuits.

Among the many significant achievements this past year was October's announcement of a partnership between HonorHealth and Arizona State University, in which HonorHealth will serve as the primary clinical partner for ASU's new School of Medicine and Advanced Medical Engineering.

One of the reasons we were selected by ASU for this venture is because of the great work that has been done over the past two decades here at HonorHealth Research Institute. It's a strong foundation for future research and education.

This HonorHealth-ASU partnership did not come about by chance; we earned it. For nine years in a row, *U.S. News & World Report* has recognized ASU as the nation's #1 university for innovation.

Likewise, HonorHealth Research Institute is known for its innovation; for our ability to do things first, not only in the development of innovative new drugs, but in creating innovative devices, techniques and standards of care. These innovations provide an immediate impact, giving hope and answers to our patients and their families.

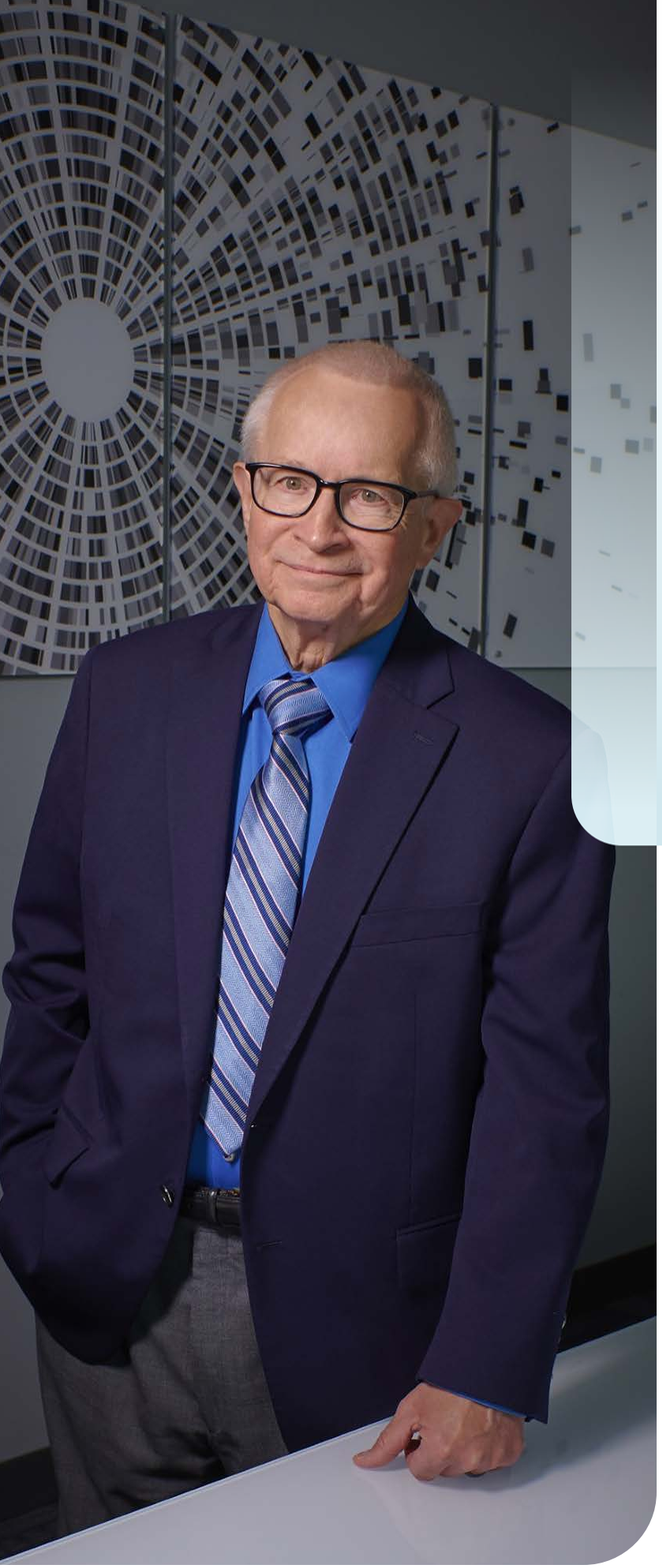
I am really proud of these accomplishments. The Institute has matured to a place where it is being recognized for its great impact in the world of healthcare, and we are positioned for the future for growth and for what I envision as an explosion of scientific discovery.

Our successes also help attract even more high-caliber talent, new technology and raise the quality of care for patients. And we continue our strong affiliations with dozens of academic institutions, private sector businesses, government agencies and others who will help take us to new heights.

We have created a unique environment. We strive to be that partner-of-choice for our sponsors, for granting agencies, for donors – for patients. We have cared for patients from all 50 states and from more than 30 nations across the globe.

At the same time, we have attracted among the world's best researchers, physicians and other healthcare workers. They could choose to go anywhere in the world, but they choose to be here – because we are *Elevating Research*.

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



'DVH' MAKES LAST CALL AT HONORHEALTH RESEARCH INSTITUTE

Dr. Daniel D. Von Hoff leaves a remarkable legacy of saved lives, following a career of collaborative caring

After a half-century medical career, the good works of Dr. Daniel D. Von Hoff, one of the world's leading experts in pancreatic cancer, could easily fill several books.

Holding the Virginia G. Piper Distinguished Chair in Innovative Cancer Research at HonorHealth was just one of the many well-earned titles and accolades that enabled "DVH" – as he is known – to act as a national and international treasure; a human clearing house of innovative ideas about how to better treat patients with difficult cancers.

He helped lead teams that developed 11 major cancer treatments, including three of the four leading breakthroughs in late-stage pancreas cancer. He watched and witnessed, and acted as a medium, as patients with cancers once thought of as death sentences – including lung, breast, melanoma and even pancreatic cancers – now see tremendous extensions in longevity and quality of life.

You might think someone nearing the end of such a storied career might linger on all their accomplishments. But ask DVH what is most important today in the world of biotechnology, and he will tell you it's not about him; it's about the potential for a bright medical future and the tremendous need for new generations of highly skilled doctors and nurses.

He leaves his highest praise for the employees of HonorHealth Research Institute, noting that if he ever needed medical care he would look nowhere else.

"HonorHealth Research Institute, number one, provides excellent care, and it's in incredibly good hands," he said. "I'm really convinced of these people – because they really provide super care – that they can take care of me, anytime. That's the highest praise (coming from a doctor or nurse). They do a great job every day. The research is important, but the way that you do it, and the caring, you just can't duplicate it. It's really special here."

56 ideas for new clinical trials

And for those who remain, DVH has a gift: 56 new ideas ready for clinical trials, resulting from an explosion of new technologies; the development of new drugs and new devices, with a unifying focus on prevention and early diagnostics based on new blood, urine and saliva tests.

And understanding the complexities and interrelationships of disease.

For example, lung cancer is the most common of the major deadly cancers. Yet, most lung cancer patients actually die of brain cancer after their malignancy has spread from the lung to the brain. So, to fight lung cancer, there is a need for better drugs to fight brain cancer; ones made of small enough molecules that they can get across the blood-brain barrier – the web of extra small capillaries that surrounds and protects the brain from many toxins.

Or identifying a new class of cancer cells called "zombie killers", which are tumor cells that evade the immune system by switching to a zombie-like state. For these, DVH says, there is a new class of antibodies that targets these zombie cancer cells known as senolytics, drugs that also will play an important role in longevity.

Being part of the magic

Because DVH has been around long enough and produced at such a high level within the medical community, he has for decades been a go-to guy when other physicians and scientists want to float a new idea.

"I'm glad to be the person that people can call on and say, 'Hey, we got this new mechanism. What do you think?' That's the way things work. You publish something, and people say, 'Hey!' That's why I keep telling young investigators to keep publishing so they know you're there, and people will bring you things. That's part of the magic."

DVH is always riding new waves. A dozen years ago, he was at the forefront of a decade-long set of life-saving cancer discoveries based on helping the patient's own immune system fight disease. After all, a lifetime of cancer surveillance, searching for and destroying cancer cells, along with eliminating other diseases, is what the immune system has always done best.

Now, to prevent and stop cancer in its early stages, DVH's focus is on inflammation: "The next big frontier is decreasing inflammation of all types." From skin cancer to ulcerative colitis: inflammation. Carcinogens: inflammation. "Inflammation is everything. It's our coronary arteries, probably Alzheimer's – it's everything that affects us as humans." And so, DVH is excited about a pipeline of new anti-inflammatory drugs.

Think we'll cure all cancers?

"The answer is, yes, I do, if we keep getting better at earlier detection," he said. "Survival has improved for every cancer, even pancreas cancer, within my short lifetime, for sure."

DVH has shown the international medical community that there is hope, even for patients with a disease as aggressive as pancreatic cancer: "It's still a bad disease. But now we know, that if you use these combination treatments, we can have more of an impact, and actually cure some people, if we can get to the disease earlier."

DVH maintains that there is tremendous hope for humanity's future.

"If the next 50 years are anything like what we're seeing now, we're going to cure a lot of cancers. Our grandchildren are going to be in a lot better shape than we were, no doubt."

But will there be enough talented collaborators? "My greatest worry is, how are we going to keep recruiting the doctors and nurses; recruiting the talent. It's just really tough."

DVH has certainly done his part, training more than 2,500 young doctors and nurse practitioners over the years in new therapy development. "They're all over the world," he said of his students. "It's really the most important thing; to train the next generation."

And what of DVH's future? Is he ready to retire from a lifetime of discovery?

