Colleagues in care

3 PAPERS, 1 DISEASE

U-M diabetes studies examine blood pressure, neuropathy and mortality

ALSO

Inflammatory Bowel Disease
Prostate Cancer
Stem Cells and Arrhythmia
MOLES GO MOBILE

UMSkinCheck tracks skin changes, offers reminders

UMSkinCheck, a new free mobile app developed at the University of Michigan Health System, walks users step by step through a skin self-exam. It allows iPhone and iPad users to create a photographic baseline of their skin and track suspicious moles or other skin lesions over time. It also provides pictures of various types of skin cancers for comparison.

The app guides users through taking a series of 23 photos, covering the body from head to toe. Photos are stored within the app and serve as a baseline for future comparisons. The app sends reminders to repeat skin self-exams on a regular basis. If a mole appears to be changing or growing, the photos can then be shared with a dermatologist to help determine whether a biopsy is necessary.

DOWNLOAD To get the free app, visit the iTunes App Store and search for UMSkinCheck.

FACULTY

EMERGENCY EXPERTISE

New chair for Emergency Medicine

Robert W. Neumar, M.D., Ph.D., a renowned expert in brain damage after cardiac arrest and head trauma, is the new chair of the U-M Department of Emergency Medicine.

On July 1, he came to U-M from the University of Pennsylvania Perelman School of Medicine, where he conducted extensive research focused on understanding the mechanisms of brain injury and developing therapies to minimize brain damage and improve the brain’s ability to recover after cardiac arrest and traumatic brain injury.

Neumar received his Ph.D. in physiology from Wayne State University, and his M.D. from the University of Pittsburgh School of Medicine, and completed fellowships at both institutions.

He takes the reins from William Barsan, M.D., the department’s founding chair, at a significant time for emergency medicine at U-M. A new, separate pediatric emergency department, an expanded adult and psychiatric emergency department, and three new Survival Flight helicopters have all made their debuts in the last year. More than 85,000 ED visits by adults and children occur at U-M each year.

Research activity in the department is increasing, including the Neurological Emergencies Treatment Trial network headed by Barsan, the Great Lakes Emergency Medical Services for Children Research Network and the Injury Center, which tests ideas for helping health professionals and the public prevent or respond to injury. Neumar is building a team that studies the biology of critical injury and illness, including causes, diagnoses and treatment.

The department trains new adult and pediatric emergency physicians at U-M, St. Joseph Mercy Ann Arbor and Hurley Medical Center, and in the African nation of Ghana.

ONLINE Read more about U-M’s Emergency Medicine capabilities in Colleagues in Care Online at med.umich.edu/cic

On the cover: Eve Kerr, M.D., Brian Callaghan, M.D., and Christine T. Cigolle, M.D., M.P.H., recently published papers on key aspects of diabetes management and complications.
Heart and Soul

New clinic aims to reduce cardiac complications of cancer treatment

The University of Michigan Cardiovascular Center has created a Cardio-Oncology clinic focused on preventing or minimizing heart damage caused by chemotherapy and radiation therapy for cancer. The new center will be led by cardiologists Monika Leja, M.D., and Elina Yamada, M.D.

“Advances in treatment have reduced cancer deaths, but in the past 10 to 15 years there’s been an emerging trend of premature heart disease among cancer survivors,” says Leja. “Using sophisticated imaging technology and biomarkers, we can better identify those patients whose hearts have been weakened as a result of cancer treatment.”

The imaging technology utilized is called “strain imaging” and it allows physicians to get a detailed analysis of specific segments of the heart in order to predict damage before it occurs. In a promising, small-scale study of breast cancer survivors, strain imaging predicted issues up to three months earlier than monitoring ejection fraction alone.

Common cardiovascular complications linked to cancer treatment include heart failure, chemotherapy-induced hypertension, acute myocardial infarction and arrhythmias.

“Our goal will be early detection and to protect patients with heart medications,” says Leja, formerly of the MD Anderson Cancer Center, who joined the University of Michigan Health System in August.

U-M’s Cardio-Oncology clinic will also treat rare, but potentially deadly, heart tumors. Heart tumors may either originate in the heart itself or spread from primary tumors in nearby organs such as the lungs or kidneys.

