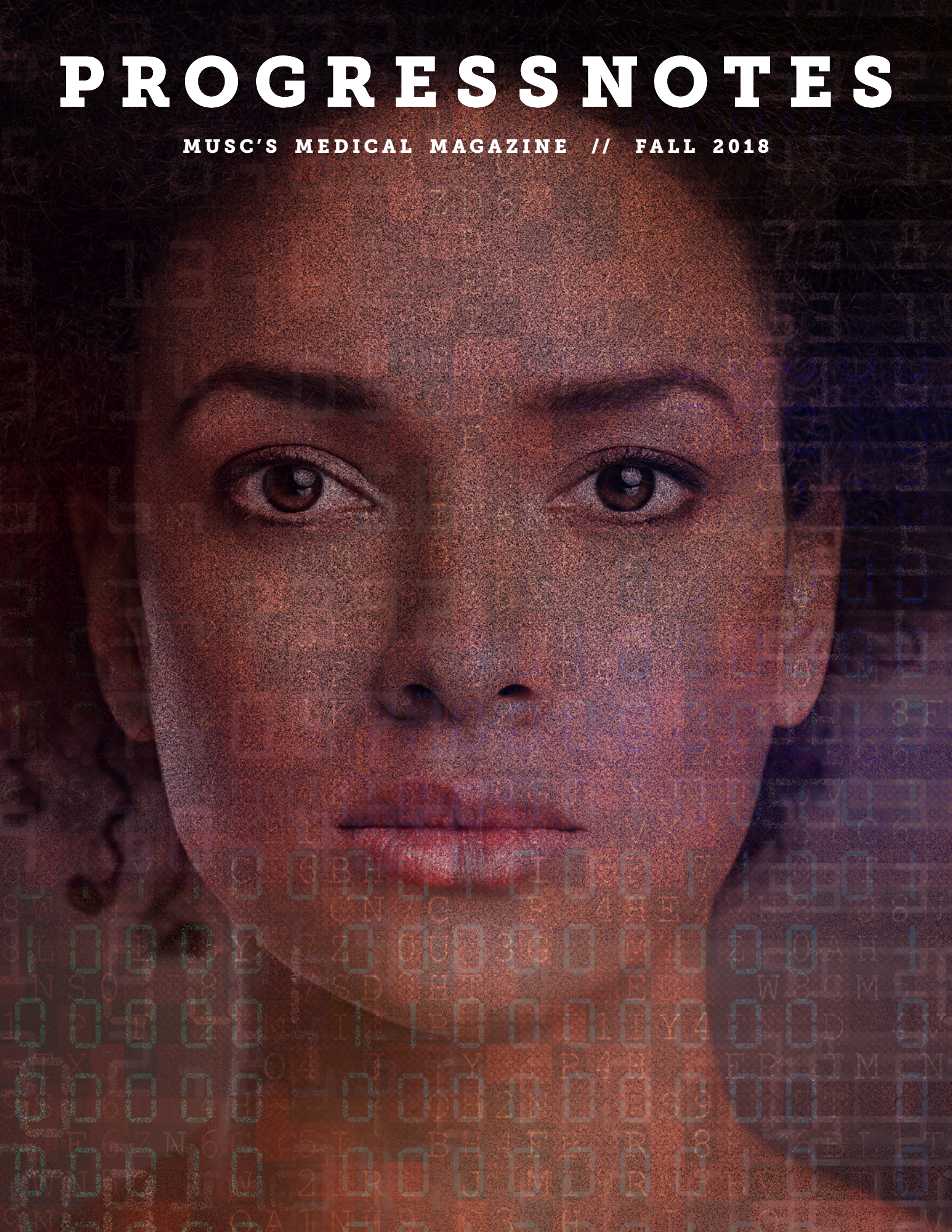


PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // FALL 2018



MUSC Ranked State's Number 1 Hospital Fourth Year in a Row

U.S. News & World Report releases annual national rankings

MUSC Health was named by *U.S. News & World Report* for the fourth year in a row as the number one hospital in South Carolina, and one of the country's top 25 hospitals in the treatment of ear, nose and throat (ENT) disorders, gynecology and cancer. MUSC's nephrology and orthopedics specialties also received national recognition, placing within the country's top 50 hospitals for those services. MUSC was high-performing in gastroenterology & GI surgery, geriatrics, neurology & neurosurgery, pulmonology, rheumatology and urology.

"For the fourth year in a row, MUSC has been named the number one hospital in South Carolina, once again being recognized for the high-quality care and tremendous value that we provide our state," says Patrick J. Cawley, M.D., MUSC Health CEO and MUSC vice president for health affairs, university. "Rankings certainly aren't why health care providers do what they do every day, but I would say that they provide further validation of how hard we are working to put patients and their families first."

U.S. News & World Report unveiled the 29th edition of the Best Hospitals rankings. Designed to help patients with life-threatening or rare conditions identify hospitals that excel in treating the most difficult cases, Best Hospitals 2018-19 includes consumer-friendly data and information on 4,500 medical centers nationwide in 25 specialties, procedures and conditions. In the 16 specialty areas, 158 hospitals were ranked in at least one specialty.

"Making these lists means we are finding new ways to deliver and improve patient care. We're tearing down barriers to accessing that care, successfully training the health care leaders of tomorrow and integrating our research discoveries in real-time whenever possible. The citizens of our state can take great pride and comfort in the knowledge that their only public, statewide hospital system is consistently cited as one of the best in the country," Cawley says.



MUSC Health Medical Video Center

MUSChealth.org/medical-video

A sampling of current videos:

Transcatheter Pulmonary Valve Replacement

MUSC Health Congenital Heart Center & Pediatric/Adult Congenital Intervention Cardiology Director **John Rhodes, M.D.**, discusses the techniques used in a procedure that implants new heart valves in both children and adults without invasive surgery.

Awake Craniotomy and Tumor Resection

Abhay Varma, M.D., a neurosurgeon at the Hollings Cancer Center, discusses the advantages of the awake craniotomy and tumor resection procedure for patients. Patients undergoing this procedure experience maximal safe resection of the tumor field without significant neurological deficits, providing maximum benefit with minimal risk.

Gamma Knife Surgery for Brain Tumors

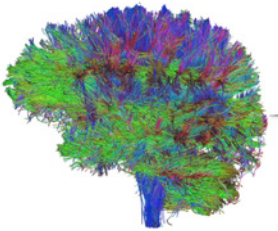
MUSC Health offers this procedure to treat brain tumors, pain syndromes, arteriovenous malformations, epilepsy and psychiatric disorders. It is as equally effective as whole-brain radiotherapy and offers significantly fewer cognitive side effects. **Nathan Rowland, M.D., Ph.D.**, a neurosurgeon with a specialty in brain and spine tumors, describes Gamma Knife Radiosurgery as a safe alternative to more invasive procedures that allows the patient to experience less recovery time.

Cleft Lip Repair - Fisher Subunit Approach

MUSC Children's Health facial plastic surgeon **Krishna Patel, M.D., Ph.D.**, performs cleft lip repair surgery and provides commentary on the steps of the subunit approach while reviewing surgical footage.

PROGRESS NOTES

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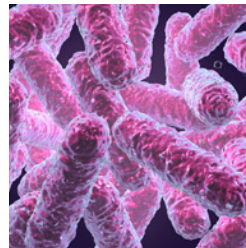
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MUSC researchers aim to link the microbiome to health and disease



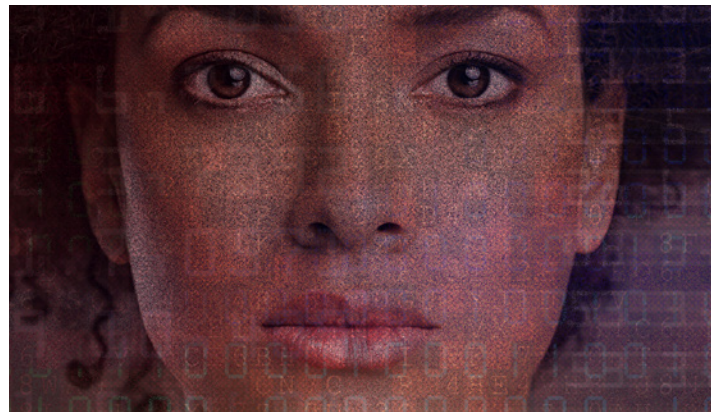
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Increasing use and knowledge gaps create need for individualized patient discussions.

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Welcome



On the cover: Machine learning algorithms, using a patient's digitized medical records, are allowing doctors to integrate large data sets to better treat patients.

CHANGING WHAT'S POSSIBLE IN HEALTH CARE

David Cole, M.D., FACS, president of MUSC, is seated with Michael Saladin, Ph.D., and Patrick Cawley, M.D., MUSC Health CEO, University Vice President of Health Affairs, as well as Siemens officials as they announce their partnership at a press conference.



PHOTO: SARAH PACK

NEWS

'Revolutionary' partnership teams MUSC with Siemens Healthineers

Partners intend to lead global change in health care system

BY LESLIE CANTU

Imagine a world where a patient's profile is completely digitized into a "digital twin." A computer can compare thousands of other digital twins to find a similar profile so doctors can begin that same treatment.

That world is one that MUSC and

Siemens Healthineers hope to create together. They announced a transformational partnership that is unlike any other in MUSC's 194-year history, says **David Cole, M.D., FACS**, president of MUSC. Siemens Healthineers and MUSC

outlined their joint vision: create a blueprint of a transformed health care system that provides safe, equitable, timely, effective, efficient and patient-centered care.

