PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // FALL 2015

New Aortic Center

Innovative treatments for complex aortic diseases

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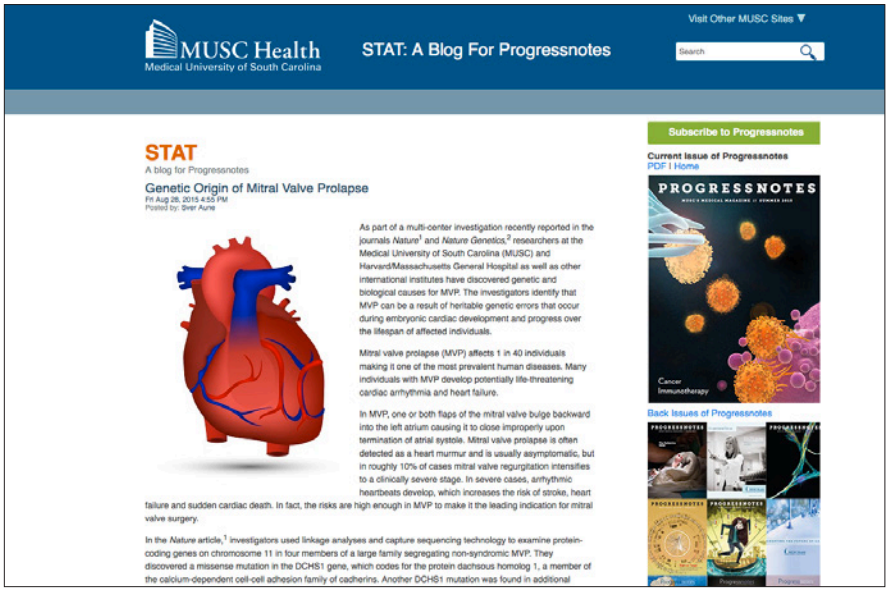

Upcoming CME Conferences

The following conferences, sponsored by the Medical University of South Carolina, will be held in Charleston, SC unless otherwise noted. Visit www.musc.edu/cme for a complete list of CME conferences.

October 22-23, 2015	MUSC 18th Annual Healthcare Leadership Conference/CSHSMD Fall 2015 Conference *Charleston Marriott Hotel*
October 23, 2015	MUSC Lean Six Sigma Healthcare Symposium *Trident Technical College, North Charleston*
November 11-13, 2015	Neonatal Pharmacology 2015: Incorporating Evidence-Based Practice into Clinical Decision Making *Francis Marion Hotel*
November 14, 2015	2nd Annual Comprehensive Stroke & Cerebrovascular Update *Mills House Hotel*
November 20-22, 2015	Rock the MOC! Neurology Maintenance of Certification Board Review Course *MUSC Bioengineering Bldg.*
December 4-5, 2015	Cleft & VPD Interactive Conference *Courtyard Marriott*
December 4-6, 2015	18th Annual Frontiers in Pediatrics *Francis Marion Hotel*

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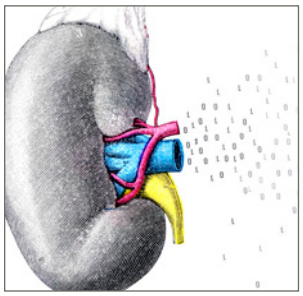
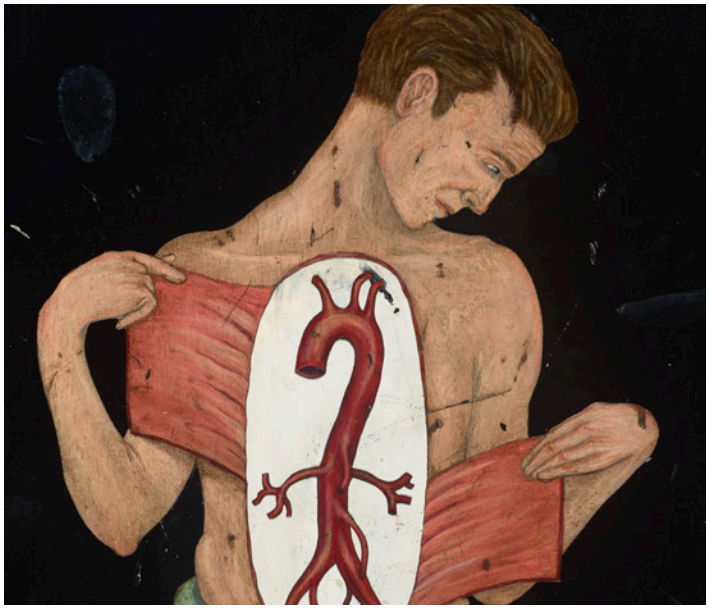




On the cover: A multidisciplinary approach to treating aortic disease. Illustration "Open" by Jason Holley.

Digital Exclusive

Strong Start

Health care management helps Medicaid mothers deliver healthy babies

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

BUYING TIME

Unique laser treatment on a child slows her aggressive tumor

BY LINDY KEANE CARTER

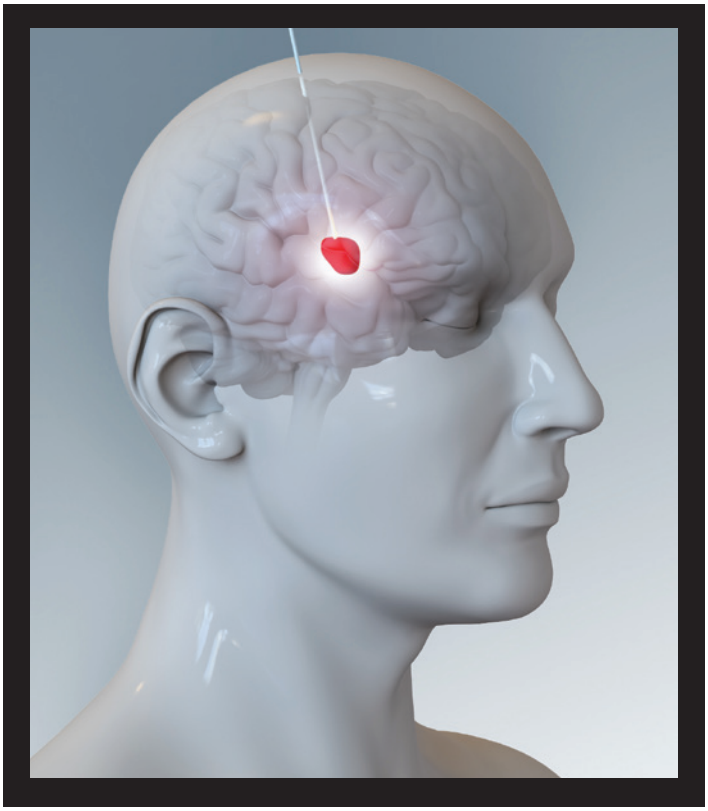


Illustration by Emma Vought

Everything about the youngster's brain tumor tied the hands of **Ramin Eskandari, M.D.**, Assistant Professor of Neurosurgery at MUSC Health. It was located near the basal ganglia and the thalamus, areas deep within the brain that are hard to reach and packed with the neurons that control critical functions, such as movement, sensory relay, temperature regulation, and sleep/wake cycles. The tumor was growing quickly, but surgery to remove it was out of the question given the damage that surgery would likely do to such high-priced real estate. That left radiation, but the patient was nine years old, too young for the inevitable brain damage of radiation. Eskandari needed to buy some time while her brain developed. He didn't have it.

"So we asked ourselves what are the ways we can hold off the tumor a little," says Eskandari. "That's when this new laser became an option."

Laser interstitial thermal therapy has been used for years to ablate brain tumors, but certain technical factors made the traditional technology less than ideal in this case. The advanced technology of a new tool, the NeuroBlate System™ (Monteris Medical Inc., Plymouth, MN), brought benefits that gave Eskandari a viable option for his patient. Fixation of the probe entry device on the head is less susceptible to shifting, the laser has a 350 degree firing range (as opposed to only straight ahead), and thermal damage to surrounding tissue is more precisely controlled. But even the solution had its downsides.

There have not been very many cases of pediatric brain tumors ablated with lasers in the U.S. In researching those few, Eskandari could not find a single laser ablation procedure that was performed in this location in the brain. The procedure would be a first for Eskandari, for the hospital, and for the state. It would be risky for the patient. She faced possible weakness or numbness afterward, difficulty swallowing, and Eskandari could not say how long that might last. "All I knew was this was a much less invasive option than surgery, which would definitely cause more damage," he says.

After presenting the case to the hospital's tumor board and oncologists, discussing previous cases with the manufacturer, and consulting with the family, Eskandari decided to use the NeuroBlate system. On May 15, the child was placed in a magnetic resonance imaging (MRI) machine that sent images to Eskandari in a control room where he was guided by the yellow and green outlines of the heat so he could avoid damaging healthy tissue. Afterward, he was prepared for the worst.

In the recovery room, the patient had weakness on her left side for about three hours. She went home without symptoms 18 hours later. If in three months when surgical swelling is gone, Eskandari sees any reduction in tumor volume plus continued normal function, he will feel that the procedure was a success. "Tumor-wise, we'll see," he says. "But even if the tumor shrinks 50%, that will give her years off of getting radiation. The best case scenario is radiation kills the rest of it and we just monitor her for the rest of her life."

This system, as well as other MRI-guided laser systems, e.g., Visualase® (Medtronic, Inc., Minneapolis, MN), also benefit epilepsy patients, whose seizures often originate with lesions deep within the brain. **William A. Vandergrift, M.D.**, Associate Professor of Neurosurgery at MUSC Health, has treated two epilepsy patients with NeuroBlate and three with Visualase. For more information on one of his Visualase procedures, visit http://academicdepartments.musc.edu/catalyst/archives/2015/7-17Visualase.html.

IMPROVING DIAGNOSTIC ACCURACY

Genomic classifier helps reduce ambiguity in lung cancer diagnosis

BY LINDY KEANE CARTER

Every year, approximately 250,000 bronchoscopies are performed to rule out cancer when suspicious lung nodules or lesions are found on computed tomography (CT) scans. But bronchoscopy has limited sensitivity (the ability to detect those patients who are truly positive for cancer) and therefore can be inconclusive, leaving the physician with the dilemma of how best to advise the patient. Should the physician recommend surgery or other invasive diagnostic procedures or wait and monitor with periodic CT scans, accepting the risk that the patient may have cancer?

In the July 16, 2015 issue of the *New England Journal of Medicine*, **Gerard A. Silvestri, M.D., MS**, Hillenbrand Professor of Thoracic Oncology in the Division of Pulmonary, Critical Care and Sleep Medicine at MUSC Health, and colleagues reported the results of two studies validating a novel diagnostic test, a bronchial genomic classifier that measures the expression of 23 genes associated with lung cancer. This gene array is detected in cells from the proximal airway but can indicate the presence of malignancy or disease processes in distant sites in the lung. The greater the number of oncogene "signatures" in the airway, the higher the likelihood that the lesion in the lung is malignant. This puts more diagnostic information in the hands of the physician trying to advise a patient of the best next step. If the patient is at low risk of malignancy, he or she can be monitored with CT scans instead of undergoing invasive diagnostic procedures that can be risky.

"We have seen promising results in the ability of this classifier to aid in predicting the absence of lung cancer when evaluating new lung masses, which makes this a potentially valuable test for patients and physicians," says Silvestri.

The two independent, prospective, multicenter, observational studies were Airway Epithelial Gene Expression in the Diagnosis of Lung Cancer (AEGIS) trials (AEGIS-1 and AEGIS-2) (NCT01309087 and NCT00746759, respectively). The studies enrolled 639 former and current smokers undergoing bronchoscopy for suspected lung cancer at 28 sites in the U.S., Canada, and Ireland. Cytology brushes collected epithelial cells from the mainstem bronchus. Patients were followed 12 months after the procedure or until diagnosis. A diagnosis of lung cancer was established either at the time of bronchoscopy or later by means of biopsy with the use of a transthoracic needle, a surgical biopsy, a second bronchscopic

examination, or other invasive procedure. The combination of the classifier and bronchoscopy increased the sensitivity to 96% (95% confidence interval [CI], 93%-98%) and 98% (95% CI, 96%-99%) in AEGIS-1 and AEGIS-2, respectively, as compared with 74% and 76% for bronchoscopy alone (P<.001).

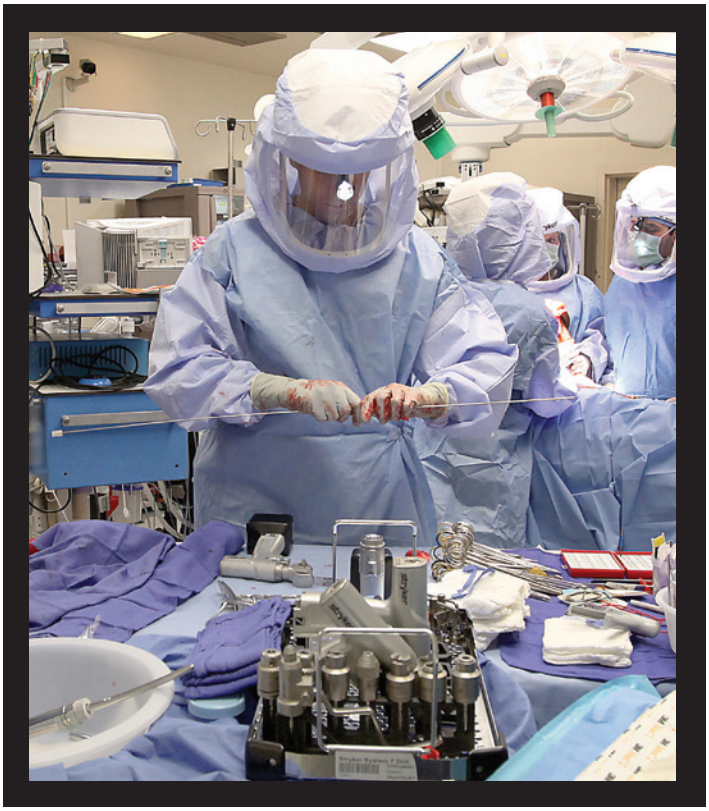
Silvestri says that there were several important findings in the study. "First, bronchoscopy is not as good as we thought it was at establishing a diagnosis of these lesions. Second, in situations where the bronchoscopy is non-diagnostic and the classifier is negative, you can really change how you practice. If I can shunt even a third of my patients away from having an invasive procedure when they are highly likely to have benign disease, then I certainly want to do that," he says.