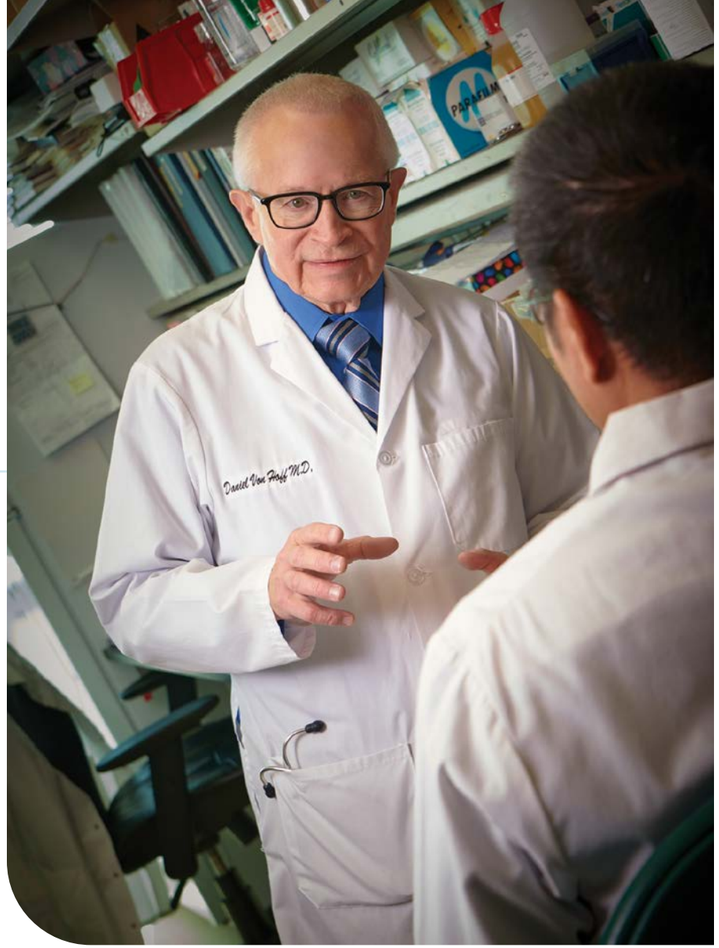
"I love it very much. It's the hardest thing ever, that I have to step away, but I realize that it's in terrific hands and I'm smiling because of it."

One of the greatest lessons DVH says he ever learned came from Randy Pausch, a professor of computer science who contracted pancreatic cancer and who penned an inspirational New York Times best seller titled, The Last Lecture.

"The most important thing," DVH said, "when you have something that you love so much, and you know you have to give it up, make sure it's in the hands of people who love it as much as you do."

DR. DANIEL D. VON HOFF

Accomplishments, Titles and Recognitions



Among the many key positions held by Daniel D. Von Hoff, M.D., F.A.C.P., FASCO, FAACR, are: Virginia G. Piper Distinguished Chair for Innovative Cancer Research at HonorHealth Research Institute; Distinguished Professor at the Translational Genomics Research Institute (TGen); Margaret Givan Larkin Endowed Chair in Developmental Cancer Therapeutics at Hoag Hospital; Medical Director of Research at McKesson Specialty Health; Chief Scientific Officer for US Oncology Research; Professor of Medicine at the University of Arizona School of Medicine, and at the Mayo Clinic in Scottsdale; Senior Consultant of Clinical Investigation at City of Hope.

Dr. Von Hoff and his colleagues were involved in the development of many FDA-approved agents, including: mitoxantrone, fludarabine, paclitaxel, docetaxel, gemcitabine, irinotecan, nelarabine, capecitabine, lapatinib, vismodegib, nab-paclitaxel, nal-IRI, pexidartinib and others.

Dr. Von Hoff has been involved in more than 425 clinical trials, secured 20 patents, and published nearly 800 scientific papers, more than 140 book chapters and nearly 1,200 abstracts.

He received the David A. Karnofsky Memorial Award from the American Society of Clinical Oncology (ASCO) for his outstanding contributions to cancer research, leading to significant improvement in patient care; and the American Association for Cancer Research (AACR) Distinguished Public Service Award in recognition of his extraordinary clinical research career and leadership in establishing the AACR/ASCO Methods in Clinical Cancer Research Workshop to educate and train young clinical investigators.

Dr. Von Hoff is the past President of AACR, the world's largest cancer research organization; a Fellow of the American College of Physicians; and a member and past board member of ASCO. An annual lecture has been created in his name by the AACR.

20 YEARS AND COUNTING

HonorHealth Research Institute continues to elevate science

Now in its 20th year, HonorHealth Research Institute continues to move forward with what CEO Mark Slater, Ph.D., describes as care, compassion and science.

In addition to its original focus on cancer, the Research Institute has expanded to cardiovascular studies, neurologic science, gastrointestinal and bariatric research, and a multispecialty division that includes numerous emerging fields of medical care.

Throughout, the Institute has maintained a consistently high level of achievement.

"I was drawn here because of the Institute's potential for having a tremendous impact on our patients and our local community," said Dr. Slater, who also serves as Vice President of Research for all of HonorHealth. "I envisioned a place that had the best of both worlds – the academic world and the community in which we practice – driven by rigorous science, great minds, the access to technology from universities and the private sector, but also the closeness to the patient and to exceptional care."

Dr. Slater conceived of an Institute that would minimize bureaucracy and be fast, nimble and efficient.

"That's how we developed an institute without walls, based on collaboration, focusing on the best science and best care, so that while we're breaking new ground with first-in-human clinical trials, we are also treating every individual the way we would want to be treated,'' he said.

This November, the Institute will celebrate its 20th anniversary with the theme: "The Best is Yet to Come."

Among the most exciting new developments is the Institute's recently created Center for Translational Science, which will translate the scientific discoveries made in the Institute's laboratories into new diagnostics and therapies, providing patients and their families with hope and answers.

The coming year also will see the flowering of a recently announced partnership in which the Institute will serve as the primary clinical affiliate for Arizona State University's new School of Medicine and Advanced Medical Engineering.

Michael Gordon, M.D., FASCO, the Institute's Chief Medical Officer, said these and other developments will further move the Institute toward a future in which new techniques, new therapeutics and new technologies developed through scientific research will result in better care for HonorHealth patients.

"HonorHealth Research Institute envisioned the opportunity to bring physicians closer into the fold by creating unique relationships so all physicians are welcome and focused on making scientific research the proverbial tip of the spear – the component that could sharply advance patient care in ways that a community-based hospital generally would not envision," Dr. Gordon said.

Dr. Slater agrees: "It's a very unique environment. We look to be that partner of choice for our sponsors, for granting agencies, for donors, who are all looking to advance the medical field as well as provide hope for our patients."

NETWORK RESEARCH PROGRAM EXPANDS RESEARCH INSTITUTE'S IMPACT

HonorHealth Research Institute's Network Research Program aligns research initiatives with HonorHealth's broader organizational goals, providing strategic guidance and ensuring efficient management of a diverse research portfolio.

In May 2024, the Research Program Manager (RPM) joined the team to strengthen Network Research and drive its growth. The RPM plays a vital role in integrating research efforts into established committees, including the Research, EBP, Development, Innovation (REDI) council, Research Quality Improvement Patient Safety (ResQIPS) Council, and the Deer Valley (DV) and John C. Lincoln (JCL) EBP and Research Councils. The RPM contributes to both the DV and JCL Interprofessional Practice Councils (IPPCs), creating opportunities to connect staff with projects across the network, and encouraging cross-campus and interdisciplinary collaboration.

These initiatives aim to enhance teamwork, overcome research challenges and streamline processes to improve project efficiency. The Network Research team is committed to supporting compliance, building strong partnerships with Research Institute collaborators, and championing the success of research initiatives.

In 2025, we aspire to foster greater interdisciplinary collaboration, expand HonorHealth's academic influence, strengthen engagement across the network, and advance impactful research that benefits our patients, the broader community, and scientific knowledge.

2024 Key Performance Indicators:

- Network Research Program newly established and launched.
- Network Research presentations: HonorHealth Research Institute Symposium, August 2024; and HonorHealth Clinical Research Festival, September 2024.
- RPM established as a voting member of REDI, ResQIPS, JCL and DV research councils.
- Stewarded or collaborated on nearly 50 projects across the network in 2024.
- Support of the multi-campus ANCC Magnet Recognition Program designation.

Justin Moser, M.D.

ELEVATING **CELL THERAPY**

HonorHealth Research Institute delivers Arizona's first commercial use of new TIL therapy for melanoma

This past year, for the first time in Arizona, patients with extensive melanoma cancer are being successfully treated outside a clinical trial at HonorHealth Research Institute with a new type of immunotherapy known as TIL (tumor infiltrating lymphocytes).

Melanoma is an aggressive cancer associated with melanin, the pigment that helps protect the body from excessive ultraviolet light, either from the sun or tanning beds. Melanin is what gives color to the eyes and skin. While melanoma may start on the skin, it often metastasizes, or spreads, to other parts of the body.

TILs are part of the body's natural immune system. They can recognize and fight specific tumors. Like tired soldiers, TIL cells can eventually weaken and begin losing the battle against cancer.

In TIL therapy, thousands of these cells are taken from a tumor. In a laboratory, they are enhanced and multiplied, creating millions of fortified immune cells that are then infused back into the patient, creating a resurgent "army" to fight the cancer.

"We know responses to TIL can be durable, with roughly half of all responses lasting two years or more," said Dr. Justin Moser, a melanoma specialist conducting clinical trials at HonorHealth Research Institute. Clinical trials conducted at the Research Institute helped lead to FDA approval of TIL therapy in February 2024.

CASE STUDY

TIL therapy is clearing up melanoma that had spread throughout patient's body

For the first time In Arizona, a patient with extensive melanoma cancer was successfully treated outside a clinical trial at HonorHealth Research Institute with a new type of immunotherapy known as TIL (tumor infiltrating lymphocytes).

Three years ago, Tena Hughes, a lifelong Phoenix resident, was about to board a plane for Uganda to fulfill a once-in-a-lifetime dream of seeing critically endangered mountain gorillas in the wilds of Africa. However, what at the time was a mandatory COVID test came back positive, and she was forced to stay home. She didn't know it at the time, but she would later attribute that test to saving her life.

Weeks later, Tena began suffering excruciating headaches. An exam in February 2021 showed she had several late-stage melanoma tumors that had spread from an unknown origin to her brain. Subsequent scans would show the cancer had also spread to her spleen and left lung. "I'd never seen it on my skin," Tena noted.

Over the next three years, she had numerous surgeries, radiation treatments and anti-cancer drugs to rid herself of the melanoma. She did not tolerate the drug therapy well and had to discontinue it. Eventually, the cancer would return and continue to spread.