Roughly 75 percent of primary cardiac tumors are benign, but they can lead to serious heart problems and interfere with the heart’s normal functioning. Leja says, “Heart tumors that are malignant require aggressive care with multidisciplinary team input, as will be provided by this clinic.”

Preventing heart disease in cancer patients is gaining more importance as aggressive cancer therapies are applied to older patients and as researchers identify a growing number of cardiovascular side effects of anti-cancer therapy. Careful evaluation of heart disease in cancer patients will likely improve quality of life but may also improve mortality as the presence or development of heart disease may significantly limit lifesaving cancer therapies.

“If we ignore what’s happening in the heart, we could lose the gains we’ve made in cancer survival,” Leja says. “Heart disease, and not cancer, poses the larger risk to the 2.2 million breast cancer survivors in the United States. About one-third of cancer patients who receive chemotherapy drugs such as trastuzumab (Herceptin) and anthracyclines will develop cardiotoxicity, meaning drugs designed to inhibit cancer cells also injure heart cells. A small percentage of these patients will have to stop therapy because of side effects.”

Organizations including the American Society of Clinical Oncology believe the rise of cardiology-oncology clinics — U-M’s is the first in Michigan — could have a great impact on treatment outcomes and patient care. A dedicated clinic has the potential to allow the safe completion of cancer treatment without significantly increasing heart risk.

Of course, not all patients undergoing cancer treatment experience heart damage. Those who should be considered for consultation in the University of Michigan Cardio-Oncology clinic include those who are newly diagnosed with cancer and also have, or are at risk for developing, heart disease; as well as those who have heart failure symptoms or are taking high doses of potential cardiotoxic therapies.

“By developing strategies to minimize cardiotoxicity, we can add years to a patient’s life,” says Leja.

“M-LINE To refer a patient to the Cardio-Oncology clinic, call M-LINE at 800-962-3555.

ONLINE Read more about strain analysis in Colleagues in Care Online at med.umich.edu/cic.

800-962-3555 M-LINE 3
A Great Partnership
UMHS partners with Great Lakes Health Information Exchange (GLHIE)

To help build a strong health information network, the University of Michigan is partnering with the Great Lakes Health Information Exchange (GLHIE) and is inviting referring physicians to join the partnership.

“This venture is part of our bigger vision of linking patient records throughout the state of Michigan and beyond,” says David A. Spahlinger, M.D., executive director of the U-M Faculty Group Practice and senior associate dean for clinical affairs. “The goal is to better coordinate care and to be better partners in the care of patients referred to the University of Michigan.”

“We will be able to exchange information with other providers as never before,” says Andrew L. Rosenberg, M.D., associate professor of anesthesiology and of internal medicine, and chief medical information officer. UMHS’s electronic medical record (EMR) system, MiChart, an Epic program, will feed into GLHIE. The Health System plans to manage referrals and data sharing through GLHIE.

GLHIE’s low-cost Elysium EMR supports meaningful use requirements for Medicare/Medicaid incentive payments and other payers’ performance improvement programs. Providers can also “subscribe” to a patient and receive all clinical information as it is sent to GLHIE — of special help if the provider is interested in Primary Care Medical Home and/or Accountable Care Organization (ACO) initiatives.

“Over time, our providers will be able to view a patient’s information regardless of where it originated. This is helpful when patients have been cared for at locations that are not part of the same health organization,” Rosenberg says. “I don’t have to make individual connections. They’re there for me. Our providers and referring colleagues will appreciate the convenience of not sifting through pages of paper records and the ability to see the records of every participating provider taking care of that patient.”

Lawrence Hennessy, M.D., whose Okemos Allergy Center participates in GLHIE, agrees: “It avoids repeating expensive tests, which delays getting a diagnosis. It’s nice to have U-M in the system because we refer a fair number of patients to them.”

The high number of records will also be a boon for research projects directed at improving the quality of patient care, and will capture crucial public health and syndromic surveillance data.

“The ability to do innovative work is a plus,” Rosenberg says. “Patients and families are surprised that healthcare isn’t as technologically coordinated as most other things and that there is so little information sharing,” says GLHIE founding member and board president Brian R. McCurdal, M.D., chief of orthopedics, Sparrow Health System. “It’s an idea whose time has come.”

