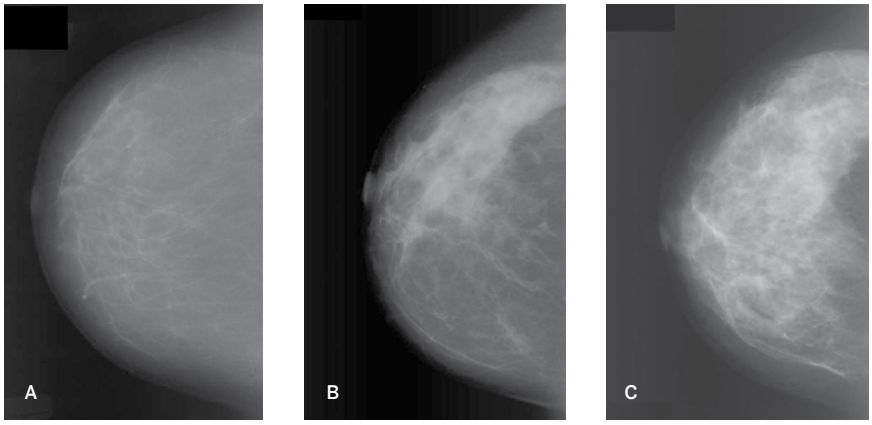
In the Lab

Hidden Risk

Examining the link between breast density and cancer



Mammograms representing (A) low, (B) moderate, and (C) high breast density from three pre-menopausal women of similar age and with similar breast size.

THERE ARE MANY VARIATIONS TO women's breasts, but the important differences are more than meets the eye. One of them — high breast density — is a major risk factor for breast cancer.

Some women's breasts contain a lot of fatty tissue. Others have more dense glandular tissue that changes in response to hormones associated with menstruation, pregnancy and menopause. Women with dense tissue in more than 75 percent of the breast have a risk of breast cancer that is four- to six-times higher than women with mostly fatty breast tissue.

Breast density is the third-strongest known risk factor for breast cancer, after age and mutations in the BRCA1 or BRCA2 genes, but no one knows why.

Julie Douglas, Ph.D., an associate professor of human genetics, hopes to find out with help from 1,500 Old Order Amish women in Lancaster County, Pennsylvania. She is the principal investigator on a five-year, $3 million NIH-funded study to identify genes that affect breast density. Doing so is the first step to understanding the link between breast density and cancer, which Douglas says could account for about one-third of all cases of the disease.

"One of the advantages of studying the Amish is that they have unique cultural and reproductive behaviors that reduce the effect of non-genetic factors such as delayed childbearing, use of contraceptives and hormone therapy," Douglas says.

The most common and inexpensive way to measure breast density is with a mammogram. Fatty tissue appears dark on a mammographic image, while dense tissue and tumors show up as white. It's harder to spot tumors against a white background, which is why radiologists are interested in the amount of density in the image.

Douglas says the study wouldn't be possible without the expertise of U-M collaborators Heang-Ping Chan, Ph.D., professor of radiology, and Mark Helvie, M.D. (Residency 1986), professor of radiology and director of the breast imaging program. The pair and their colleagues developed a computer-assisted method that classifies each pixel in a mammographic image as black or white, then calculates breast density by finding the ratio between the number of white pixels and total pixels in the image. "It gives us a reproducible quantitative measurement," Douglas says.

To analyze the complex set of factors related to breast density, Douglas collects massive amounts of data about the Amish women enrolled in the study. A Lancaster radiologist takes screening mammograms for each woman and sends thems to the U-M to be digitized and scored for density. DNA is extracted from blood samples. Blood tests measure individual levels of hormones and other factors. Characteristics like height, weight, body mass index and number of live births are captured and recorded in a database.

Since all the women in the study are descendants of original Lancaster County settlers, Douglas has been able to connect them in one 13-generation pedigree.

"We have hundreds of pairs of sisters, thousands of pairs of first cousins and tens of thousands of more distantly related cousins," Douglas says. "Having all these pair-wise relationships will allow us to compare genomes of related women with similar breast density scores and identify genes in common." —SALLY POBOJEWSKI

MORE ON THE WEB

COURTESY OF JULIE DOUGLAS

UTI Vaccine Shows Promise

MEDICAL SCHOOL SCIENTISTS HAVE TAKEN A MAJOR STEP TOWARD a vaccine to prevent uncomplicated urinary tract infections — a disease that strikes 53 percent of women and 14 percent of men at least once in their lives. Untreated urinary tract infections can lead to permanent kidney damage, and people with repeated UTIs can develop resistance to antibiotics used to treat the condition.