Finding hope at the Research Institute

It was during lung surgery that Tena's doctor told her that if she didn't get on a comprehensive treatment plan, the cancer would continue to come back. The surgeon suggested Tena consider enrolling in clinical trials at HonorHealth Research Institute.

Almost instantly after the TIL treatment, Tena's tumors began shrinking.

"Within two days after receiving her TIL infusion, her tumors started shrinking, which is consistent with a quick, durable responses associated with TIL therapy," said Dr. Justin Moser, a melanoma specialist conducting clinical trials at the Research Institute.

Tena's treatment was the first commercial use of TIL in Arizona, following the FDA's commercial approval of the treatment.

Interestingly, Tena has actually been waiting for TIL therapy for nearly three years. Soon after she was initially diagnosed, she scrambled to learn all she could about her disease, eventually discovering a book, Life Force, about potential futuristic medical cures, including TIL therapy.

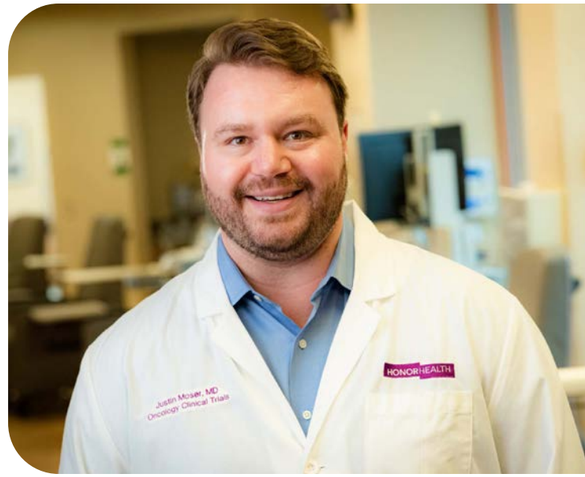
"I just dog-eared every chapter in that book," she said. "I told myself, 'If I stay alive long enough, this is going to be available to me.' As fate would have it, it was."

Writing book about her cancer journey

Tena, a mother of four sons who for years used her real estate license to buy, remodel and sell homes, said that she was told that if she had gone to Africa as she had originally planned, she might not have survived the trip.

Now, she is writing a book about her cancer journey, and because of the videos she's posted on social media about her disease and treatment, she was recently invited to share her story at a medical conference.

"There's been so many reasons why I feel I have a purpose here. My future, the way I see it, is helping other people," Tena said. "I think that's where I've been called; to help other people (by sharing) how I chose to combat my cancer through exercise, nutrition and mindset."



CASE STUDY

New TIL therapy controlled melanoma with a single knock-out blow for mother of three

Crystal Crowley contracted melanoma 11 years ago, but it wasn't until she arrived at HonorHealth Research Institute that she found freedom from this insidious and difficult-to-treat type of skin cancer.

Crystal has been through the cancer wringer. What started with a mole on the top of her head, eventually spread to her neck, lymph nodes, chest, lungs, lower back, brain and hip bone, decimating this wife and mother of three girls who once prided herself in being in peak physical condition.

Now, the former Physician's Assistant at Children's Hospital Colorado in Denver, has come full circle, regaining her health thanks to a new therapy offered by the Research Institute. Known as TIL (tumor infiltrating lymphocytes), this treatment relies on the body's own immune system to fight cancer.

"This therapy is probably the best option for patients with refractory melanoma, and it offers the potential for long-term disease control with a single treatment," said Justin Moser, M.D., an associate clinical investigator at the Institute's Oncology Research Division, who specializes in melanoma. Crystal's melanoma was considered refractory because it became resistant to the 18 previous cancer therapies she had undergone over more than a decade, including drug therapy, radiation and surgery.

Crystal was one of the few patients in the nation to receive this therapy as part of a clinical trial, and one of the first in Arizona to receive this form of TIL therapy. The Institute was the first in Arizona to offer the treatment under an expanded access clinical trial protocol and was the first in Arizona to offer this treatment commercially.

Crystal's challenging journey

Crystal's melanoma was almost eliminated once before. As she approached a 5-year mark of having no detectable cancer in July 2020, she felt a new bump on her neck above her left collar bone.

"That was so crushing at that time. We thought that I was cured and would never have to deal with this ever again. That was really very difficult," she recalled.

Then in March 2022, the cancer showed up in her lungs, an indication of stage 4 disease, Crystal said: "It was very disheartening. I was at one of the lowest places in my life."

By February 2023, the cancer spread to Crystal's brain, hip bone, additional lymph nodes in her neck and multiple nodules in her lungs.

"Once you've progressed through two or three lines of therapy, in general your melanoma is not considered curable. But we know from the study we did that roughly 30% of patients who receive TIL will have a response," Dr. Moser explained. "TIL is one of the few therapies that is able to provide long-term disease control for refractory melanoma, and the only one to do so in a single treatment."

This therapy consists of a melanoma tumor of at least 1.5 cm being 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, ready to attack the cancer.

'Best care I've ever received'

In September 2023, after connecting with Dr. Moser, Crystal underwent TIL treatment. She praised the HonorHealth staff for their expertise: "The nurses there were so phenomenal. I've been doing this a really long time, and this was the best care I've ever received in my life. They were empathetic and caring, and just amazing."

She received her first post-TIL cancer scan in December 2023 and only two tumors remained, one in her upper left chest and the other in her lower back. By March, her scans showed only one weakened tumor remained just below her left clavicle.

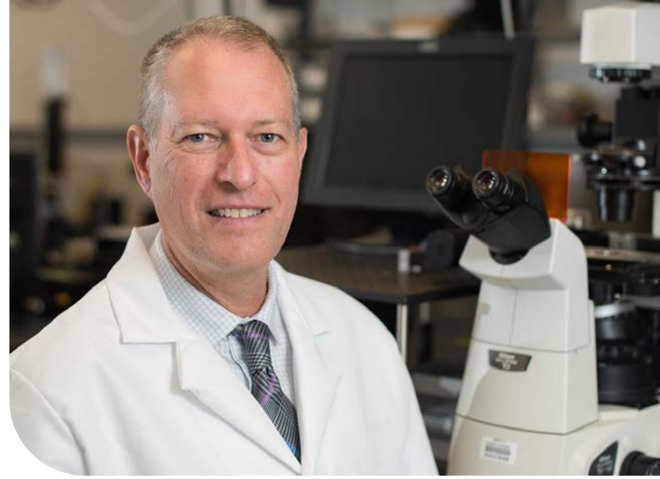
"I feel like I have a whole new lease on life because of this. It's just the greatest gift I've ever been given," said Crystal, who is back to working out, including weights, and running circles around her children. "The response that I've gotten is just beyond our wildest dreams. Getting back to doing the things I love has been phenomenal."

"I FEEL LIKE I HAVE A WHOLE NEW LEASE ON LIFE ... IT'S JUST THE GREATEST GIFT I'VE EVER BEEN GIVEN"

— CRYSTAL CROWLEY

ELEVATING
TECHNOLOGY

New NASA blood tests should speed diagnoses for HonorHealth Research Institute



Frederic Zenhausern, Ph.D., MBA

Technology designed to conduct simple-to-take blood tests for astronauts in the near-weightlessness of low Earth orbit may soon help HonorHealth Research Institute to speed up diagnoses of cancer patients here on Earth.

Launched in 2021, the *SpaceX Inspiration4* – with the first-ever all-civilian space crew – experimented with a new blood test developed in Arizona for NASA that can be administered by non-medical personnel, in near-zero gravity, producing immediate results without needing additional laboratory analysis, according to a study published in the journal *Nature*.

The blood test known as the Vertical Flow Immunoassay was developed by researchers at the University of Arizona College of Medicine – Phoenix. The test was designed to perform multiple rapid assessments of the physiological and molecular effects of time spent in space.

At the Research Institute in Scottsdale, the test could soon be used to quickly check on the health of patients, especially those undergoing immunotherapy or cellular therapy, which employ the use of CAR T and bispecific antibodies in the treatment of cancer.

Checking toxicities

"Some of our treatments, which activate the immune system, are associated with high-risk toxicity called Cytokine Release Syndrome (CRT), and central nervous system toxicity," said Michael S. Gordon, M.D., FASCO, Chief Medical Officer of HonorHealth Research Institute. Both types of toxicity can be severe and even life-threatening.

"Certain tests take up to two weeks to come back from the laboratory, which might negatively impact the ability to act to treat the patient," said Dr. Gordon. "Here, we have a technologically advanced test that can give you an at-the-bedside analysis."

Since August, when the Research Institute announced its intention to use this new technology to provide immediate monitoring and analysis of patient conditions, several types of cytokines have been successfully tested on this new platform.

"We are progressing quite well," said Frederic Zenhausern, Ph.D., MBA, a senior investigator at the Institute, who notes that the new technology has three distinct advantages: it can detect multiple biomarkers and analyze various disease states simultaneously; it provides more sensitive and precise measurements than previous technologies; and can even provide DNA analysis, providing molecular-level diagnostics.

"You need to monitor the patient very closely," said Dr. Zenhausern, who also is director of the Center for Applied NanoBioscience and Medicine at the UA medical school, where he led a team of students and faculty that designed the original test for NASA. He also was a co-senior author of the study published in *Nature*, one of the world's premier scientific journals.

"It was the first time that we could use that technique in space," said Dr. Zenhausern. "It's a very simple-to-use system and yet it allows us to do multiplex detection of various biomarkers."

Scientists analyzed dried blood spot samples that four astronauts collected before, during and after their spaceflight, monitoring antibodies against 80 different viruses.

Monitoring antibodies

Dr. Gordon said the Institute hopes to use the system to monitor CAR T antibodies in the treatment of blood cancers, including multiple myeloma, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia, but also to monitor bispecific antibodies in the treatment of multiple myeloma, non-Hodgkin's lymphoma, and – for the first time – in a solid tumor: small-cell lung cancer.

Earlier detection could allow for earlier intervention before toxicity arises, Dr. Gordon said, or it could indicate some patients who are at such a low risk for toxicities that they don't need to be kept and monitored in the hospital as long, perhaps even at all.

"Instead of sending blood to a central laboratory, something that could not be done in the midst of space exploration, it provides us with the same type of benefit at the patient's bedside," Dr. Gordon said. "We see ourselves as being in the right place at the right time to develop technologies such as this."