Creating a digital twin is a long-term idea. But the partners plan to reduce the door-to-treatment time for stroke patients in the near term. Currently, the national average time is 90 minutes, but faster times lead to better outcomes. MUSC is faster than average but further decreasing this time could reduce hospital admissions by 383 days and save \$2.2 million in follow-up care and \$1.7 million in long-term disability. To accomplish this, patients will go directly to the angiography room for real-time imaging, providing faster diagnosis.

MUSC and Siemens Healthineers also plan to create a digital twin of the new MUSC Shawn Jenkins Children's Hospital and Pearl Tourville Women's Pavilion, which will allow them to test processes and workflow changes in the digital replica prior to implementation.

The MUSC Health hybrid operating room, an OR integrated with an imaging room, will also be reengineered, says **Patrick J. Cawley, M.D.**, CEO of MUSC Health and vice president of Health Affairs.

Cole said that the two organizations have worked together for 20 years and have found their values and purpose align.

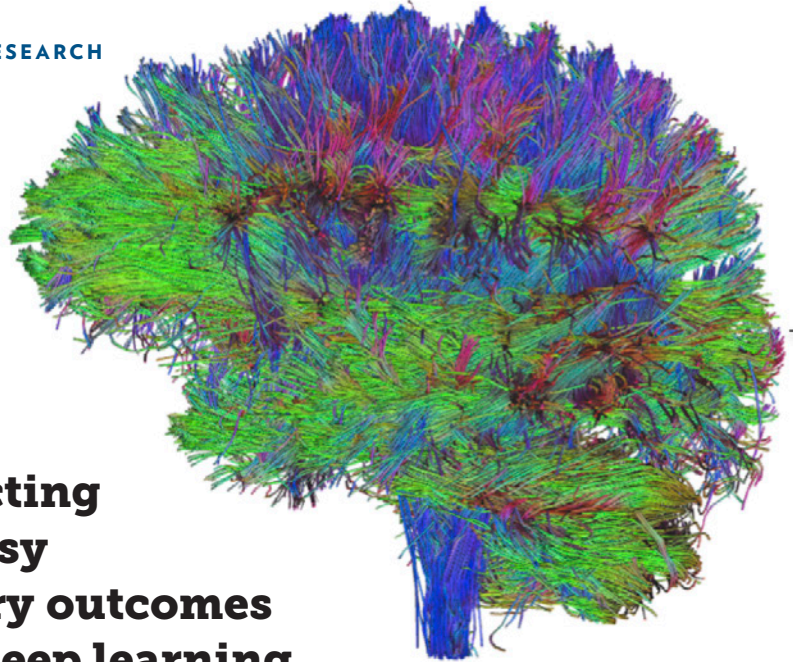
"We anticipate our global work will be transformational - remolding and establishing health care processes, systems and structures in ways that are life altering and lifesaving. Our advances will be designed with scalability and replicability. We will start here, echo across the state, and impact the world," Cole says.

Bernd Montag, Ph.D., CEO of Siemens Healthineers, says the two organizations need each other in order to transform health care. A dialogue is necessary between the experts in medicine and the experts in technology in order to make real the possibilities of the digital revolution.

For a long time, Siemens focused on technical improvements. While these are important, they don't address the bigger problems. "It is not only about improving the machines. It is about changing the entire system and having not only a better product but better medicine," Montag says.

Lisa Saladin, Ph.D., executive vice president for academic affairs, and Cole say they're excited about the opportunities the partnership will provide, exposing students to cutting-edge technology and allowing them to conduct research to show the impact these clinical changes have on patient outcomes.

CLINICAL RESEARCH



Predicting epilepsy surgery outcomes with deep learning

BY CAROLINE WALLACE

Using deep learning, a subset of artificial intelligence involving statistical computation, MUSC Health neurologists have developed a new method that may one day help both patients with medication-refractory epilepsy and their physicians weigh the pros and cons of brain surgery. In addition to the potential clinical implications, these findings, published in the September 2018 issue of *Epilepsia*, highlight how artificial intelligence is driving change in the medical field.

Although brain surgery is often recommended to patients who do not respond to medication, many hesitate, in part due to the operative risks and in part due to limited success. To overcome this, **Leonardo Bonilha, M.D., Ph.D.**, and his team searched for a better way to predict which patients are likely to be seizure free after surgery.

The team turned to deep learning due to the massive amount of data analysis required. "In this study, we incorporated advanced neuroimaging and computational techniques to anticipate surgical outcomes with the goal of enhancing quality of life," explains Neurology Department Chief Resident **Ezequiel Gleichgerrcht, M.D.**

The whole-brain connectome, the key component of this study, is a map of all physical connections in a person's brain. The map is created by in-depth analysis of diffusion magnetic resonance imaging (dMRI), which patients receive as standard-of-care prior to surgery. The neurologists used deep learning to examine the connectome, allowing for patterns to be automatically learned.

Today, post-surgery outcomes are predicted using clinical variables that are only 50 percent accurate, while deep learning predictions were 79-88 percent accurate.

"We are using artificial intelligence as an extra tool to make better informed decisions regarding a surgical intervention that may hold the hope for a cure of epilepsy in many patients," summarizes Gleichgerrcht.

CLINICAL RESEARCH

Globin Intrigue

Refining a new gene therapy for sickle cell disease



PHOTO: BRENNAN WESLEY

Julie Kanter, M.D., listens to a patient in MUSC's nationally-ranked hospital.

BY SVER AUNE

Gene therapy for people with severe sickle cell disease (SCD) has been designed to insert an engineered beta-globin gene into patients' stem cells to increase levels of therapeutic hemoglobin. Now in a phase 1 clinical trial (NCT02140554), the therapeutic hemoglobin is designed to counterbalance the defective hemoglobin that does a poor job of carrying oxygen and causes intravascular sickling, resulting in organ injury and pain.

In SCD, abnormal hemoglobin causes red blood cells to become sickle-shaped and to break down faster than normal, resulting in poor delivery of oxygen throughout the body. As a result, people with SCD experience acute episodes

of pain known as sickle cell or vaso-occlusive crisis and multi-system organ damage. Gene therapy is designed to prevent vaso-occlusive crisis by inserting a gene to produce "normal" hemoglobin, which would improve the shape and oxygen-carrying ability of red blood cells. Stem cells are collected from a patient via apheresis and then transduced with a virus that carries a gene for the therapeutic hemoglobin protein, called T87Q. The transduced stem cells, which are given back to the patient through an infusion, produce red blood cells that carry hemoglobin T87Q.

Refinements to the process of stem cell collection and transduction have

increased production of hemoglobin T87Q, bringing people with SCD closer to a cure, according to pediatric hematologist **Julie Kanter, M.D.**, who leads the clinical trial at MUSC. "The interim results indicate significant improvement in transduction and therapeutic globin production, demonstrating the potential for curative intent," says Kanter.

In the first group of patients, stem cells were collected through multiple bone marrow harvests. For the second group of patients, the protocol changed to use a new process called plerixafor mobilization with apheresis, which helps release stem cells into the bloodstream, allowing them to be collected through a blood draw. The method greatly improved the number and quality of stem cells collected. Then Bluebird Bio, Inc., which makes the therapeutic globin protein, used an improved proprietary transduction process to increase the number of stem cells that were transduced with the gene for T87Q.

In patients who underwent the unrefined therapy, hemoglobin T87Q constitutes about 13 percent of their total hemoglobin. In contrast, in patients who were treated with the refined therapy, T87Q makes up between 29 and 62 percent of their total hemoglobin. Most importantly, levels of abnormal hemoglobin have dropped in these patients, indicating that the therapeutic hemoglobin protein is indeed compensating.

The trial is currently in phase 2 trials at multiple sites. The researchers plan to begin phase 3 in one to two years, which will bring the gene therapy to a larger number of people with SCD.

TRANSLATIONAL RESEARCH

A proposed combinatorial treatment strategy for type 1 diabetes

Type 1 diabetes (T1D) is a chronic condition in which the body's own immune system attacks and destroys beta cells in the pancreas. Once the beta cells are destroyed, the pancreas can no longer produce insulin. Currently, there is no cure for T1D and treatment focuses on managing blood sugar levels. Researchers at MUSC, including **Hongjun Wang, Ph.D.**, professor in the Department of Surgery in the College of Medicine, and co-investigator **Charlton B. Strange, M.D.**, professor in the College of Medicine, hope to offer patients a better alternative. Wang received a grant of more than \$2 million from the National Institutes of Health to explore novel treatments for T1D patients.

New strategies for T1D intervention should effectively target the immune system and protect/regenerate beta cells. To date, there is no single intervention that targets these areas, and novel combined therapies would be beneficial for such a complex disease.

The use of mesenchymal stem cells (MSCs) as a therapeutic tool represents a promising new intervention. Evidence suggests that MSC therapy can effectively target several injury pathways in a variety of autoimmune and inflammatory diseases, something that most pharmacological interventions cannot accomplish. In fact, recent studies from the Wang lab have shown that infusion of MSCs promotes T regulatory cell generation, a subpopulation of T cells that modulate the immune response, and prevents beta cell death. However, most human studies using MSCs alone have not been successful at sustained suppression of the autoimmune response.