The U-M vaccine works by priming the body's immune response to specific proteins on the surface of uropathogenic strains of *Escherichia coli*, the bacterium that causes most uncomplicated UTIs. When U-M scientists tested the experimental vaccine in mice, it generated a strong immune response to these bacterial proteins and prevented mice from being infected with *E. coli* bacteria in their urinary tracts. If the vaccine works as well on people as it did in mice, it could lead to the first UTI vaccine available in the United States.

Administered through the nose, the vaccine induces an immune response in mucosal tissue lining the urinary tract, which helps the body fight infection where it starts, says Harry L.T. Mobley, Ph.D., the Frederick G. Novy Collegiate Professor and chair of microbiology and immunology, who directed the research.

"The results of our initial animal studies were very encouraging," says Mobley. "Now, we hope to connect with clinicians and move on to a phase 1 clinical trial in humans." The U-M has applied for patent protection and is looking for licensing partners to help move the vaccine to market. —SP

MORE ON THE WEB

Harry Mobley and the study's first author, Chris Alteri, Ph.D., examine petri dishes containing colonies of uropathogenic *E. coli* bacteria.

Stimulus Funding Reaches Medical School

MEDICAL SCHOOL RESEARCHERS are a big reason the University of Michigan has received $47.5 million in federal research funding to date from the federal economic stimulus package known as the American Recovery and Reinvestment Act.

"Despite the recent slowdown in federal funding for biomedical research, our faculty has succeeded in obtaining government funding for many important new projects," says Steve Kunkel, Ph.D., senior associate dean for research. "These new stimulus grants will help us conduct research to solve medical challenges, speed innovations from the lab to the bedside, train tomorrow's researchers and provide upgraded laboratory facilities and equipment."

Some research awards will fund Medical School scientists studying potential treatments for epilepsy, cardiac arrhythmias and cancer. Other awards are supporting efforts to develop a vaccine to protect children from ear infections and an imaging-based system to determine if cancer treatments are working. Kunkel expects additional stimulus grants to be awarded in future months. —SP

LEFT: SCOTT GALVIN, U-M PHOTO SERVICES
RIGHT: TETRA IMAGES

In the Lab

Mice Stay Younger, Longer

In research supported by the National Institute on Aging, Richard Miller, M.D., Ph.D., studies drugs with the potential to delay disease and slow aging in mice. Treatments that slow down the aging process in mice might do the same for people someday.

Although he's tested several promising candidates, Miller says a drug called rapamycin is the new front-runner in anti-aging research. In independent studies conducted at three NIA-funded research institutions, rapamycin extended the lifespan of middle-aged mice from 9 percent to 14 percent compared to animals that didn't receive the drug.

"While other results have been promising, the rapamycin effect is bigger and worked even when started in late middle-age," says Miller, a professor of pathology and associate director of research at the U-M Geriatrics Center. —SP

MORE ON THE WEB

EMILIA STASIAK

Cell Replacement for Parathyroid Takes Major Step

USING HUMAN EMBRYONIC STEM cells, researchers at the U-M Medical School have created live cultures of parathyroid-like cells that secreted an essential calcium-regulating hormone called PTH. The research is an important step toward a new cell transplant therapy to help patients with damaged or diseased parathyroid glands.

"We used human embryonic stem cells as a model to work out the recipe to make parathyroid cells," says Gerard M. Doherty, M.D., the Norman W. Thompson Professor of Endocrine Surgery. Federally approved embryonic stem cell lines used in the study were supplied by the Michigan Center for Human Embryonic Stem Cell Research.

Humans have four rice grain-sized parathyroid glands located in the neck next to the thyroid gland. If they become diseased or are damaged during surgery, they stop secreting PTH. Without this calcium-regulating hormone, patients develop osteomalacia — a form of bone loss similar to rickets.

Doherty's ultimate goal is to use cells from a patient's thymus gland to regenerate functioning parathyroid cells. Using the patient's own cells would eliminate the need for immunosuppressive drugs to prevent the immune system from rejecting the cell transplants. If all goes well, Doherty says an effective cell replacement therapy could be available within five to 10 years. —SP

MORE ON THE WEB

Nano for Burns?