Rizwan Khawaja, M.D., MPH

ELEVATING **BLOOD CANCER RESEARCH**

HonorHealth Research Institute initiates a new clinical trial for types of lymphoma and leukemia

For the first time, HonorHealth Research Institute is offering a promising clinical trial for patients with specific types of lymphoma and leukemia blood cancers who no longer respond to current FDA-approved treatments.

M. Rizwan Khawaja, M.D., MPH, an Associate Clinical Investigator at the Research Institute's Oncology Research Division, is leading the trial, which is investigating a new way of controlling B-cell lymphomas and chronic lymphocytic leukemia (CLL) through the use of a daily pill, BGB-16673, made by the global oncology firm BeiGene. Lymphoma is a cancer associated with the lymphoid component of the immune system, and CLL is a cancer of lymphocytes circulating in the blood.

This year, lymphomas will take the lives of more than 21,000 Americans, and leukemias will kill another 23,000, making them among the nation's top 10 leading causes of cancer death. There is at the present time no cure for CLL and many types of lymphoma. Other treatment options can require extensive preparation, hospitalization and are associated with significant toxicities, explained Dr. Khawaja.

"Many elderly patients, or those with other medical problems, are not eligible for such intense therapies," he said. "The BGB-16673 trial aims to provide these patients with a simple treatment option to control their disease, with fewer side effects. And, it's a pill they can take at home."

Most common symptoms

Lymphoma and CLL mostly involve lymph nodes, which are part of the immune system and are present throughout the body.

Lymphoma can cause the lymph nodes to swell to the size of a grape or larger. Patients also present with unexplained fevers, night sweats, fatigue, and weight loss. Enlarged lymph nodes in the abdomen can press against nearby vital organs, such as the liver or kidneys, affecting their function and causing severe pain. Like other cancers, lymphoma can spread to other organs, such as the liver, spleen, bone marrow, and even the central nervous system.

For most patients, the cause of lymphoma is unclear. Sometimes it develops in cases where patients have compromised immune systems, such as when they: undergo transplants for other diseases; are on immunosuppressant drugs; contract an autoimmune disease; or have HIV/AIDS. Some other infections can also cause lymphoma.

Mechanism of action

A crucial protein in the formation of B-cell lymphoma and CLL is called Bruton's tyrosine kinase (BTK).

"There are already BTK inhibitor drugs approved by FDA to control lymphoma and CLL," said Dr. Khawaja, "but the problem occurs when the BTK protein develops mutations, leading to resistance to BTK inhibitors.

"Instead, the drug BGB-16673 is a BTK degrader," he explained. "This drug destroys that protein completely, overcoming any attempt by the cancer to mutate and evade treatment. Even among patients whose cancer was resistant to BTK inhibitors, this drug (BGB-16673) has so far shown really promising results."

B-cell lymphomas account for about 85% of the more than 80,000 cases of non-Hodgkin lymphomas (NHL) annually in the U.S.

Additionally, there are over 20,000 cases of CLL nationwide each year.

ELEVATING **COLORECTAL CANCER RESEARCH**

Combination immunotherapy has positive results against common colon cancer in HonorHealth Research Institute clinical trial

HonorHealth Research Institute is part of an international effort to create one of the first immunotherapy drug combinations to successfully treat colorectal cancer, which after lung cancer is the nation's second leading cause of cancer-related death.

An estimated 53,000 Americans will die this year from colorectal cancer. Though generally seen in older adults, it is becoming more frequent among younger adults, those age 20-50, who generally are not screened for this often aggressive cancer. Like all cancers, early detection leads to more-successful patient outcomes.

"This was the first time immunotherapy has really been shown to be working in this most-common type of colon cancer," said Sunil Sharma, M.D., MBA, who was recently named Chief of Translational Research and Drug Discovery at HonorHealth Research Institute.

Dr. Sharma is one of the authors of a three-year study of 148 patients worldwide published in the journal Nature Medicine, documenting the positive effects of a combination treatment of two immunotherapy drugs, botensilimab plus balstilimab, on microsatellite stable metastatic colorectal cancer, which is the most common type of colon cancer, and one that has generally not been responsive to immunotherapy.

The Research Institute was one of the first of the study's more than dozen major research sites, and one with among the highest enrollments.

'Immunotherapies can work'

"We've shown the proof of principle that immunotherapies can work against this disease. This creates a backbone upon which we can hopefully build even better immunotherapies," said Dr. Sharma. "It sets us up to do even more combinations on top of this platform that seems to be working. Hopefully we can actually have even better results in the future."

Sunil Sharma, M.D., MBA

This drug combination was well-tolerated by patients in the study.

Michael S. Gordon, M.D., FASCO, Chief Medical Officer of HonorHealth Research Institute, noted that the Research Institute is focused on working towards earlier diagnosis in this patient population, using more up-to-date screening technologies to forestall this epidemic of cancer.

How immunotherapy works

Dr. Gordon, who is principal investigator for the study and also an author of the research paper – Botensilimab plus balstilimab in relapsed/refractory microsatellite stable metastatic colorectal cancer: a phase 1 trial – said the combination immunotherapy is able to overcome the cancer's attempt to hijack the body's own immune system.

The combination of the two antibodies in the therapy sidestep what are known as immune checkpoint blockades, natural elements that ordinarily prevent immune cells from attacking healthy tissue, but which cancer cells also use to cloak themselves.

"If the immune system gets overly aggressive, it can attack the patient's own body. But if the immune system is shut down, it can't fight the cancer," Dr. Gordon explained. "With this therapy, you wind up with larger numbers of highly effective immune T cells that can attack the cancer."

The study found that the combination immunotherapy was most effective against cancer that had not metastasized, or spread, to the liver, citing this as a possible future target of investigation.

"For those patients without liver metastases, there appears to be a higher response rate and a prolonged interval of ongoing stable response lasting several years in some patients in contrast to those patients with liver metastases," said Dr. Gordon, adding, "There is a unique opportunity for further research."

Alarming incidence among young adults

A concern of Dr. Sharma was the surprising number of younger adults who are, for unknown reasons, developing this disease.

According to the paper in Nature Medicine: "Alarmingly, from 1995 to 2019, the number of patients under the age of 55 who were diagnosed with CRC (colorectal cancer) in the United States nearly doubled."

ELEVATING **RADIATION PROTECTION**

HonorHealth hospitals among nation's first to install radiation shields for all cardiovascular interventions

HonorHealth hospitals are among the nation's first equipped with advanced radiation protection shields at all campuses that perform cardiovascular interventions, in which low-level X-ray radiation is used to guide catheters during non-surgical procedures.

Such shields have already been studied and used for nearly three years through the HonorHealth Research Institute, where published clinical trial results have convincingly demonstrated physician radiation exposure reduced to near undetectable levels. Researchers have concluded this may potentially reduce the risk of cancer and orthopedic injuries associated with repetitive exposure to low-level radiation.

"We've been using it successfully, and now we've made the decision to do this more broadly at multiple HonorHealth campuses," said David G. Rizik, M.D., medical director of the Research Institute's Cardiovascular Research Division, a world leader in studies tracing the dangers of occupational radiation exposure among medical professionals.

A multiple Emmy Award winner, Dr. Rizik is the narrator and a co-producer of an hour-long documentary, *Scattered Denial: The Occupational Dangers of Radiation*, which was aired nationwide this past summer on PBS.

In addition to documented links to various cancers suffered by interventional laboratory personnel, Dr. Rizik said, they also are at risk for various repetitive orthopedic injuries from wearing heavy leaded aprons, the current protection intended to reduce radiation exposure.

"We have people sustaining orthopedic injury every day," he said. "We have women in the catheterization laboratory who want a safer environment in case they get pregnant."

HonorHealth leadership supports move

"HonorHealth is proud to be a national leader in efforts to protect the health and safety of our workforce, and securing these radiation shields is just the latest example of our commitment," said HonorHealth CEO Todd LaPorte.

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

Mark A. Slater, Ph.D., CEO of the HonorHealth Research Institute, praised the adoption of the new radiation protection systems and the Institute's groundbreaking research, led by Dr. Rizik, in documenting the dangers faced by medical personnel.

David G. Rizik, M.D.

"While we've seen dramatic technological advances in heart treatments, there have been few improvements in our ability to protect our physicians and nurses from the deleterious effects of radiation exposure," said Dr. Slater, who also is HonorHealth's vice president of research. "Accelerating medical innovation to enhance safety, quality of care, and patient outcomes is core to the mission of HonorHealth Research Institute."

Shields at four more hospitals

Radiation shields have been available during clinical trials at the Institute, headquartered at HonorHealth's Scottsdale Shea Medical Center.

Additional shields are installed, or planned for installation, at four additional HonorHealth medical centers: John C. Lincoln, Deer Valley, Scottsdale Osborn and Scottsdale Thompson Peak.

HonorHealth has applied to the Arizona Department of Health Services to approve using the radiation shields without also wearing the traditional heavy lead aprons, which are suspected of causing knee, hip and back injuries. Additional studies of apron use are planned at the Institute.

"HonorHealth is making a most powerful statement that they are prioritizing workplace safety; physician and nurse wellbeing and safety," Dr. Rizik said. "It's a message not only for Arizona, but also for the rest of the nation."

Documentary led by HonorHealth Research Institute focuses on injuries to doctors and nurses working in cardiology

HonorHealth Research Institute's David G. Rizik, M.D., narrated and co-produced a documentary focused on radiation and orthopedic injuries suffered by doctors and nurses who work in cardiac catheterization laboratories, where they apply the very latest non-surgical technologies to treat the world's leading cause of death, heart disease.

Scattered Denial: The Occupational Dangers of Radiation aired this past summer on PBS stations across the nation. It can be viewed at www.ScatteredDenial.org.

"The 'scatter' is radiation scatter, and 'denial' is how we've denied that this was happening until it was too late," said Dr. Rizik, research director of the Cardiovascular Research Division at HonorHealth Research Institute, the world's leader in studies tracing the dangers of occupational radiation exposure among medical professionals, and how they can be protected by a new class of radiation shields designed specifically for their labs.