The newly funded work is going further by combining MSCs with the protective effects of alpha 1-antitrypsin (AAT). AAT protects tissues from the damaging effects of inflammation by decreasing insulin autoantibodies and promoting T regulatory cell function. Using a humanized mouse model of T1D, the group will combine Wang's expertise in islet transplantation and immunology with Strange's expertise in AAT biology and genomics to monitor the sustained efficacy of this combined therapy on the immune system and the preservation/reconstitution of beta cells.

- MATTHEW GRESETH



PHOTO: BRENNAN WESLEY

Brenda Hoffman, M.D., is chief of MUSC Health's new Digestive Disease, Endocrine & Metabolism Integrated Center of Clinical Excellence.

CLINICAL CARE

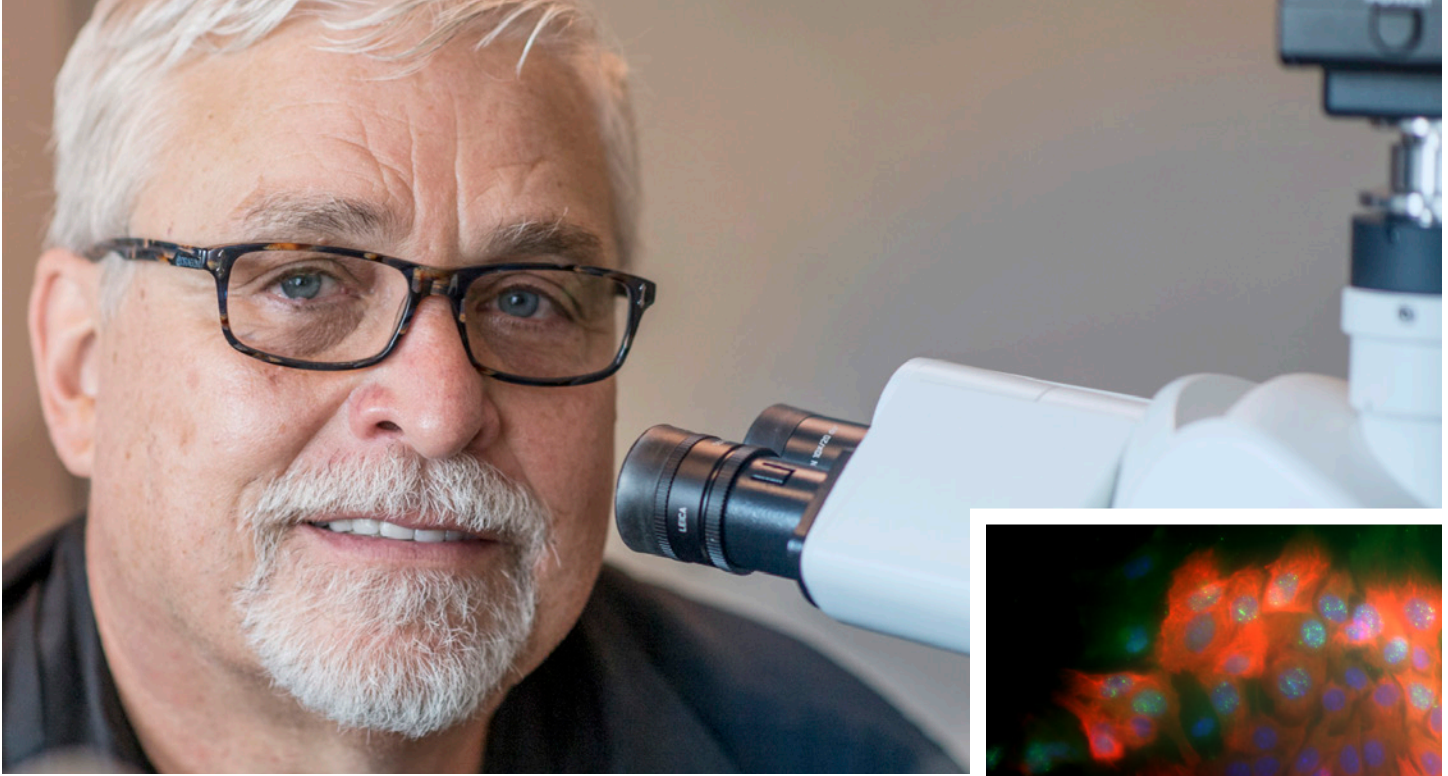
The MUSC Foregut Center

The Foregut Center at the MUSC Health Digestive Disease Center will be one of the few centers in the region that will be dedicated to diagnosing and treating complex foregut pathology. A comprehensive team, including world-class gastroenterologists and surgeons as well as radiologists and pathologists who are uniquely qualified to diagnose and treat complex foregut disease, will focus on the management of gastroesophageal reflux disease, hiatal hernia, achalasia, revision foregut surgery, benign and malignant lesions of the foregut and Barrett's esophagus.

The goal of the center is to offer the best modality of treatment for the patient that is least invasive. This may involve endoscopic, laparoscopic, robotic or hybrid methods. This center will provide the requisite platform to harness skill and knowledge across specialties to ultimately provide the patient unique solutions, which each specialty working in isolation might not be able to offer.

"The Foregut Center will serve as the tertiary referral center for the region for complex foregut pathology," says **Brenda J. Hoffman, M.D.**, chief of the Digestive Disease, Endocrine & Metabolism Integrated Center of Clinical Excellence at MUSC Health. "It is the only one like it in the state."

-LAUREN HOOKER



Michael C. Ostrowski, Ph.D., pictured above, is a professor in the Department of Biology at MUSC and a member of the MUSC Hollings Cancer Center.

DISCOVERY

A new breast cancer biomarker

Low PTEN in normal breast cells can prevent successful radiotherapy

BY CAROLINE WALLACE

A highly collaborative team of researchers at MUSC and Ohio State University report in *Nature Communications* that normal breast cells can prevent successful radiation treatment of breast cancer due to dysregulation between tumor suppressors and oncogenes (doi: 10.1038/s41467-018-05266-6). Tumor suppressors act like brakes that stop cells from undergoing uncontrolled growth, while oncogenes are the gas pedal. The tumor suppressor gene of interest in this study is PTEN, which is often mutated in human cancer cells.

An initial surprising observation that

the stroma, or supportive connective tissue, in some women without cancer had abnormally low PTEN levels, fueled this study.

"The results suggest that PTEN loss in normal cells may be a biomarker for identifying breast cancer patients who would benefit from adding specific inhibitors in combination with the standard radiation therapy," says **Michael C. Ostrowski, Ph.D.**, a professor in the Department of Biochemistry and Molecular Biology at MUSC, a member of the MUSC Hollings Cancer Center and senior author on the article.

The cancer research field did not previously know that early PTEN-focused events in the breast stroma are capable of triggering malignant development in the breast.

In human breast cancer, expression of the tumor suppressor PTEN and the cell growth promoter active protein kinase B (AKT) are inversely correlated. In other words, when PTEN is reduced, AKT is significantly increased. However, researchers knew neither why this occurs nor how it could be useful clinically.

To address this specific question, the

team developed a mouse model to look at what occurs when PTEN is not expressed specifically in the breast stroma. This special model revealed that the absence of PTEN tumor suppressor in the breast stroma leads to larger mammary tumors.

Digging deeper, the MUSC researchers wanted to understand how stromal cells without PTEN could lead to such rapid growth of cancer cells. Surprisingly, connective stromal cells that do not have PTEN release more soluble factors called EGF ligands. The EGF ligands promote abnormal growth in neighboring epithelial cells, which line the surfaces of internal organs including in breast tissue.

Radiation therapy is a mainstream treatment for breast cancers as radiation causes cell death in the targeted cells. When the PTEN level is low in the breast cancer connective tissue cells, the tumor cells have a high degree of genetic instability. Genetically unstable cells do not follow the normal growth checkpoints, meaning that the cells ignore cell death signals and continue to survive and multiply.

The finding of the connection between low PTEN levels and reduced response to radiation therapy “allows for a multi-pronged attack on the tumor, by predicting who will respond the best to radiation therapy in combination with chemotherapy and other targeted treatments,” says Ostrowski.

A small clinical trial to investigate the correlation between reduction in stromal PTEN and radiation resistance could be game-changing to the field. One option is to use the PTEN data to divide the patients into groups, leading to more personalized medicine. Using this tool, physicians could decide which breast cancer patients would benefit the most from radiation and spare the patients who are not likely to respond from the costs and side effects of the treatment.

DISCOVERY

A new link between cancer and aging

Telomeres are like a biological clock for cells

BY SVER AUNE

Scientists at MUSC Hollings Cancer Center have found that lung cancer cells resist dying by affecting the aging process, in results published online May 10, 2018 in the *Journal of Biological Chemistry*. The discovery could help us better understand aging and eventually lead to new treatments for cancer.

At Hollings, research into the connections between aging and cancer is led by **Besim Ogretmen, Ph.D.**, Smart-State™ Endowed Chair in Lipidomics and Drug Discovery. His team found that cancer cells have specific ways to resist the way normal cells die. They do so by protecting the tips of their chromosomes (telomeres) from age-related damage.

As normal cells get older, the telomeres can start to break down, which is a signal for the cell to die. However, cancer cells have developed a way to prevent their telomeres from falling apart, helping them live longer, which allows them to grow and spread throughout the body.

In their new article, Ogretmen’s

group discovered a specific way that cancer cells escape death in response to telomere damage. They found that a cellular decision-maker, p16, helped cells decide to grow older or simply die.

“Telomeres are like a biological clock for our cells,” says Ogretmen. “In cancer, this biological clock is broken.”