The Percepta Bronchial Genomic Classifier (Veracyte, San Francisco, CA) will be available in 2016 at approximately 30 U.S. academic and community medical centers where a registry trial will be conducted to measure the degree to which physicians will avoid invasive procedures when the test indicates the lesion is benign.

THE GIFT OF GROWTH

High-tech extendible implant enables femur to grow despite limb salvage surgery

BY LINDY KEANE CARTER



Photograph by Sarah Pack

Dr. Lee Leddy prepares cement for an extendible prosthesis.

Osteosarcoma (bone cancer) in children is rare. Approximately 400 cases are diagnosed in the U.S. every year according to the American Cancer Society. For those children whose cancer involves the growth plate at the end of their arm or leg bone, removal of the growth plate along with the tumor is necessary, leaving them with the possibility of uneven limbs when they stop growing. Rare as well are surgeons who have used the British-made extendible prosthesis that enables the extremity to grow as it would have, a procedure that has been done in the U.S. approximately 100 times since 2002. **Lee R. Leddy, M.D.**, Associate Professor in the Department of Orthopaedics at MUSC Health, is the only orthopaedic oncologist in South Carolina who has experience with the JTS Extendible Bone Implant (Stanmore Implants Worldwide Ltd., Elstree, UK). This implant is designed to be lengthened over time by a magnet to ensure that both legs or arms will be equal in length when a child has finished growing. Leddy has implanted the prosthetic device twice in South Carolina, the most recent recipient being an eight-year-old from Columbia, SC. During the seven-hour surgery, Leddy and the surgical team first removed eight inches of the boy's femur, including the growth plate, while preserving tendons, nerves, muscles, and blood vessels. Then the team assembled and implanted the customized prosthesis. The final step was to carefully replace the vasculature and tissue around the prosthesis and close the wound.

Leddy says this prosthesis is a dramatic improvement over the ways orthopaedic oncologists have previously met the challenges of limb salvage surgery in the skeletally immature patient. "Prior to this implant, the child would often require a surgery to manually lengthen the prosthesis every three to four months," he says. "Being able to reliably lengthen the extremity without surgery is a major advantage. However, it is important to realize how critical the team approach is when treating these complex problems."

The team of specialists who collaborated on this complex case included musculoskeletal radiologists who interpreted radiographs and magnetic resonance imaging reports, pathologists who evaluated biopsy tissues, sarcoma-trained surgical oncologists who helped resect the cancer and reconstruct the extremity, operating room nurses, oncologists who made recommendations regarding chemotherapy, and physical therapists who worked with the patient to help return him to an active life.

During follow-up visits every four to six weeks, the boy will place his leg into a doughnut-shaped magnet that will drive a gearbox to extend the prosthesis nine centimeters over the next eight years, the remainder of the boy's projected growth. In his case, the magnet is proximal to the knee joint because his tumor was in the distal femur. For proximal femoral replacements, the magnet is near the level of resection. For tibia replacements, it is slightly below the knee joint.

Prior to this technology, options for a child whose growth plate had to be removed due to cancer were amputation; rotationplasty, in which the child's ankle is substituted for the knee joint; or implants that required repeated surgeries to lengthen the prosthesis. With this device, future operations are not necessary. In August 2014, **Zeke J. Walton, M.D.**, joined the Department of Orthopaedics, making him the second orthopaedic oncologist at MUSC Health who will be performing this and other procedures in treatment of complex bone cancer cases.

RESEARCH WITH A HEART

MUSC Awarded Grant to Study Health Disparities in Stroke Recovery

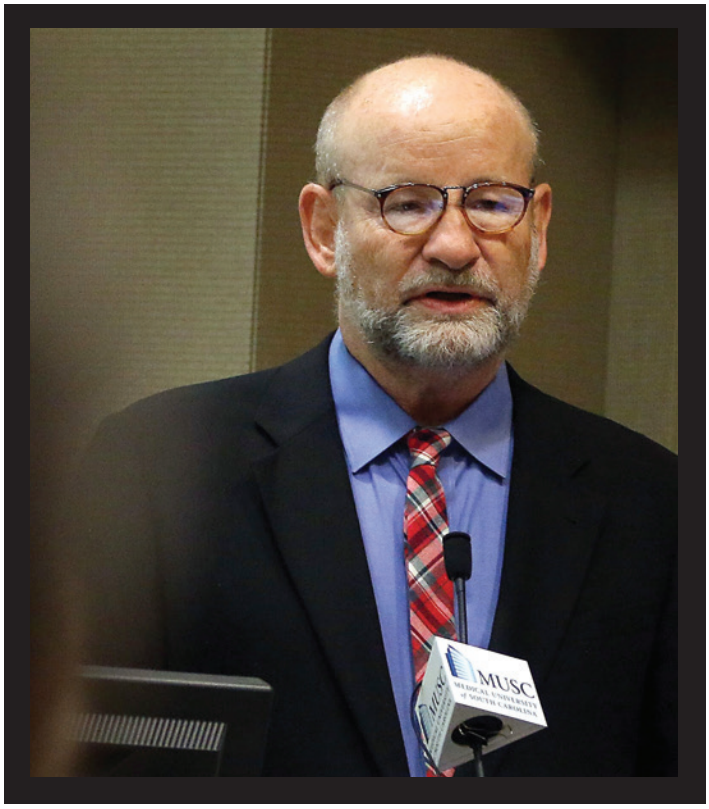
BY CELIA SPELL

African Americans are more likely to experience a stroke and be more adversely affected by it than their white counterparts. In South Carolina, the buckle of the stroke belt, African Americans are twice as likely to die from stroke when compared to whites. Less well known is that recovery after stroke is poorer for African Americans than for whites, and that access to rehabilitation (or lack thereof) does not completely account for this discrepancy.

With the support of a $4 million grant from the American Heart Association (AHA), the largest AHA grant ever given to a South Carolina institution, MUSC is endeavoring to improve stroke recovery in African Americans through a multidisciplinary project that brings together basic and translational researchers in regenerative medicine, neuroscience, and nursing. The four-year project, entitled Wide Spectrum Investigation of Stroke Outcome Disparities on Multiple Levels (WISSDOM), includes research projects with the potential to not only improve our understanding of why African Americans don't fare well in recovery but to use those insights to make a difference in the lives of stroke patients through community interventions.

Mark Kindy, Ph.D., and **Leonardo Bonilha, M.D., Ph.D.,** of the College of Medicine and **Gayenell Magwood, Ph.D., RN,** of the College of Nursing are all principal investigators of the subprojects conducted through WISSDOM. Kindy is exploring whether known stroke risk factors such as hypertension and diabetes that disproportionately affect African Americans also play a role in their recovery from stroke. To do this, he will study the effect of such metabolic factors on vascular stiffness in animal models. Bonilha is using innovative neuroimaging techniques to assess the integrity of brain tissue and neuroplasticity (i.e., the ability of the brain to repair itself) in African American and white patients so that questions about why African Americans have poorer stroke recovery than whites can be answered. Magwood is exploring whether a community-based intervention—a 12-week home-based program coordinated by a nurse and delivered by a community health worker—can improve stroke recovery after patients finish with rehabilitation.

As Director of WISSDOM, **Robert J. Adams, M.D., MS**, Professor of Neurology, will oversee the four-year project and serve as its key contact. **Daniel T. Lackland, Ph.D.**, a long-time collaborator of Adams who has devoted his 30-year career to addressing health disparities in South Carolina and beyond, will serve as WISSDOM's Training Director. **Bruce Ovbiagele, M.D.**, Chair of Neurology, will serve as the head of its advisory committee.



Photograph by Sarah Pack

Dr. Robert J. Adams, Director of WISSDOM

With this WISSDOM grant and the $10.8 million COBRE (Center of Biomedical Research Excellence) in Stroke Recovery awarded last year to found the Stroke Recovery Research Center, MUSC has been rising to the forefront of stroke recovery and rehabilitation research in South Carolina. **Steve Kautz, Ph.D.**, Chair of the Department of Health Sciences and Research and Co-Director of the Center for Rehabilitation Research in Neurological Conditions, is the principal investigator for the COBRE grant.

According to Adams, "The WISSDOM Center will synergize COBRE research by adding a special emphasis on disparity to the overall goal of learning about neuroplasticity and stroke recovery and enhancing recovery for everyone who has a stroke. I could not be happier about having the two grants more or less starting up at the same time and creating synergy right out of the gate."

BETA TESTING

Down Syndrome study may reveal an early biomarker of Alzheimer's Disease

BY SVER AUNE

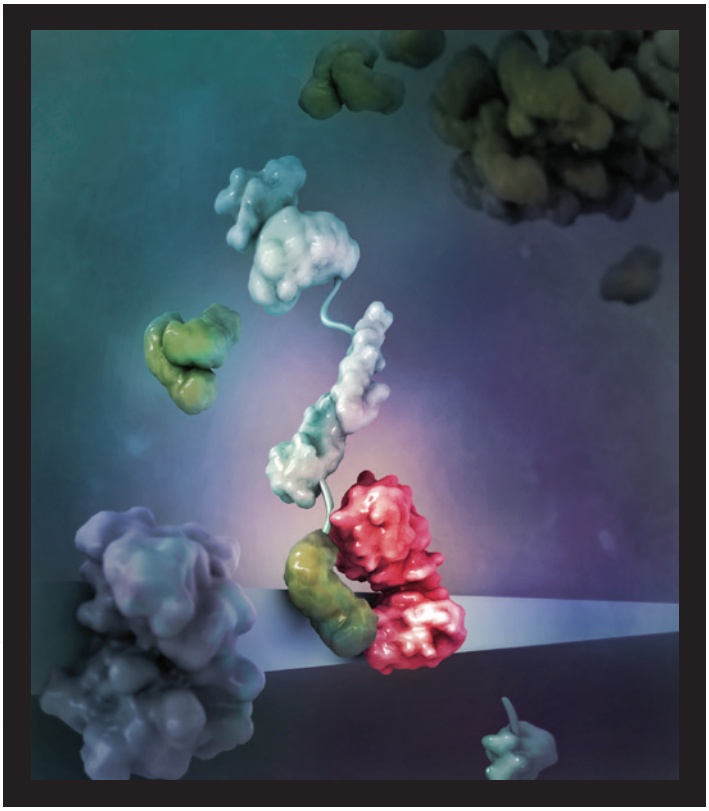


Illustration by Emma Vought

Plaque formation in AD. Naturally occurring amyloid precursor protein (green and white) is cleaved by beta-secretase (pink), freeing the amyloid-beta protein fragment (green).

People with Alzheimer's Disease (AD) develop amyloid-beta plaques and neurofibrillary tangles that cause progressive neuron loss and dementia. A clinical diagnosis of AD is typically made after this process begins, when preventive treatment may be less effective. While advances have been made in AD detection, investigators are searching for an early diagnostic biomarker that could allow clinicians to identify and treat those at greater risk for developing AD.

Intriguingly, a biomarker for AD might be discovered in people with Down Syndrome (DS). Since 1983, due to increased education about DS and higher rates of home and medical care, life expectancy for people with DS has risen from 25 years to nearly 60. This recent increase has likely contributed to the emergence of a new clinical phenomenon: people with DS who reach their thirties begin to develop AD pathology in their brains at alarming rates. As many as 80% of people with DS who reach the age of 60 have signs of AD.

While research has not yet linked an early biomarker to AD, the cause of early-onset AD in people with DS (DS-AD) could indeed lie in their genes. Down Syndrome is caused by a partial or complete extra copy of chromosome 21. Chromosome 21 carries the gene for amyloid precursor protein that is implicated in increased amyloid-beta plaque deposition in the brains of people with AD or DS-AD. However, differences may exist between the two conditions. In brains of people with DS, diffuse amyloid-beta deposits appear during childhood or early adulthood, while these deposits appear at an older age in those with late-onset AD. Mutations in chromosome 21 or other chromosomes are seen in a small fraction (about 10%) of cases of idiopathic AD.

"The Alzheimer's field has about 100 clinical trials going on. There are exactly two for people with DS and AD," says **Lotta Granholm, Ph.D., DDS**, Director of the MUSC Center on Aging. To help bridge this gap, Granholm has commenced a biomarker study that enables physicians statewide to collect potential biomarkers for early-onset AD from the blood of DS patients.[1]

Entering people with intellectual disabilities in clinical trials has been a historically delicate undertaking. Experts plan to advance their research responsibly. Granholm recently helped organize a workshop sponsored by the Alzheimer's Association, the Linda Crnic Institute for Down Syndrome, and the Global Down Syndrome Foundation, which invited AD and DS experts from MUSC and across the country to share their collective knowledge about the links between DS and AD and to offer criteria for conducting AD clinical trials in people with DS. The workshop was covered in the *Washington Post*[1] and was the subject of a recent article in the journal *Alzheimer's & Dementia*.[2]

To aid research on aging, the MUSC Carroll A. Campbell, Jr. Neuropathology Laboratory accepts brain donations from people who have suffered from a variety of aging-related brain disorders, including AD and DS, and serves clinicians and families in the entire state through the South Carolina Aging Research Network. More information can be found at scarn.org and dsconnect.nih.gov.