The documentary includes interviews with pioneers of interventional cardiac catheterization, in which multiple x-rays are used to navigate stents, valves, pacemakers and other devices through the vascular system and into and around the heart to restore patient health without resorting to the risks posed by open-heart surgery.

One doctor notes that the only ones exposed to more radiation than those working in catheterization labs are those working in nuclear power plants. Others talk about the injuries they've received from radiation exposure, including tumors up and down their heads, necks, faces, arms and legs. Most of the damage is to the left side of the body, which faces the most radiation exposure, Dr. Rizik said.

It includes footage of the internationally esteemed Edward B. Diethrich, M.D., a pioneering Phoenix cardiothoracic surgeon, who founded the Arizona Heart Institute and who died from a brain tumor in 2017: "I felt: This radiation cannot hurt me."

Other interviews with female doctors and nurses talk about the threat radiation exposure could pose to their ability to bear healthy children.

The documentary also traces the risks doctors, nurses and other staff technicians face by repeatedly wearing 20-30-pound lead aprons, the current standard protection against radiation, which doctors say left them with ruptured disks, paralysis and other potentially career-ending orthopedic injuries.

Risks outweighed by patient benefit

Dr. Rizik said the medical professionals who began interventional cardiology 40 and 50 years ago had little thought of the potential side effects of radiation or the orthopedic risks of wearing heavy lead protection. Instead, they focused almost exclusively on their ability to provide ever-improving patient care.

"Their obsession was patient care: new and novel technologies, research and finding ways to treat patients. They didn't think at all about radiation, and certainly didn't think about the downstream consequences of wearing a lead apron," he said. "We were thoroughly obsessed with being good at what we do."

Dr. Rizik compares their zeal with that of young football players, who risk physical and cognitive injuries from constant physical impacts: "They're only focused on scoring touchdowns and sacking quarterbacks."

Research Institute leads the way

In March 2023, a published scientific study led by Dr. Rizik resulted in HonorHealth Research Institute becoming 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.

Dr. Rizik describes the new documentary as "a personal journey; a journey of discovery: What haven't we done to protect our doctors and nurses. That's what Scattered Denial is."

To see the PBS documentary, "Scattered Denial," go to www.ScatteredDenial.org

ELEVATING **HEART HEALTH RESEARCH**

HonorHealth Research Institute study uses new programing for pacemakers to control high blood pressure

Rahul Doshi, M.D.

A programing algorithm, being tested by HonorHealth Research Institute for those patients with new or recently installed pacemakers, is designed so the device not only provides a steady heartbeat but also controls high blood pressure.

A clinical trial called BACKBEAT (BradycArdia paCemaKer for Blood prEssure treAtmenT) aims to use Medtronic's Astra and Azure model pacemakers to not only treat slow heart rates but also delivers electrical pulses stimulating the heart in a way that reduces the patient's blood pressure.

The clinical trial is for patients who require a pacemaker, but who no longer respond well to their current high blood pressure medication.

"It's a huge, huge health problem," said Rahul Doshi, M.D., an electrophysiologist in the Research Institute's Cardiovascular Research Division. "Many patients who require a pacemaker have uncontrolled high blood pressure".

The electrical system of the heart works by coordinating the function of the upper chambers (the atria) and the lower chambers (the ventricles) in order to function as a pump delivering blood to the whole body.

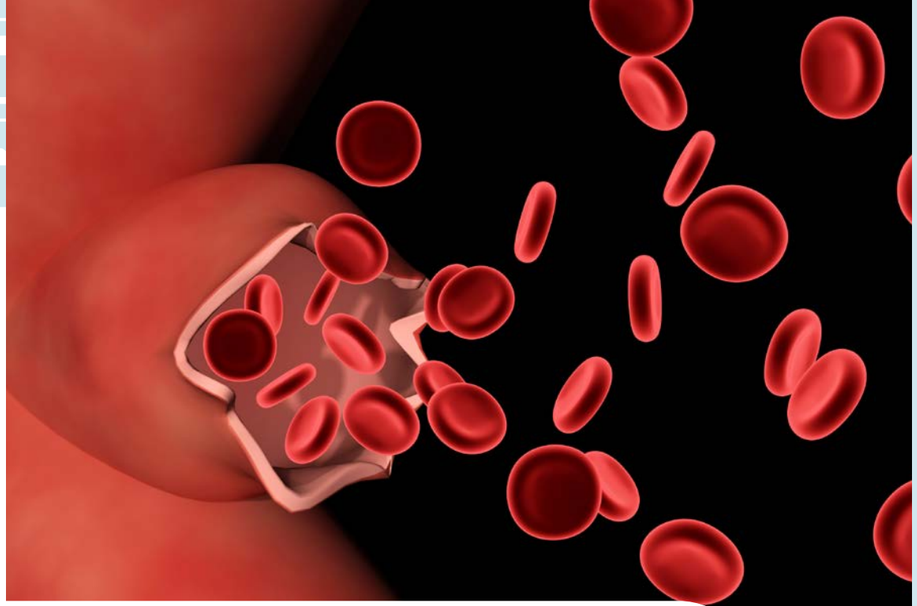
By varying the timing of heart beats for the upper and lower chambers, the new algorithm can lower blood pressure by several mechanisms and have a lasting benefit. Reducing high blood pressure lowers the risk of life-threatening strokes, heart attacks and cardiovascular diseases.

Method provides lasting benefit

"This therapy works automatically without the patient or the doctor having to do anything. You just turn it on, and it works," Dr. Doshi said. "It's very promising. It's been demonstrated in all of our preliminary data that, not only does this work, but it also has a lasting benefit if you continue the therapy."

Previous attempts to cultivate a non-drug method of controlling high blood pressure did not provide a lasting effect, Dr. Doshi said.

Watch Dr. Doshi's Arizona Horizon interview, go to tinyurl.com/2s3wkkty



ELEVATING **BLOOD VESSEL RESEARCH**

New treatment at HonorHealth Research Institute aims to prevent potential growth of Abdominal Aortic Aneurysms

More than 1 million Americans are at risk of dying from the rupture of the main artery carrying oxygenated blood from the heart to the legs, but a clinical study at HonorHealth Research Institute could help prevent such catastrophic failures.

As people get older, the wall of the abdominal aorta tends to weaken, thin and stretch, allowing this crucial artery to expand causing aneurysms.

Through the Research Institute's clinical trial called "stAAAble" (AAA stands for Abdominal Aortic Aneurysms), patients with an AAA diameter of 3.5 to 5 cm are treated with a single dose of PGG (1,2,3,4,6-pentagalloyl glucose). The drug is applied to the inner walls of the aneurysm using the Nectero Endovascular Aneurysm Stabilization Treatment (Nectero EAST®) System, which uses a catheter to move the drug through a large blood vessel in the leg up into the abdominal aorta.

The procedure takes less than an hour to complete and leaves no implant behind. Doctors then use scans to monitor the treated aorta, taking images at least every 6 months.

"This treatment could prove to be a paradigm shift in the management of aortic aneurysms. Current standard of care is to monitor patients with small aneurysms and only treat aneurysms once they've reached a size threshold (5-5.5cm)," said Hasan Aldailami, M.D., MBA, HonorHealth's Chief and Network Director of Vascular and Endovascular Surgery.

"Nectero will hopefully allow us to halt the growth of small aneurysms and obviate the need for more extensive repairs that also carry more risk to the patients, and can be complex," said Dr. Aldailami, who also is Co-Director of Aortic Surgery. "We are proud to be amongst the first in the United States to perform this procedure."

Ruptured aneurysms carry high mortality

A burst aorta is a violent and often deadly event that causes massive internal bleeding. According to one study in The British Journal of Surgery, death occurs in 81% of people having a rupture of an AAA, with 32% dying before reaching a hospital.

Worldwide, an estimated 8% of men older than 65 have AAA, and the incidence is four times higher in men than in women. In the U.S., about 1.1 million patients are estimated to have AAAs sized 3.5 to 5 cm in diameter. Besides age, risk factors include cigarette smoking, high blood pressure, coronary artery disease and dyslipidemia, a metabolic disorder characterized by abnormally high or low amounts of blood lipids.

HonorHealth Research Institute is the only site in Arizona offering this clinical trial, part of an international study of nearly 400 patients sponsored by the manufacturer, Tempe, Ariz.-based Nectero Medical.

ELEVATING **STROKE PREVENTION**

HonorHealth Research Institute is first in the Southwest to implant new stroke prevention stent

Hasan Aldailami, M.D., MBA

A patient at HonorHealth Research Institute is one of the first in the nation – and the first in Arizona and the Southwest – to undergo a non-surgical, catheter-based procedure with a new type of stroke-prevention stent that eliminates blockages in neck arteries that could potentially cause a deadly stoke by depriving the brain of oxygen.

The Neuroguard Integrated Embolic Protection (IEP) system is an experimental treatment for carotid artery stenosis, also known as carotid artery disease, a condition in which fatty-waxy deposits known as plaque builds up and blocks the normal flow of blood in the large arteries on either side of the neck. Left untreated, this condition can lead to stroke with severe complications, which could include death.

"HonorHealth is always on the forefront of surgical technology. We were an early adopter of trans-carotid stenting and have helped improve the technique," said Hasan Aldailami, M.D., MBA, HonorHealth's Chief and Network Director of Vascular and Endovascular Surgery, and Co-Director of Aortic Surgery. "This device/treatment algorithm allows us to further refine the procedure and make it even safer for our patients."

Designed by Raleigh, N.C.-based Contego Medical Inc., the *Neuroguard IEP* 3-in-1 carotid stent and post-dilation balloon system is designed to deliver a self-expanding carotid artery stent while using a special filter to prevent emboli (blockage) debris from reaching the brain. The stent is made of nitinol, a superelastic nickel-titanium metal alloy that is ideal for creating flexible endoscopic devices that can navigate narrow areas in the body and transform into a rigid shape when needed.

The first patient to undergo the procedure as part of the Research Institute's Performance III clinical trial is Roslyn "Sunny" Gomes of Glendale, Ariz., who has suffered from peripheral artery disease for years. She already has three stents in her heart and so many stents and replacement arteries in both her legs that she's lost count.

A previous scan some years ago had shown a partial blockage of her right carotid artery, but a recent set of scans showed it was 85% blocked, making her a good candidate for the new clinical trial.