To determine the clinical impact of these data, the researchers caused telomere damage in several cancer cell lines using an inhibitor. This treatment killed cancer cells with low p16 levels; however, cancer cells with high p16 levels were unaffected.

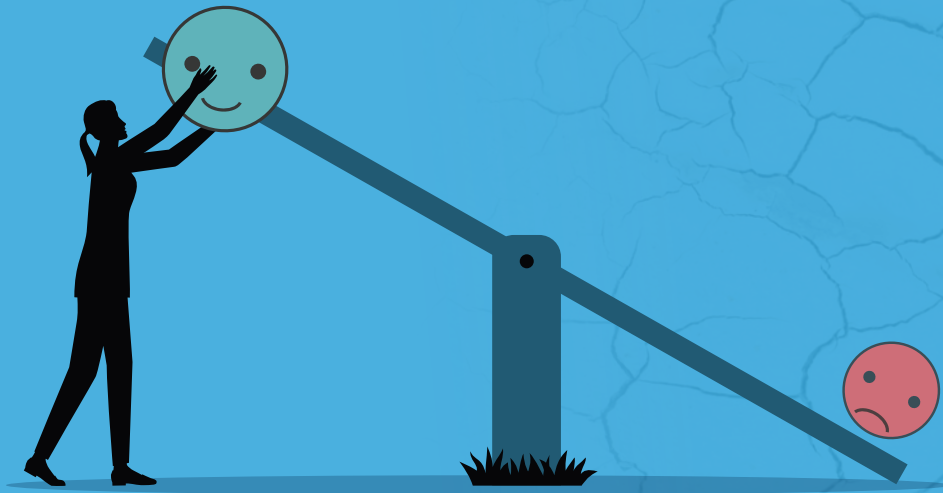
“We’re excited that there is at least one mechanism that can help us understand how aging is associated with a higher risk of cancer,” says Ogretmen.

Ogretmen’s group is enthusiastic that the inhibitor in their study might help combat cancer at many levels. The team is planning a multisite, phase 2 clinical trial in patients with hepatocellular carcinoma.



PHOTO: BRENNAN WESLEY

Besim Ogretmen, Ph.D., is the Smart-State Endowed Chair in Lipidomics and Drug Discovery and is a professor and eminent scholar for biochemistry and molecular biology.



A Delicate Balance

New clinic offers patients alternatives to opioids for chronic pain management

BY MIKIE HAYES

America is fighting the deadliest drug crisis ever. And with Americans consuming considerably more opioids than any other country, nearly 60 percent more than Canada, the No. 2 consumer according to the United Nations International Narcotics Control Board, the problem doesn't necessarily lie with illegal drugs. Prescribed opioid painkillers are actually at the heart of the issue. Two-hundred-fifty-nine million prescriptions were written for opioids in 2012, reports the American Society of Addiction Medicine. That's more than enough for every adult in the United States to have their own bottle of prescription opioids.

Part of the underlying problem is the fact that chronic pain is a real problem, affecting an estimated 100 million people in the U.S. alone. Physicians don't want their patients to suffer and mean well when they write prescriptions for pain medications. **Kelly S. Barth, D.O.**, a psychiatrist and internal medicine physician at MUSC Health who concentrates her efforts on the management of patients taking opioid medications for chronic pain, says patients with this type of persistent pain can have a worse quality of life than patients with cancer, adding that chronic pain can negatively affect their daily lives in countless ways.

Properly treating pain while not creating addiction is a delicate balance — one that has not been struck particularly well. The increase in the number of opioid prescriptions written coincides with a high number of drug overdose deaths, says Barth. Today that number surpasses the total number of gun homicides and motor vehicle crashes combined. As a result, the pendulum has swung. With data showing that Americans consume more than 75 percent of the global supply of oxycodone and 99 percent of hydrocodone, it's no wonder that the Food and Drug Administration has cracked down on the prescribing of opioids, declaring opioid misuse, abuse, dependence and overdoses have reached epidemic levels over the past decade.

In an effort to address both problems, MUSC has launched South Carolina's first comprehensive chronic pain rehabilitation program. With half of opioid prescriptions in the U.S. written for chronic pain, opioid misuse and chronic pain often go hand in hand. As a result, physicians and patients alike sought more inventive and targeted forms of treatment to address chronic pain and opioid addiction.

Barth brought the multidisciplinary program to fruition and now oversees it. She believes the new rehab program will provide patients with a more effective approach. Its objective is to aid patients experiencing chronic pain who have been prescribed long-term opioids to address it. Already, the program has distinguished itself from others because it focuses heavily on eliminating patients' reliance on opioid medication that resulted from prior treatment.

Barth explained that in order to address the nation's overreliance on opioids, it is necessary to address what's creating that reliance, which, she says, is chronic pain. The program "decentralizes" the use of opioids, while providing evidence-based non-opioid pain treatments and "giving patients the support they need to recover in a civilized way."

The Centers for Disease Control and Prevention (CDC) recommends non-drug approaches such as physical and psychological therapy to address chronic pain. Barth said MUSC's program not only includes opioid reduction and elimination and medication management, but also cognitive behavior therapy, physical and



Kelly Bath, D.O., pictured above, is a psychiatrist and internal medicine physician at MUSC Health who concentrates her efforts on the management of patients taking opioid medications for chronic pain.

PHOTO: SARAH PACK

occupational therapy, biofeedback and nutrition education. These evidence-based treatments are modeled after those employed at a highly successful rehabilitation program in Jacksonville, Florida, and also follow CDC guidelines.

Specific goals for recovery include the reduction or discontinuation of pain medication use; education is also a major component of the program, as patients learn stress management, relaxation techniques and coping skills and improve the ability to self-manage chronic pain. Ultimately, Barth says, patients will be able to reduce their reliance on both opioids and health care professionals, moving more towards a model of "wellness rather than illness."

To date, 20 patients have successfully made it through this new program, says Barth. Damian Millet, a patient nurse coordinator with the program, says the type of intensive approach that these patients received is particularly effective because it offers patients a hands-on experience with health care providers from multiple disciplines. They receive a lot of personal attention in group settings, he says. They make a great deal of progress in just three weeks — all patients were tapered off their opioids, saw an improvement in pain and functioning and showed a 40 percent decrease in disability due to pain.

To find out more about the Pain Rehabilitation Program or to enroll, email Lynn Kimball or call 843-792-6895.



PHOTO: SON NGUYEN

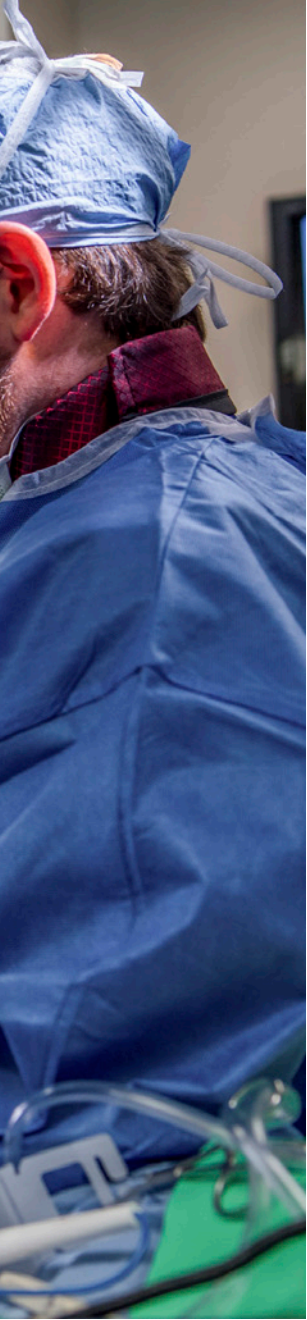
Best Foot Forward

MUSC Health performs its first 3D-printed talus replacement

BY CARIN MOONIN

The talus connects the lower leg and foot and is crucial for foot and ankle mobility. But compared to other nearby bones — the tibia, fibula and calcaneus — it receives relatively low blood supply. For this reason, it takes a long time to heal.

Talus injuries are usually high-impact or trauma-related, such as a motor vehicle accident or fall. The bone can also be weakened non-traumatically, via long-term use of corticosteroids to fight autoimmune conditions. Regardless of whether it's a traumatic or chronic injury, poor oxygenated blood flow may lead to the eventual death of the bone, known as osteonecrosis of the talus, or avascular necrosis (AVN).



AVN can be difficult to treat either conservatively or surgically. As **Christopher E. Gross, M.D.**, an orthopedic surgeon at MUSC Health, explains, treatment choices until recently haven't been optimal.

"Options range from core decompression, which is basically drilling a bunch of tiny holes into the bone to try to stimulate blood flow; to surgery to fuse the ankle and the entire hindfoot; to femoral allograft, in which bone and cartilage from a cadaver is placed into a damaged talus, along with a rod up the heel," says Gross. Most surgical options, he explains, leave a patient with extremely limited mobility — like walking around in a ski boot for the rest of your life.

A new, exciting option

A recent patient of Dr. Gross' is a 19-year-old woman, who had been taking steroids long-term due to lupus. A previous core decompression procedure had been unsuccessful, and she wanted to retain as much range of motion as possible. After reviewing all the options together, they decided to go ahead with MUSC Health's first total talus replacement.

"We only have about 18 months of data on this procedure overall. But I think it's important to have this option. We're able to

offer it with full informed consent, having a thoughtful conversation with patients and doing what's right for them," says Gross.