References

[1] Kunkle, F. (2015, May 22) Why studying Alzheimer's in people with Down Syndrome could help everyone. *The Washington Post* Retrieved from http://www.washingtonpost.com.

[2] Hartley D, et al. *Alzheimer's and Dementia* 2015;11(6):700-709.

TELL-TALE BLOOD

Liquid biopsy offers a useful diagnostic companion for targeted therapies

BY CELIA SPELL

Conventional biopsies are invasive, costly, and sometimes impossible to conduct, but they yield valuable information other methods were unable to provide—until now.

Newly developed liquid biopsies allow physicians to access the biochemical and genetic information of a tumor through a simple blood test. The FDA has not approved the technique thus far, but **Michael B. Lilly, M.D.**, Associate Director for Translational Research at MUSC's Hollings Cancer Center, is confident the technique will be approved in the coming months. Liquid biopsies obtain tumor cells or tumor-derived molecules from the blood, rather than from a direct biopsy of tissue. One type of liquid biopsy isolates circulating tumor DNA (ctDNA) from the blood.

Physicians are finding they can use ctDNA levels in the blood to diagnose and determine the prognosis of a patient while also monitoring the progression of the tumor, as supported by a study published in the February 19, 2014 issue of *Science Translational Medicine* by Bettegowda et al. The study showed that ctDNA was detectable in more than three-fourths of patients with advanced pancreatic, ovarian, colorectal, bladder, gastro-esophageal, breast, melanoma, hepatocellular, and head and neck cancers. The study also found a correlation between ctDNA levels and patient longevity, with higher levels coinciding with decreased survival.

Dr. Lilly is currently studying the usefulness of liquid biopsies in advanced-stage prostate cancer patients to identify the kinds of gene mutations present. He is also designing a clinical trial of targeted therapy in these patients in which liquid biopsies will identify potential participants.

"The liquid biopsy is a fascinating tool, but it's not going to replace studying the original tissue itself," says Dr. Lilly. "The big things are that it's easy, and it can be repeated."

One limitation of the conventional biopsy is that it delivers static information, a snapshot of the tumor at the time of the biopsy. Tumors are known to change their molecular make-up as they progress. Physicians can use ctDNA to monitor the patient's tumor over time, learning about its genetic basis for resistance, using that knowledge to choose targeted gene therapies, and watching for any sign of recurrence.

Another limitation is that the data collected through a conventional biopsy is only indicative of that particular tumor. Patients may have another nodule a few inches away that is genetically different and would require its own biopsy. However, by using ctDNA, physicians can gather information from all the tumors in the body, delivering an overall picture of the genes involved in many cancers.

Rapid advances in genetic sequencing technology have made liquid biopsies clinically feasible. Sensitive methods such as Next-Generation sequencing can detect tiny fragments of ctDNA in a string of normal patient DNA—even when they account for only 0.2% of the total DNA (allele frequency).

Studies support the use of the liquid biopsy as an informative technique that could improve treatment choices and increase survival, but there are drawbacks. For one, finding ctDNA in the blood tells the physician that the patient may have a tumor, but it does not provide any information about its location. Liquid biopsies show most promise for enabling early diagnosis and for choosing and assessing treatment for those with metastasized cancer.

Putting It All Together

The MUSC Health Aortic Center offers cutting-edge therapies and comprehensive care for complex aortic disease

BY LINDY KEANE CARTER
ILLUSTRATION BY JASON HOLLEY

As the body's main artery, the aorta is under a lot of pressure. Ideally, its walls will remain elastic enough to withstand millions of heart beats, but aging or disease can degrade the aorta to the point of bulging or tearing. For decades, MUSC Health surgeons have repaired aortic aneurysms, dissections, damage from trauma, and abnormalities, as well as improved aortic health in general. With the arrival of new therapies and expertise for treating particularly complex aortic pathology, MUSC Health has formalized these services into a new program called the MUSC Health Aortic Center. The Center offers the full spectrum of aortic care, from medical management of disease to cutting-edge procedures to research and clinical trials that advance breakthrough therapies. Specialists in Vascular Surgery, Cardiothoracic Surgery, Cardiology, Interventional Radiology, and Genetics work together to create integrated treatment plans, perform procedures, and track outcomes.

"The MUSC Health Aortic Center is unique in using a multi-specialty collaborative approach to provide the highest level of patient-centered care by combining innovative techniques with cutting-edge technologies," says **Joshua D. Adams, M.D.**, Head of Endovascular Surgery and Surgical Director of the Aortic Center.

The foundation of the Aortic Center team was laid when **Renan Uflacker, M.D.**, then-Director of the Division of Vascular and Interventional Radiology, and **Jay Robison, M.D.**, Chief of the Division of Vascular Surgery, performed the first endovascular aortic repair (EVAR) in South Carolina in 1996, only six years after the procedure was first described. They collaborated on several clinical trials using this new technology that is now widely accepted. **John S. Ikonomidis, M.D., Ph.D.** arrived in 2000 and began developing an open thoracic aortic program. As the technology progressed, Ikonomidis incorporated the minimally invasive technique of thoracic endovascular aortic repair (TEVAR) into the program. He and Uflacker performed the first TEVAR procedure in South Carolina in 2000. In 2006, Robison, Uflacker, and **Claudio Schonholz, M.D.**, Professor of Radiology and Surgery and Assistant Director of Radiology for the Aortic Center (and one of the pioneers in endovascular aneurysm repair), reported South Carolina's first physician-modified abdominal aortic graft to include a visceral artery, further advancing successful complex aortic endovascular procedures.

Interventional radiology (IR) continued to play an increasingly important role, as the IR team's advanced imaging modalities, such as

three-dimensional computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), and intraoperative fluoroscopic imaging, provided clear images to guide the microscopic instruments. With the arrival in 2004 of Schonholz and **Marcelo Guimaraes, M.D.**, Associate Professor of Radiology, a cohesive interdisciplinary team was formed.

"We have a combination of things that makes this place unique," says Schonholz. "First, MUSC has been a pioneer for these types of procedures. Second, we have senior people with a lot of experience as well as the young, newly trained surgeons such as Dr. Adams," he says. Additionally, he points out that MUSC Health can offer new devices and therapies that are not widely available, as industry invites the Aortic Center to help validate those therapies.

Thomas M. Todoran, M.D., Assistant Professor of Medicine, Director of Vascular Medicine, and Medical Director of the Aortic Center, joined the team in 2010. Fellowship-trained in cardiovascular disease, interventional cardiology, and vascular and endovascular medicine, Todoran brings a unique understanding of endovascular therapies as well as preoperative cardiovascular assessment and cardiovascular risk reduction.

"Aortic pathology is often one facet of a larger illness. Optimal care requires a global perspective of the patient's overall condition," he says. "Treatment of such complex patients ideally involves a comprehensive, multidisciplinary approach with all specialties working together to achieve the best outcomes. This is not a common practice at many institutions, but MUSC Health has made it a priority."

Adams arrived in 2013. Fellowship-trained in vascular interventional radiology and vascular surgery, he is uniquely skilled to provide a customized plan based on the patient's anatomy, aortic pathology, and associated clinical conditions. The plan may include either endovascular therapy alone or, in some cases, a hybrid approach that allows him to optimally address the most complex conditions, such as extension of an aneurysm into an internal iliac artery or complex aneurysmal involvement of the juxtarenal, paravisceral, thoracoadbominal, and thoracic aorta, including aortic dissections. These procedures include deployment of branched and fenestrated aortic endografts.

"When a patient's aneurysm involves a portion of the aorta that includes the origins of important arteries such as the celiac, superior mesenteric, and the renal arteries, branched and fenestrated endovascular aortic repair provides a way to stabilize that area," says Adams. These fenestrations (or openings) in the endograft are aligned with the target arteries under X-ray guidance, allowing the endograft to obtain proximal seal in a segment of the aorta that is often healthier. Wires and catheters are then used to navigate through the fenestration and into the artery. A covered stent is used to seal the connection between the fenestration and the artery. This maintains patency of the target arteries at the same time that flow is excluded from the aneurysm. Since there are no large incisions and no cross-clamping of the aorta, this endovascular approach to these complex cases can help avoid many of the problems sometimes encountered with open surgery.

Adams and the team of specialists at the MUSC Health Aortic Center have the most experience with managing such complex aortic problems in South Carolina. The number of fenestrated or branched EVARs they performed from July 2014 to June 2015 has ranked MUSC Health twelfth in the nation for number of those procedures, according to the University Healthsystem Consortium.

One such case involved an 81-year-old man who developed a juxtarenal aortic aneurysm years after surgery to repair an abdominal aortic aneurysm. He had been told by numerous surgeons that nothing could be done since he was not healthy enough to undergo an open aortic aneurysm repair. The patient underwent a successful fenestrated EVAR and went home the next day.

In collaboration with Ikonomidis and other members of the aortic team, Adams is also performing more advanced TEVAR. He cites the case of a 44-year-old patient who was transferred to the MUSC Health Aortic Center with an acute thoracic aortic dissection. It started at the left subclavian artery and went through the descending thoracic aorta into the visceral aorta, which caused significant narrowing of the true lumen and compromised flow to the visceral arteries and the legs. The Aortic Center's specialists deployed a covered stent graft in the proximal descending thoracic aorta over the area where blood was going out of the true lumen and into the false lumen, blocking this blood flow and restoring flow distally.

Next on the horizon, Adams says, will be using even more advanced branched and fenestrated endograft technology in the ascending aorta and aortic arch. Open surgery has been the traditional approach to repairing disease in these segments of the thoracic aorta, a challenging part of the anatomy because of the curvature and blood flow dynamics. With the arrival of newer, more conformable devices and a more precise delivery system, the endovascular approach will be possible, which will be especially beneficial for patients at high risk for surgery.

In addition, Ikonomidis and the Aortic Center team have developed treatment algorithms for the triage and management of urgent cases, and they are putting together plans for an acute aortic emergency hot line to connect South Carolina ER physicians and cardiologists with the appropriate specialist at MUSC Health.

The Aortic Center physicians are supported by a team of other skilled professionals, including experts from Cardiovascular Anesthesia services, Genetics, Rheumatology, and Infectious Disease and a nurse practitioner, Karen D. Doll, MSN, ANP-BC, CVNP-BC dedicated to coordinating care for each patient.

Breakthrough Therapies

Ongoing clinical trials at the Aortic Center offer innovative, investigational devices and medications that are not yet available as standard of care. Adams is the principal investigator for two trials that are establishing safety in branched iliac devices and for another trial evaluating cost savings and safety of performing EVAR percutaneously in the IR suite instead of an operating room. A fourth trial is expected to begin in the near future that will evaluate a conformable abdominal aortic aneurysm stent graft to be used in patients with angulated proximal necks. Ikonomidis is the principal investigator for a trial that is evaluating novel factors for hemostasis.

At the same time, the Cardiothoracic Surgery Research Laboratory, led by Ikonomidis, is pursuing basic science research in aortic aneurysm development. **Jean Marie Ruddy, M.D.**, who won several research awards while a resident in the Ikonomidis lab, has recently joined the faculty, and is investigating biomarkers and treatment strategies that could be used to screen patients, predict the presence of disease, follow the progression of disease without CT or MRI scans, and track therapy outcomes.

The MUSC Health Aortic Center combines all of these distinctions into a comprehensive program that offers the full spectrum of aortic care to patients from all over the Southeast. For more information, go to MUSChealth.org/heart/services/aorta/.

Aortic Center Directors: (clockwise from top left) Dr. Joshua Adams, Dr. John Ikonomidis, Dr. Thomas Todoran, Dr. Claudio Schonholz

The Aortic Center Team:

Vascular Surgeons
Joshua D. Adams, M.D.
Thomas E. Brothers, M.D.
Bruce Elliott, M.D.
Jacob G. Robison, M.D.
Jean Marie Ruddy, M.D.

Cardiothoracic Surgeons
John S. Ikonomidis, M.D., Ph.D.
John M. Kratz, M.D.

Interventional Radiologists
Joshua D. Adams, M.D.
Marcelo Guimaraes, M.D.
Claudio Schonholz, M.D.

Cardiologist
Thomas M. Todoran, M.D., MSc

Care Navigator
Karen D. Doll, MSN, ANP-BC, CVNP-BC

Photograph by Brennan Wesley

Dr. M. Frampton Gwynette offers telemental health services for both children and adults.

Coming to a Screen Near You

MUSC Health offers practice- and school-based telemental health services

BY KIMBERLY MCGHEE

PHOTOGRAPHY BY BRENNAN WESLEY AND SARAH PACK

Each year in the U.S., one in four adults experiences mental health issues, only 60% of whom receive treatment. One in five teens (13-18 years) and more than one in 10 children (8-15 years) experience severe mental illness, but almost half of those aged 8-15 years with a mental illness receive no treatment. Common barriers to treatment include stigma, lack of insurance, and limited availability of providers.

Medication adherence is much poorer and hospital readmission rates much higher in patients with untreated mental health issues. Increased access to behavioral services must figure in any attempt at improving population health. Indeed, expanding access to mental health services is a central tenet of the Affordable Care Act, which advocates both better integration of behavioral medicine into primary care practices and the growth of school-based health centers to extend mental health services out into the community.

In rural states such as South Carolina, most mental health providers are clustered in major urban areas, making it necessary for rural residents in need of those services to travel long distances for care, incurring transportation and child care costs and days lost from work.

Two new telemental health programs at MUSC Health—one practice-based and one school-based—are breaking down these barriers by making mental health expertise available virtually. Through MUSC Health's Virtual Tele Consultation (VTC), MUSC Health psychiatrist **M. Frampton Gwynette, M.D.**, performs mental health evaluations of both pediatric and adult patients and provides consulting services to participating primary care practices. With funding from a Duke Endowment grant, clinical psychologist **Michael A. de Arellano, Ph.D.**, of MUSC's National Crime Victims Research and Treatment Center, is gearing up to implement evidence-based mental health services for children at selected schools along the state's infamous I-95 corridor, where poverty levels rival those of the developing world.