A nominal monthly fee (usually less than $30, depending on services) pays for associated software licenses and support.

**JOIN US** Visit glhie.org for more information, or call the Great Lakes Health Information Exchange at 517-347-3373.

**ONLINE** Get a list of the participants in the Great Lakes Health Information Exchange at Colleagues in Care Online at med.umich.edu/cic.
Stem cells show promise in regulating arrhythmia

For those suffering from heart disease, stem cell biology represents a new medical frontier. A cutting-edge method developed at the University of Michigan Center for Arrhythmia Research uses stem cells to create human heart muscle patches capable of mimicking the heart’s crucial squeezing action.

The cardiac patches displayed activity similar to most people’s resting heart rate. At 60 beats per minute, the rhythmic electrical impulse transmission of the engineered cells in the U-M study is 10 times faster than in most other reported stem cell studies.

Stem cell therapy could help the 2.5 million people with an arrhythmia, an irregularity in the heart’s electrical impulses that can impair the heart’s ability to pump blood.

“To date, the majority of studies using induced pluripotent stem-cell-derived cardiac muscle cells have focused on single cell functional analysis,” says Todd J. Herron, Ph.D., assistant research professor in the departments of Internal Medicine and Molecular & Integrative Physiology at U-M. “For potential stem-cell-based cardiac regeneration therapies for heart disease, however, it is critical to develop multicellular tissue-like constructs that beat as a single unit.”

The research team’s objectives included developing a bioengineering approach using stem cells generated from skin biopsies to create large numbers of cardiac muscle cells that can transmit uniform electrical impulses and function as a unit.

“Action potential and calcium wave impulse propagation trigger each normal heart beat, so it is imperative to record each parameter in bioengineered human cardiac patches,” Herron says.

The velocity of the engineered cardiac cells, while faster than previous reports, is still slower than the velocity observed in the beating adult heart. Still, the velocity is comparable to commonly used rodent cells, and researchers suggest human cardiac patches could be used rather than rodent systems for research purposes.

In October, U-M celebrated a new collaboration of heart researchers who will work together in the Cardiovascular Research Center laboratories at the North Campus Research Complex. The bioengineering method created at U-M can be readily applied in most cardiac research laboratories and opens the door for the use of cardiac stem cell patches in disease research, testing of new drug treatments and therapies to repair damaged heart muscle.

Could stem cells heal heart attacks?

U-M was recently selected to participate in the PreSERVE AMI Phase II trial, which brings together heart experts and cancer specialists in a unique collaboration to use stem cell therapy to treat cardiovascular disease. This Phase II is expected to include 160 recent heart attack patients in a placebo-controlled, double-blind study. A composite of cardiac measures will support the primary goal to improve patient’s cardiac perfusion.

“Results from Phase I were promising,” says U-M interventional cardiologist and principal investigator Hitinder Gurm, M.D. “Patients receiving 10 million and 15 million cells showed significant improvement in resting perfusion rates at six months. The data also showed a trend towards improvement in ejection fraction, the percentage of blood pumped out of a ventricle with each heartbeat.”

RESEARCH Find out about other clinical studies that could benefit your patients with heart disease at Colleagues in Care Online at med.umich.edu/cic
The management of patients with diabetes has evolved greatly in recent years, with a greater emphasis on tight glucose control and closer attention to risk factors such as hypertension and neuropathy. U-M researchers who study patterns of diabetes care and patient outcomes have recently published intriguing papers that physicians may want to consider as they manage diabetic patients. All the researchers are members of the U-M Institute for Healthcare Policy and Innovation, which brings together more than 400 health services researchers from across U-M and partner organizations.

STUDY 1: BLOOD PRESSURE
Aggressive efforts to lower blood pressure in people with diabetes are paying off — perhaps too well, according to U-M Health System and VA Ann Arbor Healthcare System researchers.

In Archives of Internal Medicine, the team reported that there have been dramatic improvements in blood pressure control among VA patients with diabetes, with as many as 82 percent of patients having blood pressure controlled and 94 percent getting appropriate treatment. But the team also found that over 8 percent of the 977,000 VA patients nationwide with diabetes are possibly being
over-treated. Meanwhile, 6 percent were not being treated as aggressively as they could be.