The procedure, which happened in August, was the first time a 3D-printed orthopedic prosthesis had been used at the institution. (Currently, MUSC Health does not create commercial prostheses for this procedure; the talus prosthesis was created by Additive Orthopaedics, based in Little Silver, New Jersey).

Part of the reason talar replacement is even possible is because the talus is an inherently stable bone. "The talus is hard to pop out, even though muscles and tendons aren't attached to it," explains Gross. "It uses force of weight to stay in place, so it's a natural for replacement."

Contraindications for total talus replacement are minimal: those who have an active infection or arthritis in the surrounding joints.

Making it happen

To start the process, the patient's healthy leg and foot are imaged by CT scan; then the image is flipped and becomes the model for the new talus. Three models are 3D-printed: one that's an exact duplicate, and two more, each with 1 millimeter of variation in either direction to account for variability. This particular prosthesis is made of cobalt chromium, but others may also be made from titanium and cobalt.

During the procedure, the patient received a nerve block, which put her under twilight anesthesia. An incision was made at the front of the ankle, in the interval between the tibial and extensor hallucis longus tendons to expose the articulation between the talus and tibia. Soft tissue attached to the talus was dissected, and the talus was removed in four pieces. Once removed, models of the prosthesis were inserted to determine ankle stability and range of motion. After that was established, the actual prosthesis was put in place. The entire procedure took about 45 minutes, says Gross.

Faster recovery and improved quality of life

One of the exciting features of talar replacement is its faster recovery time. "When you have femoral head allograft surgery, it's difficult to make sure the new bone receives enough blood flow," Gross explains. "The patient needs to spend about 12-16 weeks off their feet. But with a 3D-printed talus, they're walking in two weeks."

As for August's patient, Gross says she's doing great, although data on the procedure is still limited. "While fusion is the gold standard for most foot and ankle procedures, people value range of motion. Eventually it's going to get easier and easier and less and less expensive to 3D-print prostheses," explains Gross.

"It's an interesting intersection of technology and medicine," he says. "We don't know what the future holds, but we do know this is promising."



To view surgical footage of a total talus replacement operation narrated by Dr. Gross, see the Orthopaedics page of the MUSC Health Medical Video Center.



PHOTOS: BRENNAN WESLEY

Acceptance and Speech

Surgical repair of cleft palate and cleft lip

BY LINDY KEANE CARTER

Each year in the U.S. about 2,650 babies are born with a cleft palate (CP) and 4,440 babies are born with a cleft lip (CL), with or without a CP.¹ Isolated orofacial clefts are among the most common birth defects in the U.S.¹

CL is an incomplete fusion of the upper lip, often extending into the base of the nose to include the upper gum and maxilla. Surgical repair is recommended within the first three to six months of life.

CP is the failure of the hard and/or soft palate to fuse to midline during development. Surgery is recommended within the first year



A patient undergoing cleft palate surgery.

of life. Because the lip and the palate develop at different gestational time periods, it is possible to have a CL without a CP, a CP without a CL, or both together.

Subsequent surgeries to optimize the child's development in breathing, hearing, speech and language may be required. These procedures are offered by three surgeons within the MUSC Children's Health Craniofacial Anomalies and Cleft Lip and Cleft Palate program: **Krishna G. Patel, M.D., Ph.D.**, specializes in pediatric facial plastic and reconstructive surgery; **Christopher M. Discolo, M.D.**, specializes in pediatric head and neck surgery; and **Jason P. Ulm, M.D.**, specializes in craniofacial and aesthetic surgery. Together, these surgeons perform an average of 50 new CP and CL repairs every year and hundreds more follow-up surgeries in adults as well as children.

Cleft lip and cleft palate surgery

The challenge of CL repair is achieving symmetry of the lip contour and the nose. Most often, the lip length on the cleft side is too short. The most common repair technique, rotation advancement, addresses the foreshortened cleft lip length by first rotating the cleft-sided lip down and then advancing the edges of the cleft together.

One of the challenges of CP surgery is restoring the orientation and function of the soft palate musculature. This abnormally positioned muscle prevents normal palatal function from occurring. The most common consequence of this malfunction is velopharyngeal insufficiency (VPI) which results in hypernasal speech and reduced intelligibility. Proper muscle function maximizes the potential for normal speech outcomes.

To reorient the muscle and prevent VPI, the MUSC Children's Health surgeons perform one of the more challenging techniques: the CHOP Six Flap modified Furlow Palatoplasty. This technique, offered by few institutions, advances the tissue to the midline to close the cleft in the anterior half of the palate. In the posterior half, the muscle is freed of the abnormal attachments to the hard palate and then rotated 90 degrees and placed into the correct orientation. Rotating the tissues/muscles 90 degrees also allows for simultaneous closure of the cleft in the posterior half of the palate. Unlike other techniques, this approach increases the length of the palate, which is important in enabling clear speech.

Subsequent surgeries

Oronasal fistula (ONF) is a common complication following CP surgery, occurring in 4 to 35 percent of cases.² The two main ONF



Facial reconstruction of a cleft lip before (left) and after (right) cleft lip surgery.

symptoms are nasal regurgitation and speech problems, such as hypernasality. ONF develops primarily because of repair under tension and, in some cases, postoperative infection, especially in adults.

Among children, the ONF rate was found to be 4.9 percent in a 2015 analysis of 11 studies comprising 2,505 children.³ The ONF rate among surgeries performed by the MUSC Children's Health's cleft team is less than 1 percent. Repair of ONF is challenging because scarring has often compromised blood supply to the palate. The surgery requires raising multiple tissue flaps to close the fistula.

The MUSC Children's Health surgeons spend significant time during the primary palatoplasty relieving tension off of the incision line, which decreases the risk of fistula formation. Additionally, strict postoperative guidelines, such as mandating a soft diet and no pacifiers, are followed to decrease the risk of fistulas.

Multidisciplinary care

The cleft team at MUSC Children's Health comprises not only specialty- and subspecialty-trained surgeons, including pediatricians, orthodontists, pediatric dentists, otolaryngologists, oral and maxillofacial surgeons, but also speech-language pathologists, audiologists, genetic counselors, nurse coordinators and social workers. Comprehensive, coordinated care ensures that patients receive their care at the correct time, which lessens their need for future surgeries.



To watch a video of surgical footage narrated by Dr. Patel, visit the Pediatrics page of the MUSC Health Medical Video Center (<http://MUSChealth.org/medical-video>).

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MACHINE LEARNING in Medicine

MUSC is developing machine learning algorithms that harness
big data to transform patient care

BY KIMBERLY MCGHEE

The avalanche of medical data now available to clinicians and researchers represents an unprecedented opportunity to transform health care and realize precision medicine. High-throughput screening of patient samples yields multi-omics data (e.g., genomics, proteomics, glycomics), the electronic health record (EHR) provides information on clinical care and history, and wearables provide real-time updates on a patient's activity and vital signs. However, the sheer volume of these data is daunting and can overwhelm and frustrate clinicians.

Machine and deep learning, subsets of artificial intelligence (AI) that have been waiting in the wings for decades, are now taking center stage because they cannot only handle these burgeoning datasets, they need them if they are to continue to grow “smarter.” In supervised machine learning, for example, labelled pairs of inputs and outputs are used to train an algorithm, which infers the relationship between the pairs and predicts outputs for new input values. In unsupervised learning, the algorithm is provided unstructured, unlabeled data and is left to its own devices to classify and order the data. Eventually, however, machine learning's ability to learn from the data plateaus. Deep learning avoids that “plateau” effect, continuing to grow smarter as it parses more data by transforming them through a series of layers or nodes before integrating them again. Machine and deep learning are widely thought to hold the key to unlocking the promise of big data. In their book *Deep Learning*, Ian Goodfellow

and Aaron Courville contend that machine learning, along with deep learning, are “the only viable approach[es] to building AI systems that can operate in complicated real-world environments” precisely because they can learn from experience.¹

Recent achievements by deep learning algorithms lend credence to that assessment. When trained on appropriate datasets, deep learning algorithms have referred patients for more than 50 sight-threatening diseases as well as a panel of ophthalmologists,² distinguished malignant melanomas from benign moles with better sensitivity than dermatologists (95 vs 88 percent)³ and detected metastases in sentinel lymph nodes better than pathologists.⁴ None of these algorithms is intended to replace clinicians but rather to support them in detecting disease earlier so that appropriate treatment can begin as soon as possible.

An electronic safety net

At MUSC, a data science team in MUSC's Informations Solutions, including Chief Data Officer **Matthew Turner**, Director of Analytics **Brady Alsaker** and lead data scientist **Matthew Davis**, uses machine and deep learning to predict patient risk and outcomes. Their analytics predict which patients are at highest risk of dying while in the hospital, of being readmitted or of visiting an ER. They can also identify — in real-time — patients who are likely to deteriorate or to develop sepsis, so that preventive measures can be taken.

“We see this as an AI safety net,” says Turner. “The model is able to look at thousands of features in real time versus a human being that looked at 40 or 50 variables. It looks at all of those microcorrelations in real time and puts together a risk prediction of how likely it is that this patient will descend into sepsis.”