Practice-Based Services

Primary care offices are being asked to serve as medical homes for their patients and to integrate specialty services such as behavioral medicine into the practice. The million dollar question is, of course, how to achieve such integrated care. Telehealth may offer a solution. A recent article in *Lancet Psychiatry* by researchers at MUSC Health and the Ralph H Johnson Veterans Affairs Medical Center reported the results of a study showing that mental health services provided via telehealth are as good as those provided in person.[1]

Practices affiliated with MUSC Health's VTC can refer patients with mental health issues for evaluation and medication management to Gwynette, who is board-certified in both psychiatry and child and adolescent psychiatry. The patient meets with Gwynette via HIPAA-compliant, secure two-way video conferencing, and then Gwynette

Photograph by Sarah Pack

Dr. Sarah Allen of Waccamaw Community Care considers MUSC's telemental health services a blessing for her patients

pauses the session to contact the PCP to discuss the case and his recommendations. Once the two have reached consensus, Gwynette reconnects to the patient and explains the treatment plan. "I've been really jazzed about the ability to talk to the PCPs in real time and I love being able to tell patients that I just talked to their doctors," says Gwynette. "Their eyes say this is how it is supposed to be."

Gwynette has received almost 200 referrals through the program since it began in November 2014. Two of the highest users of the service are James Simmons, M.D., of All Children's Pediatrics, which serves patients in the Beaufort, SC area, and Sarah Allen, M.D., of Waccamaw Community Care in Myrtle Beach.

"My philosophy is that if medicine is going someplace we would like to get there first," says Simmons. "Telehealth is where medicine is going." Simmons, who prides himself on running a progressive and technology-friendly practice, was quick to see how the VTC could benefit his practice. "Telehealth makes it easy for my patients," says Simmons. "They can see a lot more specialists."

Patients and their families have been very appreciative of easy access to mental health services. "We had a young man just the other day whose Mom came in and told me he had done extraordinarily well since Gwynette has been able to modify his medications," says Simmons. He is attempting to expand screening for mental health issues, such as teenage and postpartum depression, and appreciates the opportunity to confer with Gwynette about patients identified as having a mental health issue. "We can pick his brain if we need to."

Allen, who is an MUSC alumnus, has been offering services through the VTC since April and is particularly excited to be able to offer telemental health. "The wait time up in the Grand Strand area for a psychiatrist is months," says Allen. "For someone with a mental health issue, that wait time is huge and really unacceptable." Through the VTC, she is able to schedule patients for a visit with Gwynette within a couple of weeks. "The access is unbelievable," says Allen.

She also believes that providing specialty care such as mental health services via telehealth leads to truly integrated care and a much better experience for the patient. "At MUSC I was part of a team, but in the community I am really on my own," says Allen. "For me to be able to talk to a psychiatrist in real time and have him say 'I think you are on the right track, here is something else I would consider, and I am happy to see your patient again to follow up and see if the changes we have implemented are working,' that's such a blessing."

The VTC was founded in September 2012 by **Samir M. Fakhry, M.D.**, Chief of the Division of General Surgery, with funds from a Duke Endowment grant. Since its inception, VTC has received 1172 referrals to its broad coalition of MUSC Health specialists (as of August 2015), saving patients 91,574 driving miles, 1831 travel hours, and $14,241 in fuel costs. Program coordinator **Laura Langston** provides training to practices and assists them with equipment setup. She has helped motivated practices get up and running in as few as six weeks. For a list of currently available specialty services and a map showing the locations of current VTC sites, visit muschealth.org/telehealth/vtc/index.html. Those interested in affiliating with the VTC should contact Langston at langstl@musc.edu.

School-Based Services

It is estimated that 20% to 25% of children and teens in the U.S. are affected by mental health issues, and yet only 36% of them receive treatment.[2] This is unfortunate, because one-half of all chronic mental illnesses begin to manifest by age 14. If they go unnoticed in childhood, years may pass before they are diagnosed, delaying treatment that is more effective if begun early. Children with untreated mental illness do not perform as well academically; indeed, the National Alliance on Mental Illness (nami.org) estimates that 50% of students with emotional or behavior disorders drop out of school.

One answer could be providing mental health services to schools via telehealth. In 2015, MUSC Health was awarded a three-year $600,000 Duke Endowment grant (PIs: **James T. McElligott, M.D.; Michael A. de Arellano, Ph.D.**) to provide school-based telehealth and telemental health services to underserved South Carolina counties. **Regan Stewart, PhD,** is leading the mental health component of the project with the support of school-based tele-health nurse practitioner **Kelli Garber, MSN, APRN, PPCNP-BC,**

Photograph by Sarah Pack

Dr. James Simmons of All Children's Pediatrics demonstrates the technology used for telemental health sessions.

and program manager **Elana Wells, MPH**. Its ultimate goal is to establish telehealth services in 15 schools in Williamsburg, Sumter, Charleston, and Bamberg counties and to create a sustainable model for continuing the project after funding ends. de Arellano will direct the efforts to establish telemental health programs in selected schools and to adapt evidence-based protocols for the management of mental health in adults to a pediatric population. Telehealth will be used both to triage patients in need of mental health services—deciding which ones are appropriate for outpatient therapy and which ones require a greater level of intervention—and to conduct therapy. On-site evidence-based mental health services can benefit students and improve the culture of a school, as de Arellano knows firsthand. Under the supervision of de Arellano and **Cristina M. Lopez, Ph.D.** of the College of Nursing, interns from MUSC have served as on-site counselors at R.B. Stall High School in North Charleston, providing trauma-focused cognitive behavioral therapy. Principal Kim Wilson admits that he underestimated the need for this program: "When Mike [de Arellano] first approached us with this, I was thinking this will be a great program but it probably won't last. Within three weeks, we had a waiting list of kids and families who were needing this kind of attention."

Currently, therapists are available five days a week, even through the summer. "I don't see how we ever did without it," says Wilson. He is convinced that the program played a role in graduation rates increasing from 48% to 65%: "I'm positive that some of the kids needing these services would never have stayed in school. Now they have a chance and the same hopes and dreams as other kids."

As part of the Duke Endowment grant, de Arellano is hoping to provide on-site counselors "virtually" to selected schools in Williamsburg County. He has already provided such services to a high school in Florence County in a past collaboration with McElligott. He and his staff are currently meeting with school officials to determine their needs and hope to tailor programs to fit the needs of the selected schools. If the program proves successful and sustainable, he plans to expand it to schools without access to mental health services in other counties. "No matter where children are in South Carolina, they can have access to high-quality, evidence-based mental health treatment," says de Arellano, describing his vision for the program.

To learn more about the school-based telehealth program available through the Center for Telehealth, visit http://www.muschealth.org/telehealth/school-based/index.html. Schools interested in joining the program should contact Wells at navon@musc.edu.

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THE BIG DEAL ABOUT BIG DATA

MUSC Health partners with IBM Watson to offer data-driven care for kidney transplant patients

BY CELIA SPELL

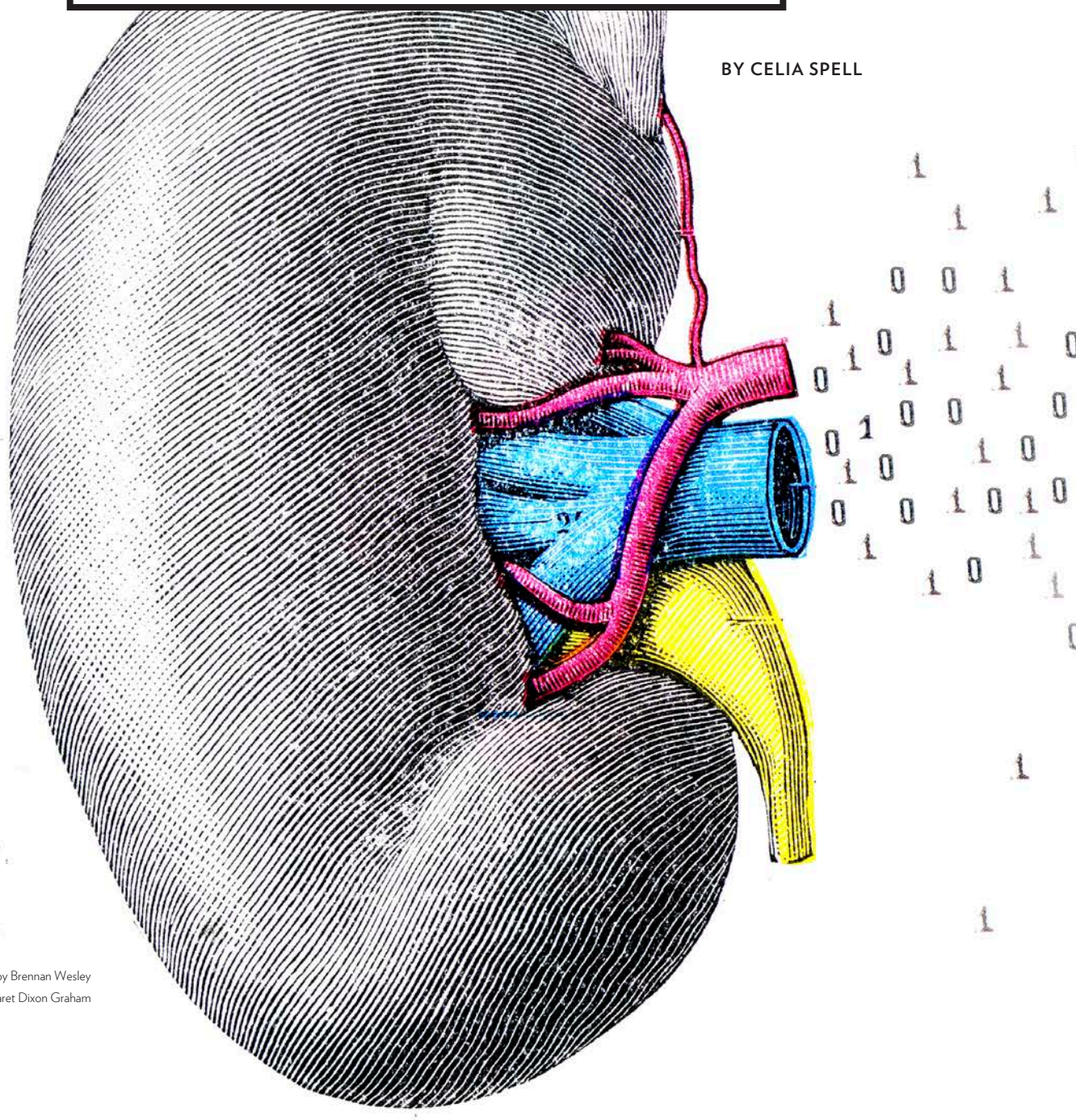

Illustration by Brennan Wesley and Margaret Dixon Graham

Hospitals collect reams of data every day, including the number of patients admitted, their vital signs, the length of their stay in recovery—and that's just the beginning. Processing all of this information can be difficult, so hospitals have started partnering with IT companies to help consolidate and reveal the implications of these data. MUSC Health has decided to harness the power of IBM Watson to do just that.

This treasure trove of data can be overwhelming to anyone trying to pick out patterns and trends, but IBM Watson has been working with businesses and other hospitals to make this process smoother. **Titte Srinivas, M.D.**, a transplant nephrologist and Professor of Medicine at MUSC Health, wants to incorporate this technology into the management of his kidney transplant patients by practicing data-driven care. Information about treatment history, risk factors, and outcome trends will help inform and guide their care.

"I want the electronic medical record to become the intelligent brain that guides us toward better outcomes, not what most clinicians see it as now—an expensive, passive data repository," says Srinivas.

Watson, a commercial cognitive computing system created by IBM, was all over the news in 2011 for winning Jeopardy! Since then, the program has been modified for healthcare applications. MD Anderson is using IBM Watson to help select patients for targeted gene therapies. CVS Health announced its own partnership with IBM Watson in *Fortune* magazine on July 29 to help healthcare professionals crunch data more effectively. MUSC Health is one of only a handful of hospitals using Watson to analyze data, and it is the first to use it for transplant patients.

Watson will strengthen the Kidney Transplant Program at MUSC Health by cataloging all of its information. As a computing system, Watson can read and understand both structured and unstructured data, meaning it can process both numbers and longer, freestyle notes. Since Watson comprehends natural language, physicians no longer have to read through pages and pages of information to access the most important aspects of a patient's health. The program can do it for them. Srinivas says it is important to look at the information we already have and analyze it. He wants to "use our past data to guide our future practice."

The Scientific Registry of Transplant Recipients (SRTR) currently predicts various outcomes associated with kidney transplant, but it mainly captures baseline data and does not incorporate dynamically evolving information that accumulates during patient care. The predictive models that will be built using Watson will consider patient variables such as cholesterol levels, blood pressure, drug levels and dosage, and the clinical events that happen after the transplant. By improving upon the SRTR variable, physicians at MUSC Health can offer the best possible treatment based on the trends in this information. For instance, if trends in the data show that patients with particular vital signs respond best to a specific type and dosage of medication, then the transplant physician would prescribe them that medicine at an appropriate dose.

Srinivas has been working with **David J. Taber**, **PharmD**, of the Division of Transplant Surgery and **Patrick D. Mauldin, Ph.D.**, of the Division of General Internal Medicine & Geriatrics to bring IBM Watson to MUSC Health, and they are confident this program can help kidney transplants be more successful. "Our ideal is that you die of natural causes 25-30 years after the transplant," Srinivas says.