That suggests it might be time to reconsider the current one-size-fits-all approach to blood pressure control, and turn to a new model that adjusts the blood pressure goal according to the individual. Modern electronic health record systems should help make this possible.

“Appropriately treating blood pressure in people with diabetes is extremely important, and good blood pressure control should still be the goal to reduce risk of heart attack, stroke and other conditions,” says first author Eve Kerr, M.D., director of the Center for Clinical Management Research at the VAAAHS and professor of internal medicine at the U-M Medical School.

The team looked back at electronic records from people with diabetes and high blood pressure who were treated at any of 879 VA hospitals and clinics in 2009 and 2010. Almost 714,000 of them were between the ages of 18 and 75.

Drawing on the expertise of dozens of VA clinical and measurement experts, they developed a “clinical action measure,” or way of assessing the appropriateness of a patient’s care by looking at treatment factors and contraindications, not just the target blood pressure.

Appropriate hypertension management was defined as a blood pressure either less than 140/90 or less than 150/65; or having appropriate management of elevated blood pressure (medication intensification or being on three or more hypertension medications). Potential overtreatment was defined as having blood pressure that was less than 130/65 while also receiving three or more hypertension medicines or having recent medication increases.

One-goal-for-all benchmarks were set years ago when blood pressure control for people with diabetes was poor across the board. But now, a more sophisticated approach is likely needed, Kerr notes.

As a first step, the VA system will adopt the blood pressure clinical action measure to motivate appropriate blood pressure management for patients based on their risks and treatment characteristics. The same could be done in non-VA settings, says Kerr.

The studies suggest that a more personalized approach to diabetes management could lead to better outcomes.

STUDY 2: NEUROPATHY
Aggressive control of blood sugar levels in people with diabetes can help prevent neuropathy, according to a new systematic review in The Cochrane Library by a team led by a U-M neurologist. However, the review suggests that optimal target levels need to be established to prevent serious complications.

Up to half of patients with diabetes develop neuropathy in their feet and legs, and strict glucose control has been seen as a way to stave the condition off. But evidence for the effects of this approach has not been systematically reviewed until now.

The results analyzed in the review are drawn from six studies investigating the risk of neuropathy in people who received enhanced glucose control treatments including extra insulin injections, medication and diet changes.

The review looked at evidence in Type 1 and Type 2 diabetes separately. In two studies involving 1,228 people with Type 1 diabetes, significantly fewer people developed neuropathy each year with enhanced glucose control treatment compared with routine care. In four studies involving 6,669 people with Type 2 diabetes, the reduction in new cases of neuropathy was small and not statistically significant.

“Overall, this evidence suggests that a more aggressive approach to controlling sugar levels can be effective in delaying the onset of neuropathy in diabetes,” said lead author Brian Callaghan, M.D., assistant professor in the Department of Neurology at the U-M Medical School. “The results also highlight the differences between Type 1 and Type 2 diabetes. The less dramatic effect of enhanced glucose control in Type 2 diabetes may indicate that other factors, besides high glucose levels, may be important in causing nerve damage in these patients.”
However, the risk of adverse effects associated with the treatment, including hypoglycemia, was higher with enhanced glucose control. The researchers say further research is needed to optimize target levels for safe treatments that will both prevent neuropathy and minimize serious side effects.

“Although these results show clear benefits for preventing neuropathy in people with diabetes, they should be weighed against potential adverse effects,” said Callaghan.

“Future studies must establish target levels for glucose control that will balance benefits and side effects.”

**STUDY 3: MORTALITY**

Middle-aged and older adults with diabetes — even those living in nursing homes or having multiple other health issues — may survive longer with careful management of their diabetes risk factors.

Those findings, published in the *Journal of Gerontology,* revealed that even older adults may benefit from interventions that can prevent or delay retinal, neuropathic, cardiovascular and renal complications of diabetes.

“We went into this thinking that people in the limited health group would have substantial mortality, but with the exception of patients over age 76 with the poorest health status, all showed strong survival rates,” says lead study author Christine T. Cigolle, M.D., M.P.H., an assistant professor of Family Medicine and Internal Medicine at the U-M Medical School and research scientist at the VAAHS.