The data scientists work closely with academic researchers in the Biomedical Informatics Center (BMIC) to develop their predictive analytics. These researchers are drawing on diverse data, including the unstructured data residing in clinicians’ notes in the EHR, to develop predictive analytics for precision medicine; predict patient preference; decide whether a patient would benefit from a targeted therapy; and revolutionize the way that research is conducted. Chief Research Information Officer **Les A. Lenert, M.D.**, directs BMIC, which is home to the biomedical informatics program of the South Carolina Clinical and Translational Research Institute. “We want any investigator on campus to know that they can come to us to build a predictive analytics solution and test it at the point of care using Epic,” says Lenert. “And we also want to make it possible for researchers to use the health system as a tool or environment for testing algorithms for predictive analytics.”

Unlocking the power of clinical notes

To be robust, predictive analytics must tap into the richest data in the electronic health record — those that reside in clinicians’ notes. Traditionally, however, computers would be able to “read” only structured data that had been entered as code. Natural language processing, another subset of AI, enables computers to begin to understand human language. This is important because clinicians, pressed for time, may not do an exhaustive search of the EHR for a relevant clinical detail, such as an allergy, and instead rely on the latest clinical note, which may or may not be comprehensive and accurate. If data relevant to allergy were immediately available via a clinician dashboard, they would be far less likely to be missed.

Stephane Meystre, M.D., Ph.D., an associate professor at BMIC and in the Departments of Public Health Sciences and Psychiatry and Behavioral Sciences, has developed a program that he hopes will one day be able to do just that. “This is not simple keyword searching,” explains Meystre. “It involves syntax and complex semantics.” In other words, the algorithm can recognize that a word’s meaning is changed by its context. For example, it must recognize negation so that it does not mistakenly attribute to the patient diseases excluded by the differential diagnosis in the clinician’s note.

To teach the program about what information to extract and context, Meystre asks specialists to read clinicians’ notes and annotate the information they want to be able to find (e.g., noting that “denies chest pain” is a symptom that is negated). Those annotations are then used to train the algorithm what to look for in clinical notes. The resulting data can then be presented to physicians in a dashboard for validation. They can also be used for research, quality improvement, or other secondary uses of clinical information.

Natural language processing could also improve voice recognition, perhaps enabling the creation of a digital “medical scribe” that could record what was said by whom during a patient visit and enter those data into the EHR, to be later validated by the physician.

Precision medicine bioinformatics

According to **Lewis J. Frey, Ph.D.**, an associate professor in the Department of Public Health Sciences and a member of BMIC, precision medicine, at its simplest, is “wrapping data around a patient at an individual level to improve outcomes.” Precision medicine informatics, the field in which Frey specializes, analyzes all of that information in order to recommend optimal treatment that is personalized for each patient. The patient’s response to a certain treatment can be “predicted” based on how well groups of patients with similar features have responded to that therapy in the past. On the basis of these predictive analytics, patients can be pointed toward the therapies most likely to help them and be spared the rigors of therapies that likely will not.

Frey also helped develop a predictive analytics platform — the Clinical Personalized Pragmatic Prediction of Outcomes (C3PO) — that was used at Ralph H. Johnson VA Medical Center to cluster patients with diabetes who were undergoing knee or hip surgery by A1C levels and predict outcomes for each group. Because it was designed as infrastructure-as-code, it could then be reused and expanded to examine how chronic stress affects prostate cancer outcomes for the MUSC Transdisciplinary Collaborative Center (TCC), the goal of which is to support precision medicine in minority men’s health. Infrastructure-as-code enables the computer infrastructure required to run a predictive analytics algorithm to be cloned in the cloud or on as many computers as are necessary at a new institution. “Infrastructure-as-code is a new way of programming architectures,” explains Frey. “You write the commands that create the machines that run the analyses. You set up all the scripts and then it instantiates the machine as needed in the new environment. So you have coded the infrastructure.”

Predicting patient preference

Lenert and **Brian Neelon, Ph.D.**, associate professor in the Department of Health Sciences, are working together to create a collaborative filtering recommender system for patient treatment preference, much like those that Netflix or Amazon uses to recommend you new products based on the past purchasing history of people like you. There are three stages to developing such a system: first, eliciting patient preferences via surveys; second, clustering patients into preference phenotypes based upon their responses; and, third, using satisfaction and quality-of-life data from patients in the same preference phenotype who have already undergone treatment to recommend therapies that would be most aligned with their preferences. “Eventually you can envision developing an app for physicians and patients to use in clinical settings,” says Neelon. “Give patients a small survey instrument to help group them, load that into a system while they are waiting and then review recommendations with them during the clinic visit or at a future visit.”

Enabling citizen science

The ubiquity of smart phones and watches that can continuously track heart rates, steps taken and other health-relevant data could revolutionize clinical trials, making citizen science feasible. Compared with traditional trials that rely on study coordinators at medical centers to enroll patients from the surrounding region, citizen science trials aim to virtually enroll large numbers of participants from across the country. The much larger datasets that result from these high-enrolling trials could yield new insights into diseases and how best to treat them.

Christopher Metts, M.D., an assistant professor of Pathology and Laboratory Medicine and member of BMIC, has created a software platform that is being used to facilitate citizen science. The platform weds Apple’s ResearchKit and HealthKit to REDCap, a widely available, HIPAA-compliant data collection and management tool for researchers, via an API, basically creating a secure repository for data collected from health care apps. “By marrying those three pieces of software together, you get something that is greater than the sum of its parts,” says Metts. Using his platform technology, Metts has created more than 40 apps for specific health care use cases for a fraction of the cost one such app typically costs to develop.

At the request of Chief Nursing Officer Jerry Mansfield, Metts used one of those apps, RN Wellness, to shed light on nursing

burnout and turnover. Interested nurses were asked to answer screening questions and give informed consent on the iPhone app and then were required to “virtually” enroll in two of four available studies. Each was given an Apple watch to continuously track heart rate. At the end of each shift, participants were asked to answer a single-question survey about their stress level, and at the midpoint and endpoint of the study to complete more detailed surveys. The goal of the study was to “quantify” the stress that leads to burnout so that measures can be established for assessing the efficacy of burnout interventions in the future.

Metts hopes that the studies will also demonstrate that his platform technology can enroll and track patients in multiple clinical trials at once. Metts’ goal is to eventually make thousands of studies available via his platform. As participants answer screening questions for one study, their answers could trigger other studies being recommended to them. Although primarily a research tool for now, Metts hopes his platform technology, which rigorously anonymizes its data, could be used to implement evidence-backed interventions as well.

Future state

In the not-too-distant future, artificial intelligence, including machine and deep learning and natural language processing, is poised to begin transforming medicine. To realize its promise, many more data scientists with expertise in health care will need to be trained. MUSC and Clemson University have begun jointly offering a doctoral program in data sciences, directed by **Alexander V. Alekseyenko, Ph.D.**, an associate professor in the Department of Public Health Sciences and a member of BMIC. The program, which welcomed its second cohort of students this year, provides them training in mathematical and statistical modeling, “hacking” skills that enable them to implement algorithms, and an understanding of the data sciences needs of medicine. This joint Ph.D. degree in Biomedical Data Science and Informatics will help ensure that South Carolina has the workforce it needs to remain competitive in the health care of tomorrow and to make available to its citizens the many medical breakthroughs that machine and deep learning are predicted to bring.

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MUSC researchers aim to link the microbiome to health and disease

THE UNDERAPPRECIATED MAJORITY

BY MATTHEW GRESETH

“Our darkest fiction is full of Orwellian dystopias, shadowy cabals, and mind-controlling supervillains. But it turns out that the brainless, microscopic, single-celled organisms that live inside us have been pulling on our strings all along.”

– Ed Yong, *I Contain Multitudes: The Microbes Within Us and a Grand View of Life*

Microbes were once seen exclusively as foreign invaders and antibiotics as our principal weapon against them. In truth, we mostly live in harmony with our microbiome — the totality of bacteria, fungi and viruses that colonize virtually every niche in the human body. Indeed, bacterial cells outnumber our own cells by a factor of ten.¹ These commensal bacteria do not cause disease and often serve vital biological functions. In fact, when the balance of microbes is off, we become more susceptible to disease, suggesting that rebalancing the microbiome could have therapeutic benefit.

The past 15 years have seen an explosion of microbiome research. This was in part due to clinical successes of microbiome-related interventions, such as fecal transplants for controlling *Clostridium difficile*, and in part to advances in techniques for culturing and sequencing microbes and in interpreting the large datasets that result.¹

To ensure its clinicians and researchers can help create new microbiome-based therapies, MUSC is ramping up its microbiome

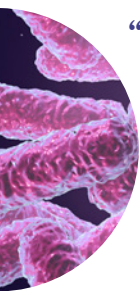
infrastructure, providing support in sequencing the microbiota and in analyzing the resulting datasets.

Building a microbiome infrastructure at MUSC

Studying the microbiome presents a major obstacle — how do you identify and classify the plethora of individual bacterial species that constitute the microbiome? The first step is to purify the DNA. The South Carolina Clinical and Translational Research (SCTR) Institute Nexus Research Laboratory, led by manager **Amy Gandy, MS**, provides processing of patient samples to extract the DNA, which contains human and microorganismal DNA. Following isolation, the Center for Genomic Medicine specifically amplifies the microorganismal DNA and then identifies the organisms present through sequencing. These data enable researchers, often with the help of bioinformaticists who specialize in analyzing large datasets, to compare microbiomes and identify differences for further investigation.

One current study is headed by data scientist and microbiome researcher **Alexander V. Alekseyenko, Ph.D.**, associate professor in the Biomedical Informatics Center and founding director of the MUSC Program for Human Microbiome Research (<http://phmr.musc.edu>), who received a \$100,000 grant from SCTR to enhance infrastructure for microbiome research. Although SCTR has performed microbiome testing for some time, this grant allows the purchase of state-of-the-art equipment. Now, SCTR will be able to extract and quantify DNA in a more standardized, automated fashion, providing greater availability and turnaround times.