Srinivas, Taber, and Mauldin are partnering with Watson to develop an alert system for patient medical records using a red, yellow, and green color system. Each aspect of the patient's condition would be flagged according to color, enabling the physician to make an informed decision about care. A patient with high cholesterol would be flagged as red under cholesterol but could be flagged green under blood cell count, for example. The flags will be built off the model generated by Watson, and this model will be run daily as data accrues. This kind of system could help physicians quickly see what may have changed since the patient's last visit or even consolidate the medical records of a patient who has been treated by multiple physicians. Most importantly, these alerts would trigger specific action plans to prevent the patient's transplant being compromised. Watson will also be used to define what determines value in transplant care by modeling costs associated with outcomes.

This vision of truly data-driven care is being brought to fruition with the support of MUSC President **David J. Cole, M.D.**, MUSC Medical Center Executive Director and Chief Executive Officer **Patrick J. Cawley, M.D., MBA**, Chief Information Officer **Frank Clark, Ph.D.**, Chief Research Information Officer **Leslie (Les) A. Lenert**, **M.D., MS**, and Chief Analytics Officer **John Long**.

The next step for Srinivas is to implement intervention trials to test this model of practice and see how it changes behavior. He plans to have validation results by October of this year.

A Class ACT

MUSC Immunologists Are Optimizing Adoptive Cell Transfer For Antitumor Treatments

Immunotherapy Takes Center Stage, Part II

Dr. Mark Rubinstein (left), Dr. Chrystal Paulos (center), and Dr. Shikhar Mehrotra (right) are working to bring immune-based therapies such as adoptive T cell transfer to cancer patients.

BY KIMBERLY MCGHEE

PHOTOGRAPHY BY BRENNAN WESLEY

Viewers of *The Emperor of All Maladies,* a recent PBS documentary about cancer produced by Ken Burns, may remember two visionary scientists who harnessed the power of the immune system to achieve high rates of objective and sometimes complete response in a subset of patients with metastatic cancer.

Steven A. Rosenberg, M.D., Ph.D., and his colleagues at the National Cancer Institute (NCI), Carl H. June, M.D., and his colleagues at the University of Pennsylvania, along with researchers at other institutions including Sloan Kettering, Loyola, Children's Hospital of Philadelphia, MD Anderson, and Baylor, are using adoptive cell transfer (ACT) to reinforce the ranks of a patient's own T cells—the body's warriors—and train them to better target the patient's cancer.

ACT involves harvesting T cells from a patient; expanding, conditioning, and sometimes reengineering them *in vitro*; and then reinfusing them into the same patient where they can direct an antitumor response (see Figure on page 21). Some have wondered whether this personalized approach to cancer care is feasible, but the impressive and durable clinical responses seen in some patients with ACT therapy have drawn the interest of the pharmaceutical industry, which is now partnering with academic centers to translate these promising therapies to the clinic.

The Medical University of South Carolina (MUSC) has been actively engaged in T cell immunology for almost two decades, since former Chair of Surgery and current MUSC President **David J. Cole, M.D.**, who studied with Rosenberg at the NCI, opened an immunology laboratory focused on ACT in the early 1990s and recruited talented immunologists such as **Shikhar Mehrotra, Ph.D.**, and **Mark P. Rubinstein, Ph.D.** They work closely with researchers in the Department of Microbiology and Immunology, chaired by **Zihai Li, M.D., Ph.D.**, and in particular with **Chrystal M. Paulos**, **Ph.D.**, who studied with June and the NCI's Nicholas P. Restifo, M.D., to continue to optimize ACT therapy through preclinical and clinical studies. Translation of innovative laboratory findings into the clinic is fostered by the Center for Cellular Therapy, which features a cGMP Class 6–compliant clean room suite, directed by Mehrotra. Such a facility, which provides a sterile environment in which the patient's cells can be manipulated *ex vivo* before reinfusion, is key for developing ACT and makes MUSC an ideal site for clinical trials of immune-based therapies.

The T cells used for ACT include naturally occurring tumor-infiltrating lymphocytes (TILs) and T cells that are genetically engineered with antigen specificity via a chimeric antibody receptor (CAR) or aT cell receptor (TCR).

Tumor-Infiltrating Lymphocytes

TILs are naturally occurring T cells that attack cancer early but somewhat ineffectually—they quickly become exhausted in the immunosuppressive microenvironment of the tumor and cancer cells quickly learn to evade them. Rosenberg recognized that TILs harvested from the patient's excised tumor and expanded *in vitro*—outside the immunosuppressive environment of the tumor—had the potential to direct an effective anti-cancer immune response. As early as 1994, Rosenberg and Restifo reported that a third of patients with metastatic melanoma receiving TILs through ACT showed an objective response, with a subset showing a complete response.[1]

Unfortunately, the infused T cells often did not persist and so many responses were not sustained. The addition of a lymphodepletion regimen, typically chemoablation alone[2] or together with total body irradiation (TBI),[3] enabled better persistence of the T cells because it removed immune agents that contribute to the immunosuppressive tumor microenvironment. Rosenberg, Paulos, and colleagues showed a direct correlation between increased intensities of TBI and the treatment efficacy of ACT.[4]

Of the 194 patients with metastatic melanoma treated with TILs grown from fragments of melanoma tumor plus IL-2 at the NCI, 107 (55%) have shown objective responses; a significant percentage of those treated with a chemoablative regimen or TBI had a complete response (20% and 40%, respectively).[3] A subset of patients has remained recurrence-free at five to ten years of follow-up.[3] As the field continues to develop, the benefits of high-dose TBI for improved treatment efficacy will need to be weighed against its associated risks.[4]

Lion Biotechnologies, which is partnering with the NCI to take TIL therapy into the clinic, is opening a phase 2 trial (NCT02360579) to study the efficacy and safety of using autologous TILs (LN-144) followed by IL-2 in patients with metastatic melanoma who have undergone a preparatory chemoablative regimen for lymphodepletion prior to reinfusion.

Engineering Tumor Specificity into T Cells

Although TILs can be harvested from any sort of tumor, those harvested from melanoma have shown the strongest antitumor efficacy thus far. To help extend the benefit of ACT to other types of cancer, Rosenberg, June, and others began engineering antigen receptors on the surface of T cells to improve their targeting of a patient's cancer. In essence, either CARs or TCRs are transduced via a viral vector onto the surface of the harvested T cells, and then the T cells are amplified and conditioned before being reinfused.

Chimeric antibody receptors

CARs combine the best antitumor traits of antibodies and TCRs. They are hybrids, composed of the targeting moiety of an antibody and the signaling component of a TCR. Like an antibody, they can efficiently target tumor antigen or other cellular components on the cell surface. Like a TCR, they can activate T cells to direct a robust immune response.

Rosenberg, June, Michel Sadelain, M.D., Ph.D., of Memorial Sloan Kettering Cancer Center, and others developed a CAR targeting the CD19 protein that is overexpressed in many B-cell cancers such as chronic lymphocytic leukemia (CLL). After reinfusion, the CAR-expressing T cells expanded more than a thousand fold, and each of them was estimated to kill 1,000 CLL cells. Two of the three treated patients went into complete remission.[5] In a more recent study, 27 of 30 children and adults with acute lymphocytic leukemia (ALL), including 15 who had previously undergone stem cell transplant, achieved complete remission, with responses lasting up to 24 months.[6]

Unfortunately, all B cells in the body, including those in healthy tissue, express CD19 and so were targeted by the CAR-expressing T cells as well. Indeed, in the ALL study, 73% of patients developed

B cell aplasia but were successfully treated with immunoglobulin replacement therapy. Approximately 27% experienced the cytokine release syndrome (CRS), a consequence of the release of cytokines from the large number of infused T cells and the cells they target. Fever, nausea, chills, low blood pressure, an abnormally rapid heart rate, and shortness of breath are among the symptoms that characterize CRS. The symptoms can be easily managed, but a few patients may experience a more severe and potentially fatal "cytokine storm," which can be treated effectively with tocilizumab, an antibody targeting the interleukin (IL)-6 receptor.

TCR-transduced T cells

In contrast to CARs, which are man-made, TCRs are naturally occurring. The body contains millions of different types of TCRs, a few of which can effectively target the patient's tumor but are likely present in too few numbers to effectively destroy it. In TCR-transduced T cell ACT, the receptors that best target the patient's tumor are transduced into harvested T cells using a viral vector. After transduction, the T cells, which now express the selected receptors in great number on their surface, are amplified and conditioned before being reinfused. Unlike CAR-expressing T cells, which target only antigen or other components on the tumor cell's surface, TCR-transduced T cells can recognize and destroy antigen that has been processed from internal proteins and presented on the cell surface by a major histocompatibility complex (MHC).

In a recent pilot study, T cells transduced with an NY-ESO-1–reactive TCR were adoptively transferred into patients with advanced metastatic synovial cell sarcoma or melanoma. The NY-ESO-1 antigen is expressed on the tumor cells of 70% to 80% of patients with synovial cell sarcoma and 25% of those with melanoma. Eleven (61%) of 18 patients with NY-ESO-1$^+$ synovial cell carcinoma and 11 (55%) of 20 patients with NY-ESO-1$^+$ melanoma showed an objective response to this treatment, with three- and five-year survival rates of 38% and 15% for the former and of 33% for the latter.[7]

A recent preclinical study at MUSC using a unique mouse model developed by Mehrotra showed that the high-affinity TIL 1383I TCR, isolated from MHC class I–restricted CD4$^+$ T cells obtained from the TILs of a patient with metastatic melanoma, could control the growth of melanoma when expressed in CD3$^+$ T cells.[8] MUSC immunologists have an ongoing collaboration with researchers at Loyola University, where this high-affinity TCR is being used in an ACT trial (NCT01586403; PI, Michael I. Nishimura, Ph.D.). Efforts are being made to obtain funding for similar clinical trials at MUSC.

A number of academic and industrial partnerships have formed to bring CAR and TCR-transduced T cell ACT therapy to the clinic, including those between the University of Pennsylvania and Novartis; Baylor, Bluebird Bio, and Celgene; Memorial Sloan Kettering Cancer Center, the Fred Hutchinson Cancer Research Center, and Juno Therapeutics; the National Cancer Institute and Kite Pharma; and the Cellular Biomedicine Group and the Chinese PLA General Hospital.[9]

Optimizing ACT Therapy

Although the results obtained with ACT therapy have been impressive, not all treated patients respond or have a durable response. As TIL therapy and the first of the CARs and transduced TCRs make their way through the clinical trial process, intensive research is underway to optimize ACT so that more patients can benefit. Three areas of special interest are identifying new populations of T cells, conditioning the harvested T cells *ex vivo* with cytokines or co-stimulators to improve efficacy and persistence, and finding ways to counteract the immunosuppressive microenvironment of the tumor.

Identifying new types of T cells for ACT

Most commonly, a combination of cytotoxic (CD8$^+$) and helper T cells (CD4$^+$) are used for ACT. The CD4$^+$ cells not only help activate CD8$^+$ cells but have been shown to mediate powerful tumor immunity in mice and in humanized models of solid tumors.[10] Of growing interest are Th17 cells and Tc17 cells, which are IL-17-secreting CD4$^+$ and CD8$^+$ cells, respectively. Th17 cells can either promote or suppress tumor growth, and research by Paulos, Li, Mehrotra, and others to identify the factors that destine them to one or the other of these fates is ongoing.[11] These cells are of great interest because they maintain stemness and have the potential to be much more persistent after ACT than cells that have already differentiated into cytotoxic effector cells. According to Paulos, "We found that these cells last in the body a long time, longer than other subsets of T cells."

Improving conditioning regimens

Harvested T cells are exposed to cytokines and costimulatory molecules to preferentially expand a subset of T cells or to improve efficacy and persistence. IL-2 is the cytokine most commonly used for T cell conditioning, but many others are under investigation. Recently, Rubinstein, Mehrotra, Paulos, and Cole reported that IL-12 improves the transduction efficiency of CD8$^+$ cells[12] and enhances their antitumor efficacy.[13] Paulos, Rubinstein, Cole, and colleagues also showed that TBI-induced IL-12 enhances Tc17 cell–mediated immunity, suggesting that IL-12 may also be crucial for expanding

antitumor Tc17 cells for ACT.[14] Paulos, June, and colleagues found that the inducible costimulatory molecule (ICOS) preferentially expands Th17 cells,[15] and Paulos, Rubinstein, Mehrotra, Cole, and colleagues reported that it also expands Tc17 cells.[16]

Counteracting the tumor microenvironment

When reinfused T cells encounter the highly immunosuppressive tumor microenvironment, many do not survive to direct a robust immune response. For instance, the oxidative stresses of the tumor microenvironment prove too much for some of the heterogeneous T cells that result from expansion *ex vivo*. Mehrotra and colleagues have shown a direct correlation between a T cell's antioxidant capacity and its antitumor efficacy[17] and have demonstrated better antitumor responses with ACT using tumor-reactive cells with higher surface expression of antioxidant-reduced thiols.[18]

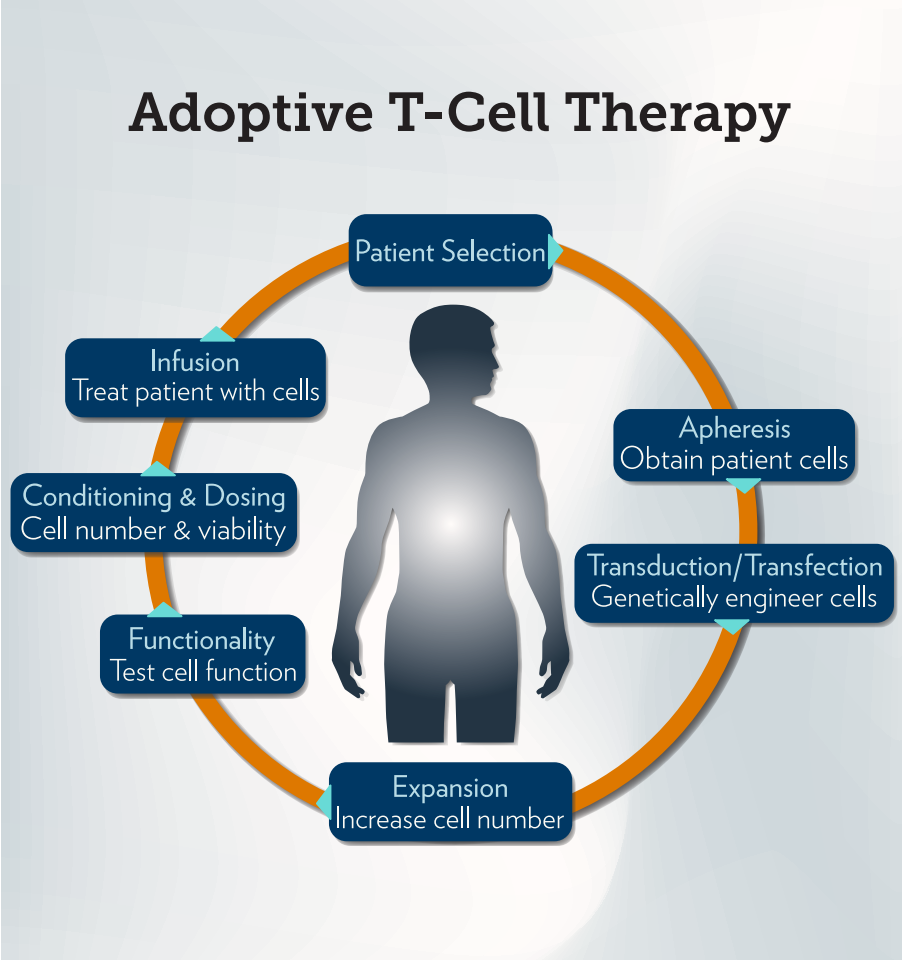

Image courtesy of Nexcelom Bioscience, adapted by Margaret Dixon Graham.