The study found that while adults in the older age groups were more likely to have difficulty managing the disease and to have poor health status, middle-aged adults constituted the largest number of diabetes patients to have self-management difficulties.

Blindness, cognitive impairment and having multiple diseases requiring multiple medications were among issues that complicated their ability to manage their diabetes.

The finding that medically complex patients survive to five years also supports inclusion of older patients in clinical trials to determine whether their outcomes replicate those of younger, healthier diabetes patients.

The research was based on nationally representative data from the U-M Health and Retirement Study.

Diabetes patients have a significantly higher risk of heart failure, arrhythmia and death, even when hypertension isn’t a factor — and Rodica Pop-Busui, M.D., Ph.D., leads studies that explore why at the University of Michigan.

Pop-Busui, an endocrinologist who is the principal investigator at the U-M Comprehensive Diabetes Center, has been the PI on several landmark diabetes trials funded by the National Institutes of Health. Her clinical research helps define mechanisms of chronic diabetes complications and the role of cardiovascular autonomic neuropathy in the development of heart failure, and searches for new therapies for diabetic neuropathy and other complications — a crucial part of diabetes research at Michigan.

These studies aim to shed light on why diabetes patients have such high cardiovascular risks and how to develop viable therapies for them. Among current clinical trials are:

1. “Cardiovascular autonomic neuropathy and myocardial dysfunction in diabetes,” which focuses on evaluating cardiovascular risks in diabetes patients and how wide glucose fluctuations may affect heart function. Patients with Type 1 diabetes without evidence of complications are eligible. Patients are followed for three years while continuing care under primary physicians.

2. A study to test whether the antidiabetic drug Byetta can improve the signs and symptoms of diabetic nerve damage (neuropathy) in adults who have Type 2 diabetes and who are 18 to 70 years old.

3. A multicenter clinical trial to test whether salsalate, a non-steroidal, anti-inflammatory drug, may prevent diabetic nerve damage among patients with Type 1 diabetes.

For more information on these and other clinical trials, visit umclinicalstudies.org

Ongoing studies are exploring neuropathy in people with diabetes, including the role it plays in heart function.

RESULTS Get linked to the journal articles in Colleagues in Care Online at med.umich.edu/cic

RESOURCES Get diabetes clinical care guidelines and find out about ongoing diabetes clinical studies that are currently enrolling patients in Colleagues in Care Online at med.umich.edu/cic
More Is Better

Continuous hormone therapy for prostate cancer more effective than intermittent therapy

Many men with metastatic, hormone-sensitive prostate cancer live longer on continuous androgen-deprivation therapy than on intermittent therapy, according to a 17-year study led by SWOG.

Earlier data had suggested that intermittent treatment in men with newly diagnosed metastatic prostate cancer may delay a cancer relapse, and that the rise in testosterone may result in an improvement in the patient’s quality of life.

However, results of the Phase III clinical trial, the largest such study to date, found that intermittent androgen-deprivation (IAD) therapy is not as good as continuous hormone therapy with regard to patient longevity.

The study’s principal investigator was Maha Hussain, M.D., F.A.C.P., associate director of clinical research at the University of Michigan Comprehensive Cancer Center. The study was conducted at more than 500 sites, enrolling 3,040 men with hormone-sensitive, metastatic prostate cancer between 1995 and 2008.

All men got an initial course of androgen-deprivation treatment for seven months. The 1,535 eligible men whose prostate-specific antigen (PSA) level dropped to 4 ng/mL or less by the end of those seven months were then assigned at random to the intermittent therapy group or the continuous therapy group.

Men on continuous therapy had a median overall survival time of 5.8 years from the time of randomization, with 29 percent of these men surviving at least 10 years. Those on intermittent therapy had a median overall survival time of 5.1 years, with 23 percent surviving at least 10 years.

“Though we see potential quality-of-life benefits with IAD,” Hussain says, “from a medical perspective, the primary findings of the study demonstrating that IAD is inferior with regard to overall survival should be the primary consideration in counseling all patients who are interested in intermittent therapy and particularly those with minimal disease.”

Maha Hussain, M.D., F.A.C.P., was lead investigator of the 500-site SWOG study.