In addition, MUSC supports basic microbiome research through a gnotobiotic animal core, directed by **Caroline Westwater, Ph.D.**, professor in the College of Dental Medicine. Animals in this facility, one of only a handful in the country, are germ-free (no microbiota) or gnotobiotic (defined microbiota). This facility enables researchers to define what microorganisms are present (or absent) in order to identify the causative agent of disease.



“At some point, we should be able to manipulate the microbiome community – then we start to change how we practice medicine.”
- Zihai Li, M.D., Ph.D.

Understanding the role of the microbiome in health and disease

MUSC researchers are already tapping into these resources to explore the role of the microbiome in human health and disease in areas as diverse as infections, lupus, skeletal health and cancer.

Clostridium difficile

C. difficile infections are a major complication for cancer and transplant patients, who are often given antibiotic regimens that destroy the normal microbiota and allow *C. difficile* to overpopulate. Antibiotics have had limited success in treating *C. difficile*, and antibiotic resistance is a major problem for a number of hospital-acquired infections. Fecal transplants provide a promising alternative. In *C. difficile* patients, transplantation of fecal matter from a healthy gut allows for

the re-establishment of a healthy microbiome and has a 90 percent cure rate, compared with 20 percent using antibiotics.² MUSC offers fecal transplants to infected patients under the supervision of **Scott R. Curry, M.D.**, assistant professor in the College of Medicine, who is also tasked with *C. difficile* surveillance. By tagging each case with a zip code, Curry tracks the movement of each case so that appropriate cleaning measures can be taken.

Candida albicans

Candida albicans is a commensal fungus found on the skin and mucous membranes of 40 to 60 percent of healthy adults. *C. albicans* becomes infectious when there is a shift in the make-up of the microbiome, known as dysbiosis. The research of Caroline Westwater, Ph.D., aims to better understand the mechanism of this shift.

“I look at the interface between the host and the microbe. There is a battle between those two things all the time. For most of us, that battle reaches a stalemate. But in some individuals it shifts and the outcome is disease,” explains Westwater.

By focusing on host-microbial interactions, the Westwater lab has identified one possible mechanism that protects the host from disease — the host synthesizes a novel peptide that exhibits anti-fungal properties. Westwater is trying to better understand how the peptide controls *C. albicans* and whether other molecules mimicking this peptide could be even more effective.

Lupus

Lupus is a systemic autoimmune disease caused by the production of autoantibodies that attack the self, resulting in inflammation of vital organs. Researchers have identified over 50 genetic risk factors for lupus; however, these changes explain the cause of only 20 to 30 percent of lupus cases. This led **Diane L. Kamen, M.D., M.S.C.R.**, associate professor of Medicine in the Division of Rheumatology, to examine the potential contributions of environmental factors to lupus.

Over the past eight years, Kamen’s group has worked with lupus patients to analyze how diet may influence the development of lupus among people at risk, particularly African American women. This large observational study explores whether a Western diet influences the risk of lupus and the severity of lupus. Kamen’s research team has taken this one step further to determine if there are changes in the microbiome that cause lupus risk and severity.

To address this question, Kamen’s group is collecting blood and stool samples from patients with lupus and controls without lupus

every two years. When combined with the already collected dietary data, this information provides a large, complex dataset to determine if there is a correlation between the microbiome and the production of autoantibodies, which appear before disease symptoms. Associations between the microbiome and autoantibody production could be a predictor, and potentially a treatment, for lupus.

“That’s the thing we’re really hoping: if we can find a connection between the microbiome and the development of autoimmune disease, then we can develop safe methods to prevent autoimmune diseases like lupus,” says Kamen.

Skeletal health

The young adult skeleton begins a state of slow, continuous deterioration around age 30, which is currently unexplained. The field of osteoimmunology, focused on the interface of the skeletal and immune systems, was recently expanded to include the microbiome.

“The gut microbiota is a critical regulator of the systemic immune response that has profound effects on bone remodeling in the young adult skeleton,” says **Chad M. Novince, D.D.S., Ph.D.**, assistant professor in the Colleges of Dental Medicine and Medicine who studies the impact of the microbiome on skeletal metabolism.

In a study published in *Scientific Reports* in 2017 (doi:10.1038/s41598-017-06126-x), Novince and colleagues examined the contribution of the microbiome to skeletal remodeling and showed, for the first time, a signaling pathway that links the gut, liver and skeleton.³ With the gnotobiotic animal core, Novince’s team monitored young adult specific-pathogen-free and germ-free mice to discern the immunomodulatory effects of the commensal gut microbiota on physiologic bone remodeling. The healthy gut microbiota was found to produce metabolites that travel to the liver, where they have profound effects on bone maintenance. Consequently, the healthy gut microbiota plays a heretofore underappreciated role in bone remodeling, inducing bone loss. These data advance our understanding of skeletal physiology and have significant implications for the prevention of skeletal deterioration in health and disease.

Cancer

As we age, we may enter a chronic proinflammatory state that dampens immune activation and may allow tumor cells to proliferate. One theory suggests that this is caused by an age-related shift in the microbiome. Several researchers at MUSC, including **Zihai Li, M.D., Ph.D.**, professor and chair of the Department of Microbiology and

Immunology and co-leader of the Cancer Immunology Program at the Hollings Cancer Center, and **Bei Liu, M.D., M.P.H.**, associate professor in the Department of Microbiology and Immunology, are studying the interplay between the immune system and the microbiome in colitis and colon cancer.

The protein CNPY2 activates the endoplasmic reticulum (ER) stress pathway and is highly expressed in the gut. Li’s group showed that mice lacking CNPY2 exhibited a reduction in ER stress activation and protection from inflammation-induced colitis. Further examination of this pathway, and its impact on the gut microbiome, may facilitate the development of CNPY2 inhibitors that provide a novel treatment for colitis and possibly colon cancer.

Liu’s work is part of the MIST (Mucosal Immunology Studies Team) initiative, a very prestigious nationwide program focused on identifying the most basic aspects of immunity. Liu’s group showed that mice lacking the chaperone protein grp94, specifically in dendritic cells, spontaneously develop colitis and colon cancer due to dysbiosis of the gut flora. They found the prevalence of the commensal bacterium, *Akkermansia muciniphila*, expanded to constitute up to 50 percent of the microbiome. Working with the gnotobiotic animal core, they will define *A. muciniphila*’s direct contribution to colitis and colon cancer. In the future, Liu will expand these studies to humans and determine if specific commensal bacteria could serve as predictive markers for colon cancer.

Looking forward

Currently, research is focused on establishing associations between the microbiome and various diseases. As the field progresses, research will need to move beyond correlative studies to developing microbiome-based therapeutic innovations.

“Right now we are still doing this survey kind of work, trying to describe this kind of correlation,” says Li. “At some point, we should be able to manipulate the microbiome community – then we start to change how we practice medicine.”

Moving forward, MUSC is positioned to lead that change. Clinicians and researchers have already begun to define the role of the microbiome in both health and disease and are ready to move towards treating disease through modulation of the microbiome.

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E-Cigarettes:

What Can I Say?

Increasing Use and Knowledge Gaps Create Need for Individualized Patient Discussions



SUBJECT MATTER EXPERTS: DR. KENNETH CUMMINGS,
DR. MATTHEW CARPENTER, DR. PAMELA MORRIS

BY KATHARINE HENDRIX



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Dr. Cummings is on the advisory committee/board for Pfizer, Inc., and is an expert witness for plaintiff's attorneys. Dr. Morris is on the advisory board for Amgen and Sanofi Regeneron. Dr. Carpenter and Katharine Hendrix have no relevant financial relationships to disclose.

On completion of this article, readers should be able to:

- Describe the current evidence regarding the health effects of e-cigarette use relative to smoking traditional cigarettes.
- Recognize key differences between vaping nicotine and smoking combusted tobacco.
- Identify knowledge gaps regarding e-cigarette use that future research should fill.
- Be able to tailor discussions about e-cigarette use to individual patient needs and health and smoking histories for those who: 1) smoke traditional cigarettes and want to quit; 2) failed previous quit attempts using guideline-recommended strategies; and 3) do not regularly smoke but report occasional e-cigarette use.

People smoke for the nicotine, but die from the toxins carried in the smoke. Separating nicotine from smoke is one way to make nicotine administration less dangerous. E-cigarettes (ECs) represent a class of products that use electricity to heat liquids containing nicotine to allow for nicotine administration with lower levels of exposure to the toxins found in cigarette smoke. By separating nicotine in an inhaled vapor without combusting tobacco, one can fundamentally change the conversation about smoking addiction and disease.¹ ECs were first introduced in the US about 10 years ago. Prevalence of EC use among US adults is approximately four to six percent but is much higher among existing smokers (38 percent have ever used and 11 percent currently use ECs).² Use of ECs is increasing rapidly and now represents the most commonly reported quitting aide used by smokers. Unfortunately, many healthcare providers are unprepared to discuss EC use with patients.

What are E-cigarettes?