FIGURE. Adoptive T-Cell Therapy.

The Way Forward

Immune checkpoint inhibitors, which take the brakes off the immune system, are rapidly becoming standard of care for some patients with advanced cancer (for more information on these inhibitors, see Part I of this article). Because these inhibitors help mitigate the immunosuppressive tumor microenvironment, it is thought they could be combined with ACT to improve the persistence of the infused T cells.

"We think that, in many cases, adoptively transferred T cells become dysfunctional as a result of the suppressive environment of the tumor," says Rubinstein. "Immune checkpoint inhibitors may help prevent that."

Studies in the Rubinstein laboratory have shown that the combination of immune checkpoint blockade and ACT achieves better results than either alone. Rubinstein is partnering with MUSC Health hematologist/oncologist **John M. Wrangle, M.D.**, to treat lung cancer patients with a combination of PD1 blockade therapy and IL-15/IL-15Rα cytokine complexes in an effort to bolster memory T cells long term.

Combining immune checkpoint blockade with ACT therapy likely holds the greatest promise for achieving objective and durable responses in a larger proportion of patients and a wider variety of cancers. "Combination therapy is the future, and immunologists and clinicians at MUSC are working hard to bring it forward," says Paulos.

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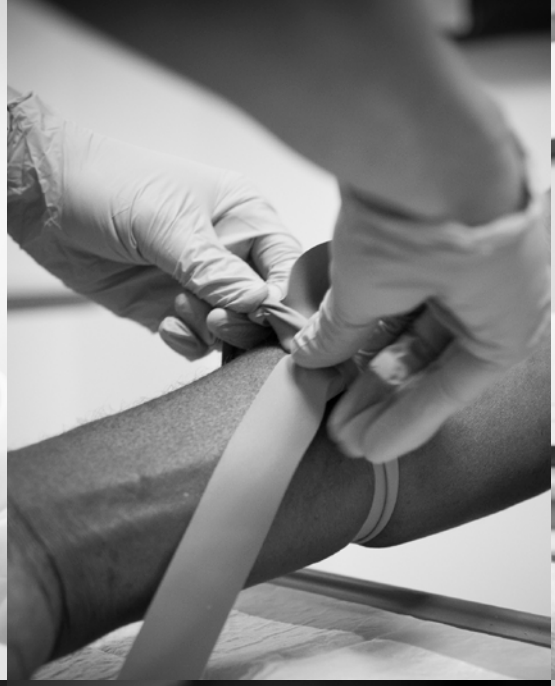

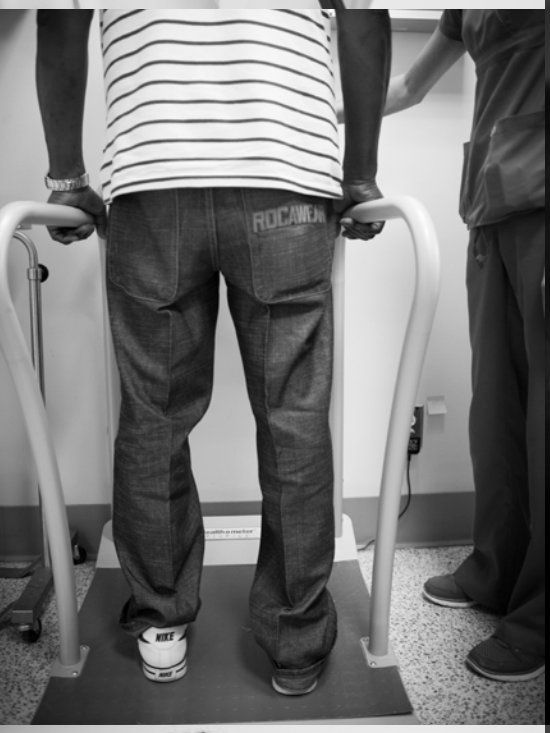
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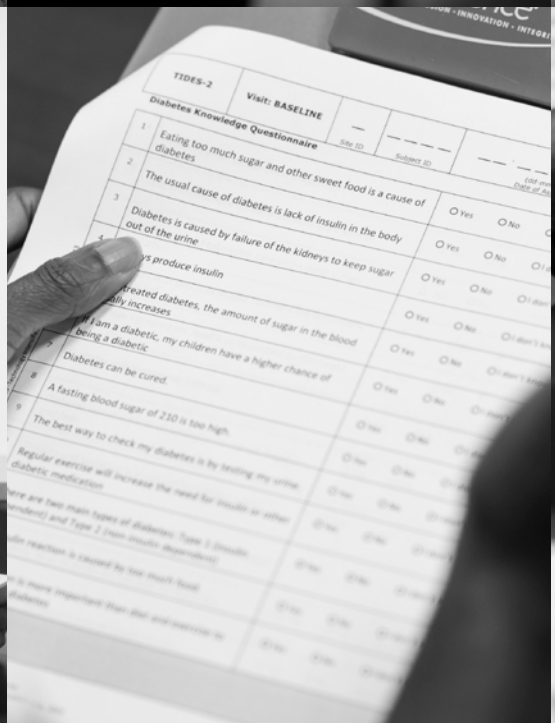
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Diabetes is caused by failure of the kidneys to keep sugar out of the urine
Yes
No

Ten Steps

Primary Care Providers Can Take Today to Improve Care for Patients With Type 2 Diabetes

BY LEONARD E. EGEDE, M.D.; KATHIE L. HERMAYER, M.D., MS; SAMUEL CYKERT, M.D.; M. FRAMPTON GWYNETTE, M.D.; CAROLYN JENKINS, PH.D., PAMELA C. ARNOLD, MSN; AMANDA PETERSON, RDN, LD; AND KIMBERLY MCGHEE

PHOTOGRAPHY BY BRENNAN WESLEY

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

- *Describe the importance of testing all patients for prediabetes or type 2 diabetes at age 45 years, with earlier testing for patients with diabetes risk factors.*
- *Treat glycated hemoglobin (AIC), blood pressure, and cholesterol to target levels and facilitate adherence by tailoring medication regimens to address patient concerns.*
- *Optimize self-management skills through culturally sensitive diabetic education and nutritional counseling.*
- *Recognize the importance of treating depression, as it can lead to poor diabetes self-management.*
- *Define the chronic care model and give examples of how it could be implemented effectively in a primary care practice.*

Date of Release:
October 1, 2015
Date of Expiration:
October 1, 2017

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The biggest challenge facing the U.S. health care system is chronic disease, which, according to the Centers for Disease Control and Prevention, is responsible for seven of ten deaths each year and accounts for 86% of the nation's health care costs.[1]

Type 2 diabetes mellitus (T2DM) is in many ways the poster child for chronic disease—it is associated with high rates of mortality and morbidity, places a heavy economic burden on the nation and on those it afflicts, and often remains undiagnosed until irreparable damage has been done.

Diabetes is the seventh leading cause of death in the U.S.; the leading cause of kidney failure, non-traumatic lower-limb amputations, and blindness; and a major cause of heart disease and stroke. Adults with diabetes are two to four times more likely to have heart disease or stroke than adults without diabetes.[2]

In 2012, diabetes-associated direct medical costs were $176 billion, two to eight times the amount spent on other chronic diseases. Patients with T2DM spend about $7,900 annually for diabetes-related medical care, much of it due to inpatient hospitalization and diabetes-related complications.[3]

Approximately one in ten (9.3%) people in the U.S. has diabetes, 95% of whom have type T2DM. One in three has prediabetes, defined as the presence of impaired glucose tolerance and/or impaired fasting glucose.[4] More than a quarter (27.8%) of those with T2DM and nine out of ten of those with prediabetes remain undiagnosed.[4]

Primary care providers, who shoulder much of the burden of diagnosing and managing T2DM, can help reverse these alarming trends by taking the following ten steps.

1. Expand screening to all adults age 45 and over and to those under 45 with diabetes risk factors.

Both the U.S. Preventive Services Task Force (USPSTF; draft guidelines, 2014)[5] and the American Diabetes Association (ADA)[6] recommend screening all adults age 45 and older and those younger than 45 with risk factors for T2DM (any T2DM risk factors for the USPSTF; obesity plus one other T2DM risk factor for the ADA). The USPSTF, which previously recommended screening only hypertensive patients for T2DM, changed its position because studies have compellingly shown that metformin and lifestyle modification can cut the incidence of T2DM in patients with prediabetes by more than half.[7-9]

2. Support behavior change to prevent or minimize complications from T2DM.

Smoking Cessation

The risk of developing T2DM is 30% to 40% higher for active smokers, and the risk is higher the more cigarettes they smoke. Patients with T2DM are already at a much higher risk of developing cardiovascular disease (CVD), and smoking further heightens that risk. Higher doses of insulin are needed in patients who smoke than those who do not, and research has shown that patients with T2DM who quit smoking achieve better glycemic control.[10] Physicians can support patients in their quit attempts by providing medications and devices for smoking cessation (e-cigarettes are not considered a valid form of smoking cessation) and encouraging them to contact a quitline. The Tobacco Quitline offers regular follow-up with a smoking cessation coach to any resident of South Carolina free of charge (http://www.scdhec.gov/Health/TobaccoCessation/TobaccoQuitline).

Weight Loss and Exercise

A loss of 7% to 10% of body weight should be encouraged in T2DM patients and patients with prediabetes. In the U.S. Diabetes Prevention Program (DPP) study, overweight persons with prediabetes were asked to begin exercising at least 30 minutes five days a week; 58% of the patients who lost 7% of their body weight and 90% of those who lost 10% of their body weight did not develop T2DM.[8] A follow-up study showed that prevention or delay of T2DM with lifestyle modification or metformin persisted for at least 10 years.[9] Even patients who do not attain these goals will benefit as each kilogram (approximately 2.2 pounds) of mean weight loss is associated with a reduction of 16% in future diabetes incidence.[8]

Exercise need not require a gym membership, which could be prohibitively expensive for some patients. Walking briskly for 30 minutes a day (as part of an accumulated steps program with a goal of 10,000 steps five days a week for 12 weeks) has been shown to improve glucose metabolism and pancreatic cell function in T2DM as effectively as 30 minutes of daily aerobic exercise, with better adherence by patients.[11]

The primary care office should help patients find resources for lifestyle intervention, whether they be available at the community health department or provided by an insurer as part of a wellness or chronic disease management program. In 2015, Medicaid began offering reimbursement for intensive behavioral therapy for obesity (BMI >30 kg/m^2). For more information, visit CMS.gov.

3. Ensure that patients receive diabetes self-management education and nutritional counseling.

T2DM is a complicated disease, and effective self-management requires patients to test their glycemic levels regularly, know when and how to take medications, and choose a healthy and carbohydrate-controlled diet. Certified diabetes educators (CDEs), whose services are reimbursable by Medicare and other payors for T2DM patients, can help patients "learn the ropes" and do so in a way that is appropriate to the patient's educational level. The National Certification Board for Diabetes Educators offers a tool to search for CDEs by zip code (available at http://www.ncbde.org/find-a-cde/).

Patients with T2DM who manage their diet appropriately are more likely to achieve good glycemic control with lower doses of medications.[12] Registered dietitians can help teach patients about portion control, interpreting food labels, and planning carbohydrate-controlled meals and can help adapt patients' favorite dishes or dishes favored by their culture to meet their dietary requirements. Physicians can find registered dietitians, whose services are covered for patients with T2DM by Medicare and other payors, in their area at http://www.eatright.org/find-an-expert.

For regions without a registered dietitian, telehealth may provide the answer. Nutritional counseling programs, such as that provided by Virtual Tele Consultation (VTC) at MUSC's Center for Telehealth, enable T2DM patients at a primary care office, even in a remote area, to benefit from the services of a registered dietitian stationed elsewhere. (For a map of all VTC locations, see MUSChealth.org/telehealth/vtc/index.html.) Research has shown that telehealth-delivered nutritional counseling is as effective as that provided in person and can improve access to these services in underserved communities.[13]

Primary care offices should offer diabetes education and nutritional counseling to uninsured patients. Free patient education materials are available from the Academy of Nutrition and Dietetics (http://www.eatright.org/resources/food/nutrition), the South Carolina Academy of Nutrition and Dietetics (http://www.eatrightsc.org/), and the American Association of Diabetes Educators (https://www.diabeteseducator.org/patient-resources/aade7-self-care-behaviors).