Chemo pain relief

The antidepressant drug duloxetine (Cymbalta) helped relieve chemotherapy-induced peripheral neuropathy in 59 percent of patients, a new study finds. This is the first clinical trial to find an effective treatment for this pain.

Researchers looked at 231 patients who reported painful neuropathy after receiving the chemotherapy drugs oxaliplatin or paclitaxel. Patients were randomly assigned to receive duloxetine or a placebo for five weeks and asked to report on their pain levels weekly throughout the study. The researchers found that 59 percent of patients who received duloxetine reported reduced pain, while only 39 percent of those taking the placebo did.

Results were reported at the American Society of Clinical Oncology annual meeting.

Duloxetine has previously been shown to help relieve painful diabetic neuropathy. It is believed to work by increasing neurotransmitters that interrupt pain signals to the brain.

RESEARCH Find out about other clinical studies that could benefit your patients with prostate cancer in Colleagues in Care Online at med.umich.edu/cic

800-962-3555 M-LINE
New pathways for relief

Patients who are not responsive to current medications may benefit from a new direction in IBD treatment. The study of ustekinumab in Crohn’s disease examines the safety and effectiveness of Stelara (ustekinumab), a drug from the family of immune suppression drugs with a target that is different from most current therapies.

Most existing biologics for IBD work by blocking an inflammation-causing protein called tumor necrosis factor (TNF). Stelara, marketed to treat psoriasis, blocks interleukin-12 and interleukin-23, two other immune-system proteins linked to inflammation. Interleukin-23 is an immune-system signaling molecule that is overactive in those with Crohn’s disease.

The UNITI study is enrolling patients with moderate to severe Crohn’s disease who have failed conventional therapy. Patients will be assigned to three treatment groups, with two-thirds receiving active drug and one-third receiving placebo. If they complete the initial eight-week phase, they will be eligible to enter a maintenance phase, and people who benefit from ustekinumab can continue to receive the drug for free for up to three years.

While many medications studied for IBD are readily available, the use of immune-suppressive drugs originally designed for other conditions is not one-size-fits-all.
"The dosing for IBD is often much higher," says U-M gastroenterologist Peter Higgins, M.D., Ph.D., a principal investigator of dozens of IBD-related clinical trials at the University of Michigan Health System. "And the kind of doses needed to be effective are often only available through clinical trials."

RAISING THE STAKES FOR BLOCKING INFLAMMATION

Researchers worldwide are enrolling patients in the OCTAVE Trials, which are studying the benefit of tofacitinib for the treatment of ulcerative colitis. U-M is currently enrolling patients with UC.

Drugs are not universally effective in treating UC, a chronic inflammatory disease of the colon. A recent report in the New England Journal of Medicine illustrated the potential for tofacitinib in successfully controlling the inflammatory response in rheumatoid arthritis. Tofacitinib was actually a bit better than Humira (adalimumab) for patients with rheumatoid arthritis.

In the Phase II studies, tofacitinib produced an 80 percent clinical response rate. Tofacitinib, an oral medication, is now being tested in a Phase III clinical trial at the University of Michigan and is part of the trend of finding new therapeutic targets. Tofacitinib suppresses the Janus kinase (JAK) enzyme, another known trigger of inflammation, and may be especially helpful for patients who did not benefit from anti-TNF therapy.

However, recent studies have suggested that the return of inflammation can be detected with stool tests before symptoms occur. This might allow patients to stop their medications, and with careful monitoring, identify the return of inflammation and re-start therapy before symptoms start. The Calprotectin-Directed Humira Therapy study (CADHUM) will look at whether patients in remission can safely stop taking adalimumab (Humira) with close monitoring and re-dosing if inflammation returns. The key is consistent monitoring," says Higgins. "Patients get into trouble when they stop taking medications and also stop seeing their physician."

Those enrolled in the trial will have periodic lab tests — taking blood and stool samples — to identify biomarkers of inflammation. Higgins says inflammation can be identified three to six months before patients experience symptoms of pain, diarrhea and tiredness. If and when lab tests show elevated biologic markers, Humira therapy will resume.

RESEARCH For more information about these and other IBD clinical trials that may benefit your patients, email higginsSCTeam@umich.edu or visit Colleagues in Care Online at med.umich.edu/cic
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