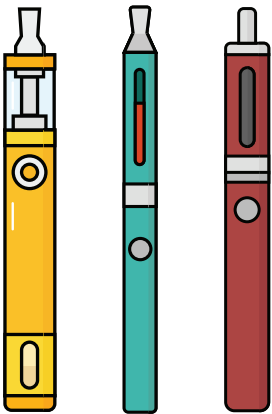
The US Food and Drug Administration (FDA) regulates ECs as tobacco products because nicotine is derived from tobacco, although the majority of ECs do not contain any tobacco.³

ECs contain a battery, e-liquid reservoir, heating element or atomizer and mouthpiece. They operate by atomizing or heating the e-liquid (nicotine and flavoring chemicals dissolved in propylene glycol and/or glycerin) into a vapor that users inhale (a.k.a., “vaping”). Many ECs can be user-adjusted to deliver more or less nicotine

per puff. A newer class of ECs, called “heat-not-burn” devices, do contain some tobacco but do not involve complete tobacco combustion. They generally deliver nicotine in a similar vaporized manner but with slightly higher levels of toxins than ECs.

Unknown Health Impacts

Because ECs are relatively new products and used differently from cigarettes, long-term studies documenting health outcomes are not available. Thus, many questions remain unanswered including the potential impacts of: long-term nicotine exposure, inhaling aerosolized e-liquid, heating e-liquids to high temperatures and ECs on population health indices.⁴



Known Health Impacts

Biomarker studies of EC users clearly show lower levels of exposure to toxins found in cigarette smoke. That said, EC vapor is not benign, and some products have been found to contain carbonyl compounds, oxidants, aldehydes, particulates and volatile organic compounds, albeit at lower levels than generally found in cigarette smoke.⁵ Nicotine, which is the primary psychoactive ingredient in cigarette smoke and EC vapor, is known to be

addictive and potentially unsafe for pregnant women and those predisposed to cardiac problems. However, for non-pregnant, healthy adults, exposure to nicotine in the absence of tobacco smoke appears to be fairly safe. Nicotine may contribute to acute cardiovascular events and accelerated atherogenesis, but studies of “snus” users (a low nitrosamine smokeless tobacco) have not found increased risks of myocardial infarction or stroke. That said, studies do suggest nicotine may contribute to acute cardiovascular events in those with underlying coronary heart disease.⁶ Still, the risks from ECs appear to be far lower than from cigarette smoke exposure.

Comparison to Smoking Tobacco

Even if EC vapors contain harmful toxicants, studies consistently show that this vapor contains substantially fewer toxicants than tobacco smoke. It is generally agreed that ECs pose much lower health risks than smoking.⁴ A study comparing combusted tobacco and EC emissions that calculated lifetime cancer risks concluded that the cancer potency of ECs was less than 0.5 percent of tobacco smoke.⁴

Although ECs may pose some cardiovascular risk, particularly in people with existing cardiovascular disease, comparisons indicate that the cardiovascular risks of vaping are probably lower than for smoking.⁶ Biomarker studies (including for acrolein, a potent respiratory irritant) find similar levels among EC users and non-smokers.⁴ No second-hand exposure risks from EC vapor have yet been identified.

A 2018 review concluded that vaping poses a fraction of the risks of smoking and switching from smoking to vaping conveys substantial health benefits.⁴ Even if smokers partially switch and engage in

“dual use” of both combusted cigarettes and ECs, individual harm is likely reduced as well, though quantifying this level of reduced risk is difficult, as some dual users predominantly smoke and only occasionally vape, while others predominately vape and only smoke occasionally.

Discussing E-cigarettes with Patients

While we wait for conclusive studies and guideline updates, EC use is increasing. Although not FDA-approved for cessation, ECs are the most popular quit aid among smokers and evidence indicates that EC use may increase cessation rates.⁷ Other reasons for EC use are curiosity, flavor and perception of lower health risks than smoking.

US smoking cessation guidelines were last updated in 2008 and do not address ECs.⁸ So, how might providers discuss EC use with their patients? Extensive literature on health behavior change emphasizes tailoring discussions to the individual’s readiness and prior attempts to change.⁹ That is, different types of patients need different information.

Type 1: The patient is ready to quit. Provide the currently recommended strategies of counseling (individual or group) and medication (FDA-approved nicotine replacement gum, inhaler, lozenge, nasal spray, and/or patch and/or bupropion or varenicline). Of these, varenicline and combination nicotine replacement has shown superior efficacy.

Type 2: The patient is not contemplating quitting. Discuss the health risks of smoking, strongly encourage smoking cessation and provide information regarding counseling and cessation aids that can be prescribed when they are ready to quit. If the patient is unwilling to try FDA-approved methods to quit, discussion of ECs as an alternative is warranted.

Type 3: The patient previously tried quitting with evidence-based, FDA-approved strategies but failed. Discuss switching from smoking tobacco to using ECs. Emphasize that: 1) ECs are less harmful but not harmless; 2) long-term effects are unknown; and 3) the goal is to eventually stop using ECs.

Type 4: The patient does not smoke combustible tobacco but occasionally “vapes.” Advise against using ECs—especially for adolescents and young adults. Emphasize that: 1) ECs are not harmless; 2) nicotine is addictive and harmful; and 3) many health impacts are unknown.

The information below provides responses to questions that patients may ask about ECs.¹

What is the best way to stop smoking?

- Behavioral counseling combined with FDA-approved stop-smoking medications (ie, nicotine replacement therapies, varenicline, bupropion) is the most effective treatment.
- ECs have not been approved as a stop-smoking treatment by the FDA. However, smokers who cannot stop smoking with FDA-approved medications may benefit from ECs as a cessation aid, though evidence is limited.
- Because ECs deliver nicotine, they are likely to help reduce urges to smoke and ease withdrawal from cigarettes.

Are ECs safe?

- ECs are not risk free, but evidence suggests they expose users to much lower levels of toxins when compared to combustible tobacco cigarettes.
- Long-term risks are unknown, but common side effects include irritation of the mouth and throat and dry cough. You should stop using ECs after successful cessation of tobacco cigarettes.
- Ingestion of nicotine liquids can be dangerous. Keep e-liquids in childproof containers and out of the reach of children.
- Protect EC devices from extreme temperatures by not leaving them in direct sunlight or in a vehicle during freezing temperatures.
- Avoid vape battery explosions by:
 - a. Using devices with safety features such as button locks, vent holes and overcharging protection;
 - b. Keeping batteries in a case to prevent contact with metal objects (i.e., coins, keys);
 - c. Not charging the device with a phone or tablet charger;
 - d. Not charging the device unattended; and
 - e. Replacing batteries if they get damaged or wet.

What type of EC should I use?

- There are many different models of ECs with different levels of nicotine delivery and flavors, and more advanced models deliver nicotine more efficiently and seem to work best for those trying to quit smoking tobacco cigarettes.
- Carefully read and understand the manufacturer's recommendations for use and care of the EC. If the device did not come with instructions or you have further questions, contact the manufacturer.
- Go to the FDA website for updates on ECs and safety information at: <https://bit.ly/2noucJr>.

How should I use EC?

- Daily EC use is generally more effective for quitting smoking than intermittent use.
- It may take practice to deliver the proper amount of nicotine needed to relieve the urge to smoke.
- Stop use of combustible tobacco cigarettes as soon as possible and discontinue ECs when you are comfortable that you have quit cigarette smoking for good.
- Avoid dual use of cigarettes and ECs if possible.
- ECs may be used along with an FDA-approved stop-smoking medication such as a nicotine patch or varenicline.

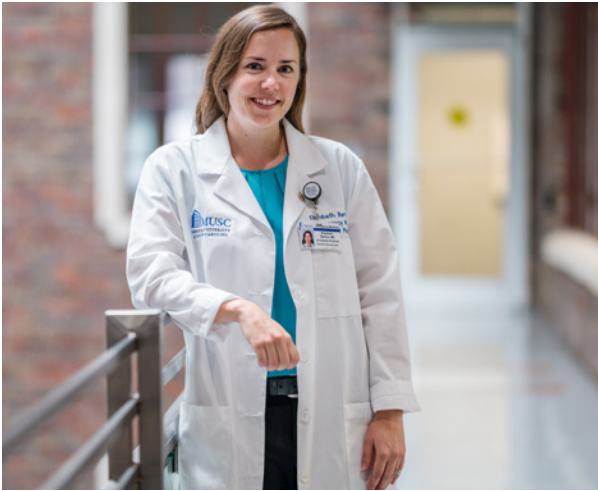
Where can I use ECs?

- Many public places do not allow smoking or use of ECs indoors.
- While the risks from secondhand vape are lower than from secondhand smoke, it is best to vape outdoors and not around others.

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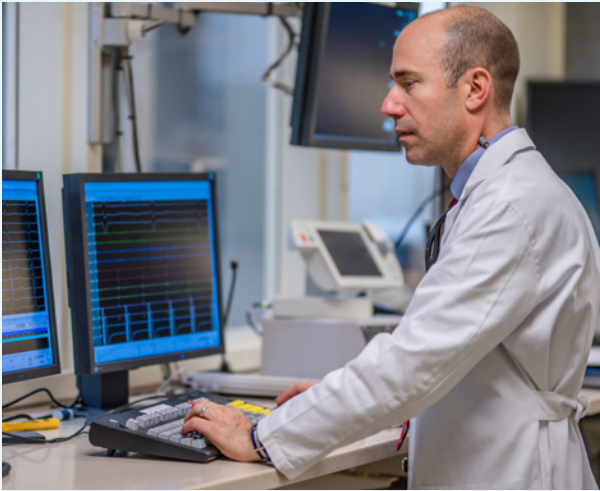
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