4. Recognize that certain populations are at greater risk.

The burden of T2DM is especially heavy in the African American, Hispanic, and Native American populations, which report a 50% to 100% increased burden of illness and death associated with T2DM as compared to white Americans.[14] Diabetes may also be harder to control in African American populations: racial/ethnic disparities in AIC levels and control were reported in a study of a national longitudinal cohort of veterans.[15] Primary care offices can begin to combat racial disparities by recognizing and committing to reduce them and by designing, implementing, evaluating, and sustaining a quality improvement initiative that aims for equity.[16]

5. Address patients' concerns when choosing medications.

Effective and inexpensive medications are available to treat the ABCs (AIC, blood pressure, cholesterol) of T2DM—metformin for glycemic control, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for hypertension, and statins for dyslipidemia, for example. Nonetheless, poor medication adherence continues to be a major challenge for diabetes management, with half of patients failing to take their medications as prescribed.[17] A study by Egede et al[18] showed that T2DM patients with poor medication adherence had 41% higher inpatient costs and estimated that reducing medication nonadherence would save the U.S. $661 million to $1.16 billion annually.

A recent meta-analysis[19] showed that cost and depression were the two main causes of medication nonadherence in T2DM. (For more on depression, see Step 7.) Physicians should take the time to learn about their patients' needs and, if cost is an issue, prescribe generic medications to treat the ABCs, taking care not to exceed about $50 per month.

6. Change or intensify medications if targets for ABCs, particularly blood pressure, are not met.

Control of the ABCs, especially blood pressure, is crucial in those diagnosed with T2DM to prevent CVD such as myocardial infarction and stroke and microvascular complications that can lead to blindness, end-stage renal failure, and amputation of lower extremities. The ADA's *2015 Standards of Medical Care in Diabetes*[6] suggest the following targets: blood pressure less than 140/90 mm Hg, AIC less than 7%, and low-density lipoprotein cholesterol less than 100 mg/dL. However, stricter targets (e.g., blood pressure <130/80 mm Hg; AIC < 6.5%) may be appropriate for younger patients with little CVD to help stave off future complications, while less stringent AIC goals (<8%) may be appropriate for patients with limited life expectancy, advanced complications, a history of hypoglycemic episodes, or comorbid conditions.

Failure to meet targets, especially for blood pressure, should prompt physicians to increase the dose of the medication and/or

consider a combination regimen. Although multiple-drug strategies can be complicated for patients and hurt adherence, the use of single-pill combinations, which combine two different categories of agents in a single pill, can be used to mitigate this problem.

7. Be vigilant in screening for and treating depression in T2DM patients as it can adversely affect medication adherence.

Patients with diabetes are twice as likely to develop depression,[20] and diabetic patients with depression have poorer medication adherence and outcomes than those without diabetes.[21, 22] Identifying depressive disorders (by documenting it ≥3 times in the medical record) can reduce the mortality rate in depressed patients with T2DM.[21] Although primary care physicians can manage the care of many T2DM patients, those with treatment-resistant depression or with depression and another comorbid psychiatric condition should be referred to a psychiatrist, as depressed patients with diabetes may be candidates for aggressive treatment with serotonin reuptake inhibitors.[23] Telehealth-based mental health counseling has a growing evidence base and has been shown to be noninferior to in-person counseling.[24]

8. Take full advantage of the electronic health record to monitor and follow up with your T2DM patients.

Primary care physicians who have undergone the sometimes painful transition from a paper-based to an electronic health record (EHR) can begin to reap some of the benefits the EHR offers for management of chronic diseases such as T2DM. Not all patients with T2DM understand the importance of glycemic and ABC control or the need for frequent follow-up. Therefore, primary care practices can query the EHR using a number of parameters, such as diagnosis codes for T2DM, AIC levels, or a missed appointment, every couple of months to identify patients who have lacked consistent follow-up and need to be engaged and educated about the importance of chronic disease management. Every practice can design such a system and bring these patients in for needed care and counsel. If possible, primary care offices should assign a licensed nurse to follow up with T2DM patients to track their values and make protocol-designated changes to their medication regimen. Comprehensive diabetes management algorithms are available from the American Association of Clinical Endocrinologists at http://dx.doi.org/10.4158/EP15693.CS.

9. Re-engage patients frequently.

Effective chronic care management does not happen overnight, but real improvement can be made over time. For T2DM patients with stable glucose levels, twice-a-year visits are recommended; for those who have not achieved stable control, quarterly visits are advised. A foot examination, in which a monofilament is used to test the sensation of a patient's bare feet, should be performed at every visit. (For more information, visit http://pskills.pharm.ku.edu/ios/html5/html5-mtm-counseling/diabeticfootexam/sensory.html.) Patients should also be referred for an annual dilated eye examination. In addition to adjusting medication regimens to better meet targets, providers should ask about medication adherence while also assessing a patient's self-management skills. Some patients with long-standing T2DM know surprisingly little about their disease and would benefit from diabetes self-management education and/or nutritional counseling.

10. Realize you don't have to go it alone.

Primary care physicians cannot single-handedly provide the highly coordinated care and enhanced provider-patient communications that guidelines recommend. Moving from a traditional practice model, where the physician provides most of the care, to a team-based approach, where every care provider in the practice performs at the top of his/her training, will likely be necessary if the chronic care model, a patient-centered model advocated by 2015 ADA guidelines, is to be successfully implemented. Nurse practitioners and physician assistants are qualified to manage most cases of T2DM, with physician consultations limited to particularly complex cases. Pharmacists can also help educate patients about taking their medications appropriately, and registered nurses, licensed practical nurses, and community healthcare workers can engage in patient outreach and identify community resources. Front office staff can be directed to obtain additional history from T2DM patients, and the triage person, who typically checks blood pressure, pulse, and respiration, can be trained to perform foot examinations.

...And Some Models for the Future

mHealth Technology

As telehealth continues to expand, it will bring needed diabetes self-management education, nutritional counseling, and other services to rural areas. Smart phones will be used to text e-reminders about medication, diet, or exercise to patients between visits. New devices for remote monitoring will increasingly enable patients to regularly measure their blood pressure or glycemic level and transmit the data to the primary care office. Providers will be alerted when values exceed a certain threshold and require immediate attention, and blood pressure and glycemic levels can be plotted over time so that

the provider can make more informed choices about medication during patient visits. The TIDES2 study at MUSC Health (PI, **Leonard E. Egede, M.D.**) is assessing whether outcomes improve in African American T2DM patients when they participate in regular telephonic sessions providing diabetes education and are equipped with these types of mHealth devices. If this strategy proves successful, it could be extended to other populations.

Primary Care Extension Centers

To fundamentally address chronic diseases such as T2DM and the health care disparities associated with them, changes in the infrastructure of primary care will likely be required. For example, some have advocated for the creation of primary care extension centers in rural or disadvantaged areas, modeled on the cooperative extension service. The primary care extension center serves as the hub for the primary care practices in the region, providing in-person and telehealth support to help them manage their patients with chronic disease. Such a center could provide personnel such as CDEs, registered dietitians, and community health workers to assist in patient outreach and help practices use the EHR to manage chronic care populations.

To learn more about redesigning primary care practices to deliver optimal diabetes care, sign up for this article's sister telepresentation, also CME-eligible (see advertisement below for details). Speakers are Leonard E. Egede, M.D., Professor of Medicine and Director of the Center for Health Disparities Research at the Medical University of South Carolina, and Samuel Cykert, M.D., Professor of Medicine at the University of North Carolina at Chapel Hill.

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"You've helped me through a really rough period in my life and you never allowed me to give up. I could never repay you for what you've done."
— Strong Start patient

Strong Start

Health care management helps Medicaid mothers with complex needs deliver healthy babies

BY LINDY KEANE CARTER

ILLUSTRATION BY BRENNAN WESLEY

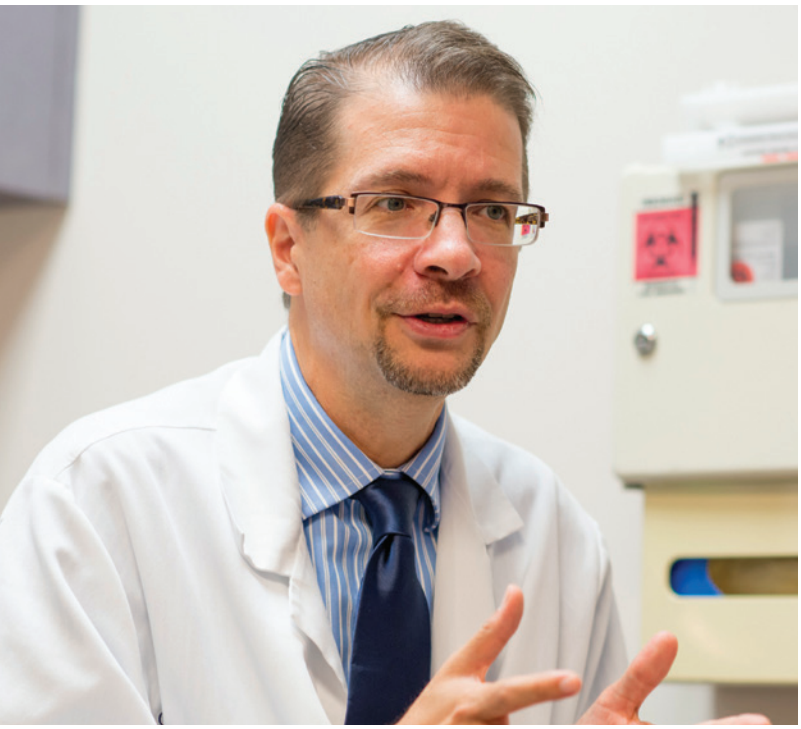
Premature birth is the leading cause of death in children under the age of five according to the March of Dimes. For the surviving infants and their families, the long-term complications and developmental delays are devastating. They are also costly for the nation. U.S. health officials have been fighting the prematurity rate on many fronts for many years and, though it has dropped from 12.3% (2003) to 11.4% (2013), it remains higher in the U.S. than in most developed nations. The March of Dimes' goal is 9.6% by 2020.

In 2012, the Department of Health and Human Services announced an initiative to reduce preterm births and improve outcomes for newborns and pregnant women. The Strong Start for Mothers and Newborns program, administered by the Centers for Medicare and Medicaid Innovation (CMMI) of the Centers for Medicare and Medicaid Services, has awarded approximately $41.4 million to 27 prenatal care providers in 30 states to serve a proposed 80,000 women. Strong Start's two main goals are to reduce preterm births for at-risk Medicaid patients and to reduce the rate of early elective deliveries prior to 39 weeks gestation. Interventions are designed to not only meet the medical needs of the women, but also address the behavioral and psychosocial factors that affect their pregnancies. The 27 awardees are testing three kinds of interventions for enhanced prenatal care: centering/group visits, birth centers, and maternity care homes.

Providers in South Carolina were awarded funding to test the maternity care home model throughout the state, where in 2013 one in seven babies (13%) was born before 37 weeks gestation. **Scott A. Sullivan, M.D.**, Associate Professor of Obstetrics and Gynecology at MUSC Health, is the principal investigator for the $2.1 million four-year grant awarded in 2012 by CMMI to MUSC Health. The preterm birth rate among South Carolina Medicaid patients is high: 14% to 15%. For African American Medicaid patients, it is even higher: 16%. "And if you look at this population in the Pee Dee region, the rate is 19% to 20%," says Sullivan. "The average gestation for African American Medicaid mothers in South Carolina is 35 weeks."

These high-risk South Carolina women are the target population that is being cared for by Sullivan and a team of Maternal and Fetal Medicine (MFM) physicians and other prenatal care providers.

The maternity care home model is built on the patient-centered medical home, which offers care from a single clinician, continuous quality improvement, patient-centeredness, and timely access. The



Dr. Scott Sullivan, Director of MUSC Health's Strong Start program

MUSC program begins with risk assessors screening the obstetric patients all over the state, identifying those who qualify for Strong Start, and referring them for the services. This high-intensity care management model is increasingly being used by organizations to cut the cost of treating the most complex patients. For example, Kaiser Permanente is creating high-risk clinics. In Kaiser's Ohio region, the 1% of patients who accounted for 27% of total costs were referred to a high-risk clinic in which a team provided home care for about 150 patients. In a commentary in the October 15, 2009 *New England Journal of Medicine,* Bodenheimer and Berry-Millett note that these patients had fewer hospitalizations, fewer emergency room visits, and lower hospital expenses. These are early results and the numbers are small, but this model bears further watching as a cost-cutting measure.

Relationship-based Care

Sullivan and three other physicians provide the MFM care in Charleston, Florence, and Beaufort, SC. Throughout the patients' pregnancies and for ten weeks after, two nurse care navigators speak on the telephone with these patients as needed to answer medical questions and keep them on track to receive scheduled prenatal and postnatal care. When necessary, a social worker connects patients with appropriate resources. The program coordinator is **Rebecca L. Timpner**. "We've learned so much about how isolated, uneducated, and unsupported our patients feel," says Timpner. "It's staggering how big the problem is. The Medicaid system is difficult to navigate for most. With the added stressors of pregnancy and other medical and psychosocial issues, it's hard for them."

Sullivan says these patients' socioeconomic stress factors are unbelievable. "Not having a home. Running from a partner. Not having heat, air conditioning, food, clothing. Moving from place to place. Now we know the reasons why a lot of our patients don't come for their appointments or fill their prescriptions."