"I feel a lot better today than I have," said Sunny, 76, days after her procedure.

HonorHealth Research Institute is one of 30 sites worldwide to offer the device. Patients are monitored for 6 months.

Amar Thosani, M.D.

ELEVATING **DIABETES TREATMENTS**

HonorHealth Research Institute trial explores a method for type 2 diabetes patients to cease taking daily insulin shots

An experimental procedure at HonorHealth Research Institute could potentially wean patients with type 2 diabetes off the need to inject insulin by returning a key segment of the intestine to its natural state.

The Revitalize study will test the effectiveness of a tool called Revita, which is designed to remodel the lining of the duodenum, the segment of the small intestine that connects the stomach to the rest of the gastrointestinal (GI) tract. The goal is to return the 10- to 15-inch-long duodenum to its natural function of helping to maintain the body's blood-sugar balance, thereby decreasing or eliminating the need for daily injections of insulin.

The procedure – in which the damaged lining, or mucosa, of the duodenum is ablated, or burned away, by superheated water – has the potential to significantly improve the health of those who suffer with type 2 diabetes, which currently sickens more than 30 million Americans.

Minimizing medications

"We're trying to change how we treat diabetes," said James Swain, M.D., medical director of the Research Institute's GI/Bariatrics Research Division and the principal investigator supervising the Revitalize study.

"The more insulin you take, the more insulin you need. So, we're trying to break that cycle," Dr. Swain added. "Revitalize is a new way to tackle diabetes without medications. We're trying to alter the physiology to improve diabetic control."

HonorHealth's Shea campus

The Revitalize procedure will be conducted at HonorHealth's Scottsdale Shea Medical Center by Amar Thosani, M.D., a leading specialist in interventional endoscopy and a board certified gastroenterologist. The first procedure as part of this clinical trial was performed June 6.

The lining of the duodenum can become damaged or altered over time due to multiple genetic and environmental factors, including a chronic diet of high-fat, high-sugar foods, explained Dr. Thosani.

"We're hoping to burn that mucosa tissue – denude it – and then have it grow back into normal properly functioning tissue," he said.

To be eligible for the Revitalize clinical trial, patients must be: diagnosed with type 2 diabetes, aged 21-70, and on a stable daily dose of insulin. Only a limited number of patients will be enrolled through the Institute for this study, which will last 1 to 2 years, depending on whether the patient initially receives the actual procedure, or is randomly assigned first to a comparative placebo process before undergoing the actual procedure.

According to the CDC: more than one in 10 Americans are diagnosed with type 2 diabetes, and another four in 10 are at risk. Diabetes disproportionately affects Hispanics, Native Americans and African Americans. About 1.4 million new cases are diagnosed annually in the U.S.

ELEVATING **CHILDREN'S DIABETES**

HonorHealth Research Institute offers first-of-its-kind Type 2 diabetes clinical trial for children ages 10-17

A first-of-its kind clinical trial is being offered by HonorHealth Research Institute for children and teenagers – ages 10-17 – with Type 2 diabetes that may enable them to control their disease with just one injection a week.

A medication, LY3209590, would strive to keep these children's blood-sugar levels more stable, avoiding the fluctuating blood-sugar levels that can result with daily injections of currently FDA approved Type 2 diabetes medications.

By switching from a daily injection to a weekly shot, there may also be an opportunity to reduce the children's pain and bruising as well as the number of infections that can result from daily shots. Plus, a general reduction in the hassle that goes with the storing, prepping and administering of daily insulin shots versus a single weekly injection.

"This will provide a more controlled release of medication over a week's time to keep the release steady without the use of an insulin pump. Instead of doing it seven times a week, you do it once a week," said James Swain, M.D., medical director of the Research Institute's GI/Bariatrics Research Division, and the principal investigator of the I8H-MC-BDDB study, sponsored by Cambridge, Mass.-based Eli Lilly and Company.

"This will be the first study to evaluate LY3209590 in pediatric patients with Type 2 diabetes," said Dr. Swain, adding that a once-a-week insulin such as LY3209590 may help to overcome commonly observed difficulties in initiating and adhering to insulin therapy. LY3200590 has been successfully tested in three studies of diabetic adults, resulting in excellent glycemic control, according to Dr. Swain.

Both the children and their parents would be compensated for their participation in the trial.

Other participant qualifications

In addition to the age restrictions (ages 10-17), participants must have HbA1c levels (a long-term indicator of blood sugar levels) of between 6.5% and 9.5%, and not have taken insulin within the past 3 months.

Qualifying participants will receive a single injection of LY3209590, followed by blood tests and other procedures at subsequent clinical visits, some in-home visits, plus a follow-up phone call. The study drug and any tests that are required as part of the study will be provided at no cost.

Type 2 diabetes in children is a chronic disease that affects the way the body processes sugar. Without treatment, the disorder causes sugar to build up in the bloodstream, which can lead to serious long-term health consequences.

The condition has multiple causes, said Dr. Swain, including genetic predispositions, excess weight and insulin resistance: "They may be naturally producing insulin but they're not sensitive to it, so they need more insulin to drive the sugars down."

James Swain, M.D., interviewed on Arizona's Family

From left to right: John Wanebo, M.D., Amir Azadi, M.D., Steven Sckolnik, M.D.

ELEVATING **BRAIN CANCER TREATMENT**

Radiation tiles help reduce side effects of removing brain tumors

Location, location, location.

What applies to real estate, can be said of brain surgery, especially when it comes to removing cancerous tumors. Every minute piece of brain matter can impact the patient's memory, cognitive abilities, coordination and motor control.

Surgeons try to remove as much cancer as possible without harming healthy brain tissue. Malignant tentacles that branch out from the tumor into healthy tissue mean that in most cases it will be impractical to remove some cancer.

For years, physicians have relied on external radiation to clean up remaining cancer cells. But even today's precision-guided external radiation can cause unintended brain damage. Plus, the brain requires weeks of post-surgical recovery before external radiation treatment can even begin. In that time, nearly half of all tumors begin to regrow.

Instead, researchers affiliated with the Neuroscience Research Division of HonorHealth Research Institute are using small radiation "GammaTiles" to line the cavity left by removing the tumor so the cancerous cells can get treatment far more quickly.

"When they remove the tumor, we place the Tiles inside the cavity where the tumor had been," said neuro-oncologist Amir Azadi, M.D., the medical oncologist for two current clinical trials:

- One for patients with newly diagnosed glioblastomas, the most aggressive and common type of cancer that originates in the brain.
- Another for patients with newly diagnosed metastatic brain tumors, in which the cancer has spread to the brain from some other organ, such as the lung or breast.

"Every single cell is critical to neurologic functions," said Dr. Azadi, who specializes in the diagnosis and treatment of brain, head and neck tumors.

Brain tumors: as big as baseballs

Brain tumors can range in size from ping pong balls to baseballs. It often takes six to eight of the quarter-size tiles to cover the cavity left by the tumor's removal. Each tile contains four seeds, each the size of a grain of rice, containing the radioactive element cesium-131, which has a relatively short half-life of about nine days. The radiation is essentially inert after about 60 days.

"The brain is like real estate. It's all about location. Every millimeter is important, so you can't be as aggressive" as with other cancer resections, said neurosurgeon John Wanebo, M.D., director of surgical neuro-oncology and cerebrovascular surgery at HonorHealth Osborn Medical Center.

Surgeons must be especially careful not to cut too close to parts of the brain that control speech, strength and motor functions (such as walking or working with your hands), he said. These require saving larger margins of healthy tissue around the edges of the tumor to help ensure no ultra-critical parts of the brain are removed.

Dr. Wanebo, who has performed more than 7,000 operations and more than 1,500 brain tumor resections, often uses colored dyes on the tumors to help ensure he removes as much as the cancer as possible before the radiation tiles are inserted.

"The Tiles provide an ability to treat the edges of a tumor with high-dose radiation immediately after a resection. Overall, I think these patients do better because they're getting high-dose radiation exactly where they need it," said Dr. Wanebo, adding that the average survival after diagnosis for glioblastoma is currently only about 15 months. "We hope this will improve the longevity of these patients."

ELEVATING **PAIN RESEARCH**

HonorHealth joins Wake Forest in search to minimize pain resulting from anti-cancer chemotherapies

While modern anti-cancer treatments may seemingly work miracles, in many instances providing enhanced survival in both early and late stage disease, a common complaint remains nerve pain, numbness or tingling in the feet and hands. This condition is called neuropathy.

Caused by nerve damage, Chemotherapy-Induced Peripheral Neuropathy (CIPN) can be a persistent condition, impacting patients for years. This condition is being addressed by a collaborative team from HonorHealth Research Institute and Wake Forest University School of Medicine.

While often treated with medications, this initiative is not employing a device or additional drugs. They are conducting a clinical trial using a program called painTRAINER, a web-based platform for delivering pain coping skills training (PCST) for patients with CIPN.

"The idea is to find non-pharmacological ways to manage pain," said Todd Levine, M.D., medical director of the Research Institute's Neuroscience Research Division. "You get pain when the nerves are sick, and they send the wrong kind of signal."

Dr. Levine said there are three classes of anti-pain medications, each with their own drawbacks:

- **Epilepsy medicines –** These decrease electrical activity, in the brain and wherever pain originates. "They're good for nerve pain, but they're not selective. So, they also decrease the signals that the nerves in your brain send, causing dizzy, dopy stupid," Dr. Levine said, and these side effects become more difficult to manage as patients get older.
- **Antidepressant medications –** These block the perception of pain, but among the debilitating side effects are weight gain, mood changes, and sleep disruption.
- **Opiates –** These can be somewhat effective but are extremely addictive.

In all cases, Dr. Levine said, they only reduce pain by about half, at best, and none address the actual causes of pain.

He recommends instead a combination of diet, exercise and self-reprogramming of how the patient senses pain; to dismiss those nerve signals that don't indicate an acute injury, such as a broken arm.

Training like Tibetan monks

"You teach the brain not to be bothered by the (neuropathy) pain as much. We're trying to retrain the brain to say, 'I can ignore that.' The alternative is Cognitive Behavioral Therapy, CBT: retraining your brain not to be bothered by the pain signals," said Dr. Levine, who likens the discipline to that of Tibetan monks, walking across hot coals who don't feel their feet burning. "Their feet are on fire, but they can block their perception of pain."

CBT can be expensive and often is not covered by insurance.

The internet-delivered painTRAINER intervention employs techniques of CBT, but because the treatment is self-administered (no therapist is required) it is administered without expense and with the ease of being able to conduct the therapy online at any time and place the patient chooses.

The painTRAINER program was developed with findings from the National Institutes of Health and already has been validated for treatment of numerous chronic pain conditions.

"Patients tolerated it well," said Dr. Levine, noting that it has been used in association with other conditions to treat pain. "It was easy for them to learn, and they had significant reductions in pain."

> ***"The idea is to find non-pharmacological ways to manage pain"***
>
> — Dr. Todd Levine, medical director of the Institute's Neuroscience Research Division

If it proves effective for CIPN patients, painTRAINER could potentially benefit tens of thousands of cancer patients and possibly be rolled out for use in other cases of chemically induced neuropathy, such as with diabetes and HIV/AIDS.

"We want to be innovative and deliver better ways to treat patients. Avoiding medication would be a great way we could treat these conditions," Dr. Levine said.

Wake Forest collaboration

One of the nation's experts in using painTRAINER is Don Penzien, Ph.D., a professor of Psychiatry and Behavioral Medicine at Wake Forest, who is working as a consultant for the Institute.

"CIPN is among the most difficult of pain problems to treat," and can lead to self-isolation and depression, said Dr. Penzien, an expert in chronic pain and headache research.

"It (painTRAINER) may not necessarily eliminate the pain they experience, but it's likely to have an impact on quality of life by reducing suffering; reducing pain-related impairments," he said. "They get as much, or more, benefit from being able to get on with their lives, and doing things and getting back out again, instead of being home and suffering."

The painTRAINER mimics the work of a therapist using a highly interactive and tailored experience based on questions asked via the computer, creating such a connection with its users that most said they felt the program understood them, said Dr. Penzien, adding that many patients said they hadn't realized how much they had given up; how much they weren't living.

This pilot study will involve 26 patients conducting eight 30-minute sessions. If the pilot is successful, the study will be expanded to a larger clinical trial with hundreds of patients. A Spanish-language version is in the works.

"For people who choose to do it, it actually tends to make quite a difference in their life," Dr. Penzien said. "It's not a cure, but it can make quite a difference."

Paramvir Sidhu, M.D.

ELEVATING
LUPUS INVESTIGATIONS

HonorHealth Research Institute elevates Rheumatology through Multispecialty Research Division clinical trial

An autoimmune disease known as Lupus gets its name from the skin scarring it produces, which for some victims looks as if they've been ravaged by wolves.

Through the 1800s, these patients were subject to ridicule and scorn, discriminated against, especially women whose symptoms were seen as signs of "hysteria," which at the time was a euphemism to explain a wide range of physical and mental ailments. Some of these patients were even locked away in asylums out of ignorance of what was actually causing their condition.

Lacking proper medical care, these patients often died of kidney failure, the organs most often affected by Lupus. To this day, kidney failure remains a leading cause of death among Lupus patients.

Unlike past centuries, modern medicine can now properly diagnose this disease, which results from an out-of-control immune system attacking its own healthy tissues. As in other autoimmune conditions, the immune system can lose its ability to distinguish between healthy tissue and diseases of bacteria and viruses.

Even now, diagnosis can be difficult, and many of the drugs used to treat Lupus have significant side effects.

It wasn't until the 1970s when some of the first significant Lupus clinical trials began by a team of immunology experts at the National Institutes of Health, including Dr. Anthony Fauci, the now-retired NIH scientist most famous for his work in battling HIV/AIDS and COVID-19. The NIH team showed for the first time how Lupus patients could survive kidney disease, using an anti-cancer drug called cyclophosphamide. Unfortunately, this medication is highly toxic and kills the immune system's white blood cells. It has also been linked to bladder cancer and leukemia.

HonorHealth starts own clinical trials

"What we're trying to do is to find specific medications that only affect the bad immune cells – lymphocytes that are damaging your own tissues – and spare the other lymphocytes we need to fight infections," said Paramvir Sidhu, M.D., the principal investigator in the first Rheumatology clinical trial under the Multispecialty Research Division of HonorHealth Research Institute.

Dr. Sidhu, who also is HonorHealth's medical director of Rheumatology, is part of an international study analyzing the safety and effectiveness of a drug called Upadacitinib for patients with Systemic Lupus Erythematosus (SLE), the technical name for Lupus.

"We hope this drug will work more quickly, be more effective and have less side effects," said Dr. Sidhu, a board-certified rheumatologist with special interest in Lupus, Osteoporosis, Psoriatic Arthritis and Rheumatoid Arthritis. "Our hope is to eventually have specific, targeted medications for Lupus, and other similar autoimmune diseases, that work quickly and stop the disease process before it damages any organs."

Possible causes of Lupus and other autoimmune diseases range from genetic predispositions to hormonal malfunction to environmental triggers, such as smoking and infections. Lupus remains one of the top 10 causes of death among young women. Survival often depends on how soon it is diagnosed and treated.

Partnering with ASU and UA

A high-level goal of Dr. Sidhu's is to elevate HonorHealth's studies to the national forefront though the Research Institute's new affiliations with Arizona State University's College of Medicine and Advanced Medical Engineering, and also the University of Arizona's new Center for Advanced Molecular and Immunological Therapies.

The human immune system is not only critical in fighting infections but also is responsible for a multitude of other functions, such as disposal of aging cells and eliminating tumor cells that give rise to cancers.

"We hope this drug will work more quickly, be more effective and have less side effects"

— Dr. Paramvir Sidhu

Dr. Jonathan Moore and Dr. Suchitra Pilli are 'Rising Stars' in the Multispecialty Research Division

Pulmonary Hypertension, the diagnosis of those patients with high blood pressure in the arteries of their lungs, is about to get more attention at HonorHealth Research Institute with the additions of Dr. Jonathan Moore and Dr. Suchitra Pilli.

These 'Rising Stars' are part of the newest pursuit in clinical trials for the Research Institute's Multispecialty Research Division.

Here are their stories:

ELEVATING **PULMONARY HYPERTENSION**

DR. JONATHAN MOORE POSITIONS HONORHEALTH RESEARCH INSTITUTE TO STUDY HIGH BLOOD PRESSURE IN THE LUNGS

Pulmonary hypertension is a debilitating condition in which there is excessive blood pressure in the arteries of the lungs. There are a variety of causes, especially involving the body's connective tissues, and not the least of which is the illicit use of methamphetamine.

Patients, who range from teenagers to individuals more than 100 years old, often exhibit fatigue, shortness of breath, weight gain, and are exercise intolerant.

Jonathan Moore, M.D., a pulmonologist and critical care physician, hopes to make a significant difference in the lives of this patient population as the new director of the HonorHealth Pulmonary Hypertension Program.

For example, a 21-year-old patient with right ventricular heart failure is now back to normal.

"She's going to concerts. She's going back to work. She has no symptoms and she's tolerating her medications well," he said. "Those are the kind of stories that make you excited to work in this field because you can make an impact on a population of patients who are not being served elsewhere."

Many of his patients have heart failure that renders them unable to work. But following treatment supervised by Dr. Moore: "You see people who are really sick, really short of breath, and really functionally disabled, go on to almost be normal. It's a great opportunity to make meaningful impacts for patients."

Clinical trials underway

At HonorHealth John C. Lincoln Medical Center, Dr. Moore is conducting clinical trials as part of the Multispecialty Research Division of HonorHealth Research Institute:

- The Artisan clinical trial aims to aggressively lower blood pressure in the arteries of the lungs by infusions of a drug called Remodulin. Once safely lowered, the patients are transitioned to an oral medication called Orenitram, and have a device implanted that measures blood pressure in the lungs so they can be monitored from home.
- The Aurora registry study uses a drug called Adempas to lower blood pressure in the lungs.
- The Apex clinical trial is assessing a first-in-class treatment designed by Tectonic Therapeutic for patients with pulmonary hypertension who also develop heart failure. Currently there are no FDA-approved treatments for this condition.

"Our goals going forward are to continue to grow and develop the program," said Dr. Moore, who plans to elevate the program soon by applying for HonorHealth to become a Center for Excellence for pulmonary hypertension treatment, "which will speak to how much high-quality care we are providing at HonorHealth and showcase the research that will drive the field forward."

Key to the treatment of these patients is early diagnosis, said Dr. Moore, who completed both his fellowship in pulmonary care and critical care, as well as his residency in internal medicine, at Lenox Hill Hospital in New York. He recently completed his post-doctoral fellowship at Stanford Medicine's Vera Moulton Wall Center for Pulmonary Vascular Disease.

ELEVATING **RESPIRATORY CARE**

DR. SUCHITRA PILLI BRINGS A WEALTH OF NEW SKILLS TO THE INSTITUTE'S MULTISPECIALTY RESEARCH DIVISION

Patients with lung disorders might breathe easier thanks to the arrival of Suchitra Pilli, M.D., a Scottsdale Interventional Pulmonary disease specialist affiliated with the Multispecialty Research Division of HonorHealth Research Institute.

Dr. Pilli is the new director of Interventional Pulmonology at HonorHealth Heart Care, where she is part of the Heart & Lung Surgery Group. Interventional Pulmonologists treat disorders of the lungs and respiratory system, including: lung nodule, pleural effusion, lung cancer complications, pneumonia, tuberculosis, chronic obstructive pulmonary disease (COPD) and emphysema.

"It's a new specialty at HonorHealth, basically focused on minimally invasive pulmonary procedures," said Dr. Pilli, who earned her medical degree from Kasturba Medical College, India, followed by a residency in Internal Medicine at the University of Texas Medical Branch, and then Pulmonary Medicine and Interventional Pulmonary training at University of Texas in Houston and Washington University in St. Louis. She has been in practice for nearly two decades and is board certified In Pulmonary Medicine, Critical Care Medicine, Internal Medicine and Interventional Pulmonology.