Carolyn Nance, RN, and **Tabor Hamilton, RN**, are the two nurse care navigators who are equal parts medical advisor, mother, and life coach. Each handles about 150 to 200 patients at a given time. These nurses are available by phone 24/7 to answer medical questions and encourage prenatal care – no simple thing in this population that experiences so much insecurity.

Nance covers the state but primarily South Carolina's Lowcountry and the Pee Dee. "The issues I treat range from diarrhea and breast-feeding to domestic violence, substance abuse, eviction notices, and no food," she says. "One of my first patients had a previous addiction to cocaine. She had a heart attack, a stroke, kidney failure, had lost one baby. With the Strong Start program she delivered a healthy baby at 33 weeks, quit using cocaine, and has lost more than 150 pounds. Many times she called me during the pregnancy when she was tempted to do cocaine. I was able to reel her in. Her baby is now more than one year old. I'm still in contact with her. She sends me pictures."

Nance estimates that she prevents at least three emergency room visits a week. "I do a lot of triaging over the phone," she says. "I convince them that if they'll call me back to talk about their back pain, for example, they don't need to go to the ER."

Hamilton's patients are all over South Carolina. "A lot of these girls don't have much family support at all," she says. "Sometimes their parents are deceased or they are estranged from them. Sometimes their parents are in prison, all sorts of things. We provide a support system for them."

Hamilton cites the 20-year-old patient who went to the ER every day (and made frequent false abduction claims to the police) because of what Hamilton eventually realized was a need for attention. "Her mother passed away when she was 12. She needed a lot of social support. Once I got her under my wing and she knew she could trust me, she just stopped going to the ER, stopped calling the police, and did well with her pregnancy."

In August 2014, a social worker was added to the team. **Sarah Friedrich, LMSW,** connects patients with the resources they need,

such as emergency housing, affordable housing, financial assistance, transportation, employment assistance, and assistance signing up for benefits. She also helps mothers obtain infant supplies and gain support through parenting and childbirth classes.

Sullivan says he's learned that noncompliance is not necessarily a character flaw or recalcitrance. He cites the patient who would not take her insulin. Nance discovered that she had no permanent home, no transportation, and thus found it hard to get her prescription filled. Once Nance got her a place in a homeless shelter, arranged for transportation, and arranged for her to use the pharmacy at MUSC when she came for her prenatal care, she took her insulin regularly. "In the usual doctor's office or clinic, we don't screen people for those problems except at the opening visit and sometimes they don't exist at the opening visit," Sullivan says.

Timpner believes that the patients' ability to text Nance and Hamilton at any hour, day or night, has been a huge part of the program's success. "I think that kind of access is what keeps them from going to the ER," she says.

Outcomes

At the conclusion of the grant in 2016, Strong Start sites will be reporting to CMMI on outcomes. These measures will include ER visits, total costs, length of hospital stay for mother and baby, total dollars spent in terms of pregnancy, regular prematurity rates, breastfeeding rates, and rates of prematurity: late preterm (34 to 36 weeks' gestation), very preterm (less than 32 weeks) and very early preterm (28 weeks). Already, the MUSC site is able to document an increase in compliance for postpartum visits. Before Strong Start, 40% of patients returned for their postpartum appointment. Now the rate is closer to 70%, reports Sullivan.

Nance and Hamilton have several success stories of being able to extend the delivery date of complicated patients (some with preterm birth histories) by several weeks past 35 weeks.

In an evaluation of the program's first year provided to CMMI, the Urban Institute reported that women being served by Strong Start thus far have lower than average Cesarean section rates, higher rates of breastfeeding, and in some cases, lower rates of preterm deliveries than the nation as a whole. For the full report, visit http://www.urban.org/research/publication/strong-start-mothers-and-newborns-evaluation/view/full_report.

While it is too early to make broad generalizations about the effects of Strong Start, these early data suggest some positive trends that merit attention as public and private health care officials work toward better birth outcomes for the nation's youngest citizens.

In the larger health care environment, case management will not be adopted widely without changes in payment policy. For-profit hospitals will need to have an incentive to use effective hospital-to-home care management. Similarly, primary care practices are not likely to hire registered nurse care-managers if they are not reimbursed for that person's work or don't receive a share of the savings generated.

The Medicaid population in South Carolina is growing, says Sullivan. Programs such as Strong Start provide the kind of health care delivery innovation that is smart business and compassionate as well, as it gives mothers and the support they need to deliver a healthy baby.

Interview

Carolyn D. Britten, M.D., Appointed Director of the Division of Hematology/Oncology

Dr. Carolyn D. Britten, new Director of the Division of Hematology/Oncology

Carolyn D. Britten, M.D., Director of Phase 1 Clinical Trials at MUSC Hollings Cancer Center, has been named Director of the Division of Hematology/Oncology in the Department of Medicine at the Medical University of South Carolina. Britten holds the Charles Westfield Coker Endowed Chair in GI Oncology, which is affiliated with the South Carolina SmartState™ Centers of Excellence. She will continue in her role as Associate Director for Clinical Investigations at the MUSC Hollings Cancer Center. Shortly after Britten was appointed to the position, *Progressnotes* spoke with her about her plans for the division.

PN: Can you give us an overview of how you plan to advance the division?

CB: Over the next three years, I expect to grow the division both in terms of the number of medical oncologists and the programs we offer. Specifically, we will work with our scientists to develop clinical trials that serve our patient population, and we will continue to build an academic fellowship program.

As a division, we want to be a referral center for patient care and research. In addition, we want to serve as the academic home for hematologists and medical oncologists within our institution and in the greater community.

PN: What are some of the most significant trials you've opened at MUSC as Director of Phase 1 Clinical Trials and why are they significant?

CB: We have a number of really exciting trials and they fall into two major categories. In the first group are trials of agents that are directed against specific molecular abnormalities within the cancer. In the MUSC Pathology Department, we're able to sequence our patients' tumors and identify mutations that are potentially driving those tumors. We have a number of trials that are aimed at targeting those putative drivers, such as AKT, PI3K, and RAF. The second group of exciting trials employs immune checkpoint inhibitors. We used to think that only a handful of tumors were immune responsive. However, recent results with immune checkpoint inhibitors have shown that the immune system is very important in a broad spectrum of tumors. We have participated in first-in-human trials of agents targeting the PD1/PDL-1 axis, and we have upcoming trials that will pair these agents with other novel immunotherapy drugs.

PN: What is the importance of having a robust phase 1 clinical trial program in a cancer center?

CB: Phase 1 trials provide access to novel anticancer drugs for patients with advanced malignancies. These trials often accept patients who have rare cancers or those who've had a lot of prior treatment. These patients don't easily fit into larger phase 2 or 3 trials. Furthermore, phase 1 trials are often the mechanism by which we translate the findings of our own scientists into novel treatment strategies.

PN: The implementation of phase 1 trials across the country is changing, isn't it?

CB: In this era of personalized medicine, many early-phase cancer trials match the molecular subtype with a specific targeted drug. These trials often incorporate biomarkers in an effort to identify which patients are most likely to benefit. This has changed the way we select patients for phase 1 trials. In addition, the size of phase 1 trials has changed. In the past, a small phase 1 clinical trial would be followed by phase 2 and then phase 3 trials. But now some phase 1 trials are enrolling a few hundred patients using expansion cohorts. There are a number of reasons for this. First, it potentially allows the drug development timeline to proceed more quickly. Second, it allows one to look for an efficacy signal in the first trial before proceeding to either a randomized phase 2 or phase 3. It's all about getting the drugs that help patients into the clinic in a timely fashion.

PN: Does having a phase 1 trial then, especially this more abbreviated model, make it more likely we can offer more innovative drugs with some efficacy data to patients in South Carolina?

CB: Phase 1 trials are still primarily exploratory, but yes, participation in these larger trials allows us to offer more patients access to novel therapies in South Carolina.

PN: Do you foresee working with community physicians in some way?

CB: Ultimately, we want to provide community oncologists with a connection to MUSC Health oncologists. Ideally, patients would receive most of their care closer to home, but when they need tertiary- or quartenary-level care, they would come to MUSC Health in Charleston. Highly specialized trials, for example first-in-human phase 1 trials or trials of cell-based immunotherapies, will be performed on campus. But phase 2 and phase 3 trials will be performed both on campus and in the community with our partners. As a starting point, under the leadership of **Dr. Chanita Hughes Halbert**, AT&T Distinguished Endowed Chair in Cancer Equity and Professor in the Department of Psychiatry and Behavioral Sciences, we have an NCORP grant that provides infrastructure for the implementation of cooperative group trials at community sites. We are currently working with sites in Georgetown and Greenwood, and we expect to extend this opportunity to other locations.

PN: Would you like to elaborate on why you're putting such emphasis on translational research?

CB: With its National Cancer Institute designation, Hollings Cancer Center is uniquely poised to design and implement novel clinical trials. Only through research can we improve the outcomes for our patients.

New Physicians

Carrie Busch, M.D., MSCR

Board Certification: General Pediatrics; Board Eligible: Pediatric Emergency Medicine and Child Abuse Pediatrics // Special Interests: Child abuse recognition and epidemiology, shock, trauma // Medical School: Texas A&M Health Science Center // Residency: Medical University of South Carolina // Fellowship: Medical University of South Carolina

David Cachia, M.D., MRCP

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Libby Kosnik Infinger, M.D., MPH

Board Eligible: Neurosurgery, Pediatric Neurosurgery // Special Interests: Craniosynostosis and craniofacial surgery, spinal dysraphism, Chiari malformation, spasticity, and neuro-oncology // Medical School: Northeast Ohio Medical University // Residency: Medical University of South Carolina // Fellowship: Cincinnati Children's Hospital Medical Center

W. Ennis James, M.D.

Board Certification: Internal Medicine, Pulmonary Disease // Special Interests: Sarcoidosis // Medical School: Medical University of South Carolina // Residency: Virginia Commonwealth University // Fellowship: Virginia Commonwealth University

Nagraj Kasi, M.D.

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Board Certification: Pediatrics; Board Eligible: Pediatric Gastroenterology // Special Interests: Pediatric liver diseases, pediatric liver transplant // Medical School: Rangaraya Medical College // Residency: Brooklyn Medical Center // Fellowship: University of Alabama at Birmingham

Ming Yeong Lim, M.D.

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New Physicians

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Board Certification: Pediatric Nephrology // Special Interests: Acute kidney injury, chronic kidney disease, transplant, hypertension // Medical School: Iuliu Hatieganu University of Medicine and Pharmacy, Romania // Residency: Indiana University, Riley Children's Hospital // Fellowship: Harvard Medical School, Boston Children's Hospital

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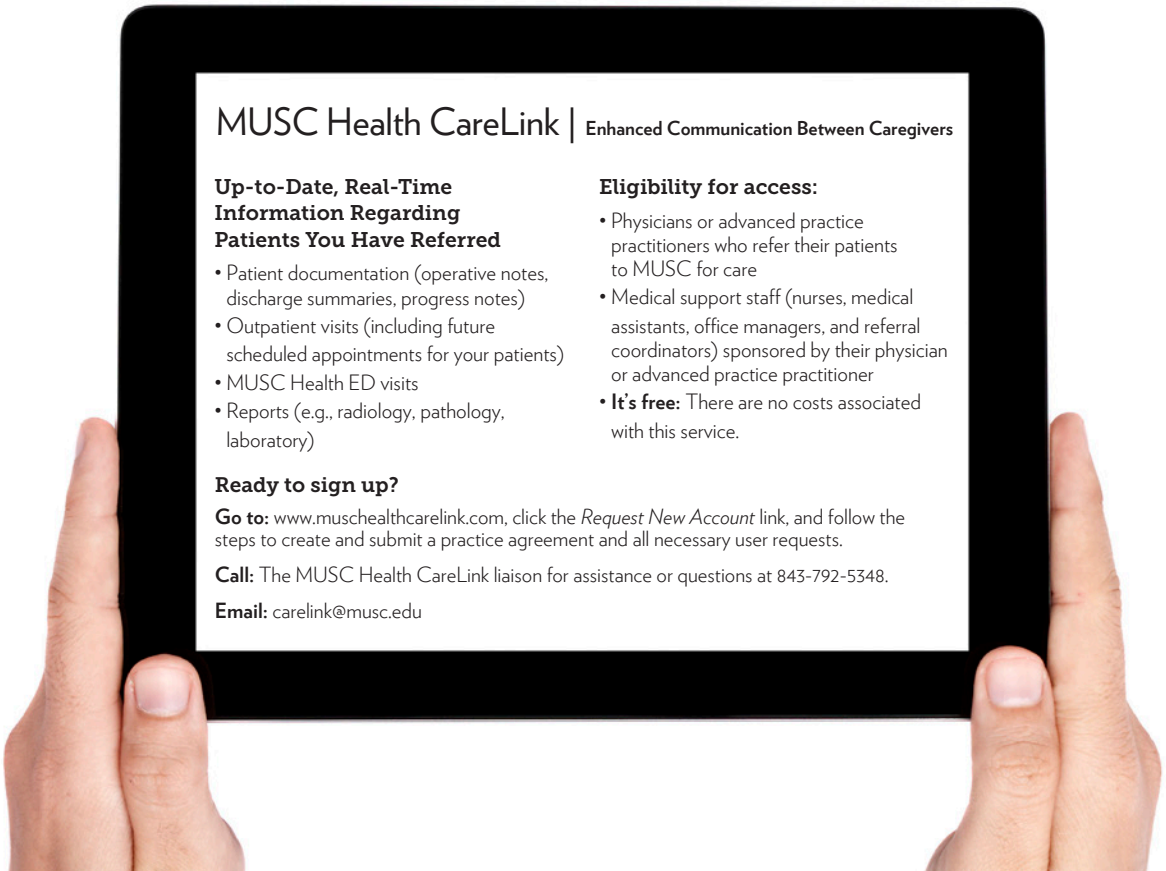
MUSC'S MEDICAL MAGAZINE // FALL 2015



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