As part of HonorHealth's lung cancer screening program, Dr. Pilli specializes in robotic navigation bronchoscopy, a device that can move into the tiny airways of the lungs to conduct biopsies of nodules to see if they are cancerous, or not.

Enhanced lung cancer screening

The device she uses has a small camera located at the end of a flexible tube, which also has a small channel to collect tissue samples (biopsy) from the lung that can be used for disease diagnosis. It's a technology that enables physicians to move the bronchoscopy tube with precision, allowing the device to reach more parts of the lung.

While the physician is controlling the robotic system, a 3-D map of the patient's lung is shown on a computer screen. This allows the physician to see exactly where the tube is in the person's lung and where it needs to go and helps guide the physician to get to nodules previously identified by CT scans.

The earlier a cancer is diagnosed, the greater the chances that the cancer can be removed by thoracic surgery.

"The potential for early stage lung cancer diagnosis is very high. I think we can get more done at HonorHealth for the patient community," Dr. Pilli said.

Focus on COPD

She also specializes in managing cases of COPD for lung volume reduction with one-way valve placements: "What you're trying to do is collapse the damaged parts of the lung, so that the healthy part of the lung can function and get more air," Dr. Pilli explained.

She joined HonorHealth Research Institute because of the opportunity to help establish a new specialty in lung disease through the Multispecialty Research Division, where she says her goal is to increase patient care in an environment that welcomes individual initiative.

Dr. Pilli's approach to patient care emphasizes fostering a relationship and caring for the whole person. She typically meets patients at the diagnostic stage of their condition, and through shared decision-making, she walks with them through their treatment journey and into recovery.

Dr. Pilli also collaborates with the Institute's Oncology Research Division as well as primary care physicians and pulmonologists throughout the Valley's HonorHealth network. In addition to her other skills, she also speaks Hindi and Telugu, adding to HonorHealth's ability to serve a diverse patient population.

From left to right: Michael Gordon, M.D., FASCO, Stephanie Franz, Aubrey Gonzales, Stacey Robideau, Jamie Cox, Jessica Miller, Mark Slater, Ph.D., Chad Adams, MPH

ELEVATING **INNOVATION AND COLLABORATION**

Third annual HonorHealth Research Institute Symposium

Over 250 colleagues came together for the third annual HonorHealth Research Institute Symposium, celebrating another year of innovation, collaboration and inspiration.

The event was built around the continued dedication and hard work of researchers and staff, the generosity of donors, and the shared passion for advancing research that brings people together.

The symposium was filled with highlights, including the impact of philanthropy, scientific and operational poster presentations, recognition of staff achievements and employee milestones.

The keynote speaker, Katie Ortman Doble, shared her journey surviving ocular melanoma. As a writer, speaker and advocate for clinical trials, Katie told her story of resilience and hope, inspiring others with her determination and passion for advancing clinical research.

Other presenters included grateful patients from each of the Institute's five research divisions who shared their powerful stories about their clinical trial successes.

Advancements in Behavioral Medicine

In November, HonorHealth Research Institute hosted Breaking Waves: Advancements in Behavioral Medicine.

Mark Slater, Ph.D., CEO of the Research Institute and Festschrift honoree, celebrated 40 years of impactful medical research.

The educational program and panel discussion highlighted the important role of behavioral factors in health, illness, response to treatment, and reviewed decades of interdisciplinary research. The event highlighted the establishment, progression, integration, and implications of the field of Behavioral Medicine, stemming from the early collaborative research of panelists at the University of California San Diego School of Medicine.

1. *Mark Slater, Ph.D., HonorHealth Research Institute Pain Management and Behavioral Medicine;* **2.** *Jason Doctor, Ph.D., University of Southern California Behavioral Insights to Encouraging Guideline-Concordant Care;* **3.** *Lauren Schwartz, Ph.D., University of Washington Family Issues in Disability and Chronic Medical Conditions;* **4.** *Donald Penzien, Ph.D., Wake Forest University Self-Management of Persistent Pain;* **5.** *Sheri Pruitt, Ph.D., Kaiser Permanente Behavioral Medicine and Digital Health Solutions;* **6.** *J.H. Atkinson, M.D., University of California, San Diego Pain, Psychiatry and Behavioral Medicine: A Retrospective of the UCSD Experience;* **7.** *Anne Weickgenant, Ph.D., Health Science Systems Coping with Chronic Pain & Illness: When Complex Illness Hits at Home for Providers;* **8.** *Joshua Klapow, Ph.D., University of Alabama, Birmingham Behavioral Scientists in Mass Media: Yes, We Need to be on TV*

ELEVATING
TO NEW HEIGHTS

2024 Statistics for HonorHealth Research Institute

In 2024, the HonorHealth Research Institute delivered transformative advancements in research and innovation, enhancing patient care. By integrating the latest scientific discoveries with clinical excellence, the Research Institute achieved remarkable successes, driving better outcomes while elevating the standard of care.

NUMBER OF CLINICAL TRIALS

241

NEW CLINICAL TRIALS INITIATED

53

RESEARCH INSTITUTE CLINIC PATIENT VISITS

3,003

FDA NOVEL THERAPY APPROVALS

4

NUMBER OF ACTIVE INVESTIGATORS

139

NUMBER OF PUBLICATIONS

210

CARDIOVASCULAR RESEARCH

Clinical Trials | **53**

New Clinical Trials Initiated | **16**

HRI Clinic Patient Visits | **203**

FDA Novel Therapy Approvals | **1**

Active Investigators | **65**

Publications | **50**

MULTISPECIALTY RESEARCH

Clinical Trials | **14**

New Clinical Trials Initiated | **7**

HRI Clinic Patient Visits | **183**

Active Investigators | **13**

CANCER RESEARCH

Clinical Trials | **108**

New Clinical Trials Initiated | **16**

HRI Clinic Patient Visits | **1,901**

FDA Novel Therapy Approvals | **1**

Active Investigators | **12**

Publications | **95**

NEUROSCIENCE RESEARCH

Clinical Trials | **56**

New Clinical Trials Initiated | **10**

HRI Clinic Patient Visits | **337**

FDA Novel Therapy Approvals | **2**

Active Investigators | **42**

Publications | **64**

GI/BARIATRICS RESEARCH

Clinical Trials | **10**

New Clinical Trials Initiated | **4**

HRI Clinic Patient Visits | **379**

Active Investigators | **7**

Publications | **1**

Making a difference in the future through HonorHealth Research Institute — and a bit of magic

The future of HonorHealth Research Institute can be summarized in a single phrase, "Make a difference."

- We want to make a difference in the lives of our patients and their families.
- We want to make a difference in the lives of people at risk by unraveling not only the secrets of cancer, but also of the neurosciences and other medical disciplines.
- We really want to make a difference in the lives of the people who – day in and day out – are working on the front lines, taking care of patients, providing that advanced degree of healthcare that empowers people who feel as if they, as an individual, are making a difference in the lives of our patients.

To do all that, we've created an environment where we can do translationally-based research; where we can partner with others; where we can apply technology; where we can establish new relationships – like with the new ASU school of medicine and advanced medical engineering – to push that envelope further and further forward for the benefit of our patients, and to find new ways, additional ways, to make a difference in everybody's life.

Our goal during this past year of Elevating Research is really characterized in a number of different ways: Elevating Research by creating connections between programs that ultimately strengthen the chain that aids patients in their battles; understanding crosstalk between disciplines; and figuring out how there is a payoff towards extending healthfulness and wellness to extend quality and quantity of life.

As a community-based hospital, we are embracing technology, we are embracing translational research, and we are expanding and enhancing the number of physicians and investigators coming in with unique ideas.

I often say to patients that what we're looking for are "scathingly brilliant ideas." (Some of you might recognize that phrase from an old Hayley Mills movie, The Trouble with Angels.) That phrase connotes freeing yourself from the limitations that exist by standardized medicine, standardized research, by what other people think we should do, and focusing our efforts on what our patients need.

It suggests a freeing of the imagination. That freeing of imagination allows people to interdigitate.

For example, in August, at our Institute's most recent Symposium, I overheard a conversation along these lines, "I had no idea you could do that. Let's get together!" That's the excitement of watching our staff interact. It's the element that drives new people who are coming here, and why never forgetting the past becomes an important part of defining the goals of the future.

I'm also reminded of a passage from a book by a friend of mine (paraphrasing): "The key is, if you walk down the street with your eyes down and your hands in your pockets, and your collar pulled up tight, you're not open to the opportunity of seeing something unique. So, the magic may occur, but it doesn't necessarily occur if you're not open to it."

I think there is a difference between our world being magical and making magic. To make magic, you not only have to have the recipe, but you also have to be open to the effects of magic and what you do, and what it does to you.

Finally, I leave you with this message of hope, enthusiasm — and a bit of magic: Suspend what you know, and trust what you believe.

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

ELEVATING **PHILANTHROPY**

The generosity of HonorHealth Research Institute supporters drives discoveries and innovations

Frederic Zenhausern, Ph.D., MBA

Help accelerate breakthrough discoveries and treatments with a charitable gift to HonorHealth Research Institute.

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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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ELEVATING **PHILANTHROPY-BACKED RESEARCH**

International study led by HonorHealth Research Institute suggests using olive nanovesicles as an advanced drug delivery system

Vesicles derived from olives could be the basis of a new drug delivery system that could be less toxic and more effectively target a patient's disease. The new treatment would not require refrigeration and is relatively inexpensive, derived using olive waste products, according to a new international study led by HonorHealth Research Institute.

These lipid-based membranes, known as nanoscale extracellular vesicles or nanovesicles, would deliver drugs in tiny packages to patients, according to the study, "Physical, biochemical, and biological characterization of olive-derived lipid nanovesicles for drug delivery applications," published in Springer Nature's Journal of Nanobiotechnology.

"The potential benefit from an improved delivery system is better results than existing treatment medications," said Frederic Zenhausern, Ph.D., MBA, a senior investigator at HonorHealth Research Institute and director of the Center for Applied NanoBioscience and Medicine at the University of Arizona's School of Medicine-Phoenix, and professor at the university's Basic Medical Sciences and Biomedical Engineering.

This study was funded in part by Desert Mountain CARE.

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Innovative advances provide immediate impact and hope for patients

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