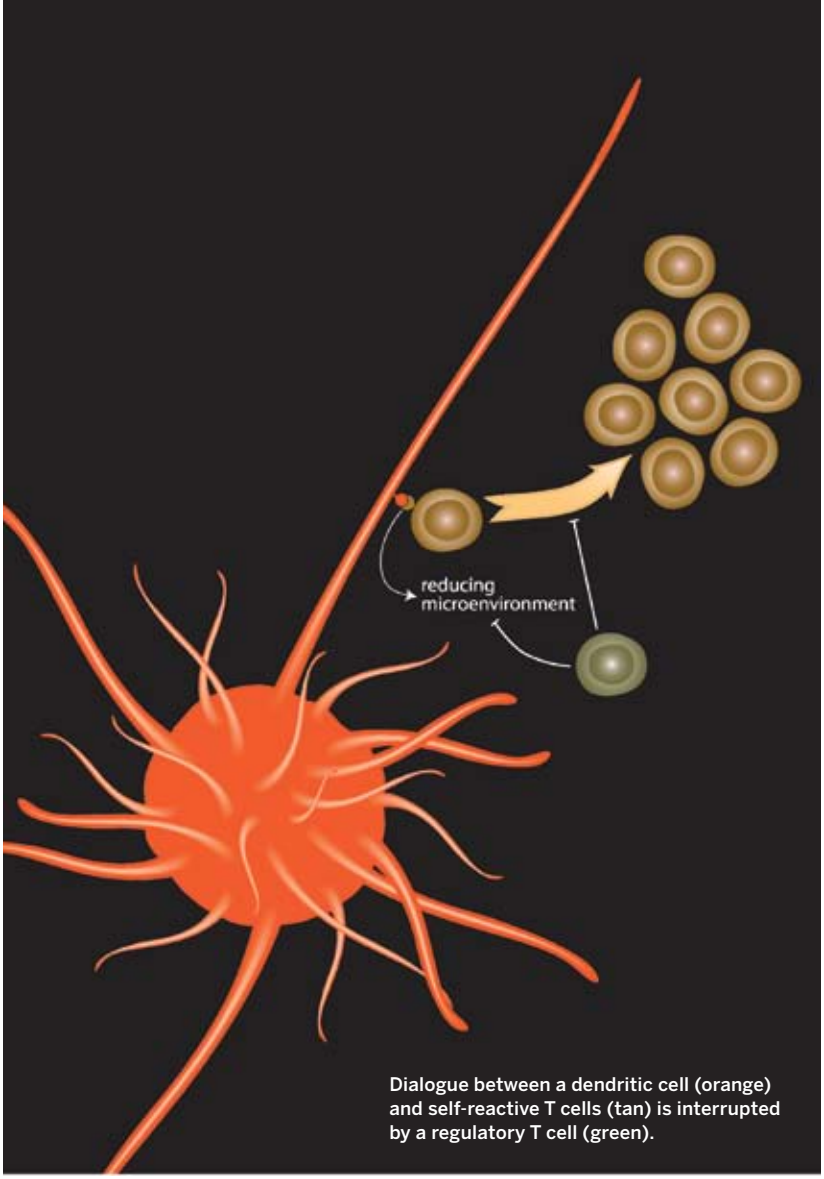
MEDICAL SCHOOL SCIENTISTS have shown that a nanoemulsion lotion, developed at the U-M and licensed to NanoBio Corporation, sharply curbed bacterial growth and reduced inflammation in animals with second-degree burns. According to Mark Hemmila (M.D. 1994), associate professor of surgery, the nanoemulsion could eventually replace existing topical antimicrobial agents, which have a limited ability to penetrate burned skin and kill sub-surface bacteria, and don't have a strong effect on inflammation. Before testing in people, additional research is needed to examine the nanoemulsion's effects on the overall healing process. —SP

MORE ON THE WEB

Targeting IPF

IDIOPATHIC PULMONARY FIBROSIS, or IPF, causes progressive lung scarring and thickening that make it difficult, and eventually impossible, to breathe. There is no treatment and the average survival time after diagnosis is less than three years. But now Medical School researchers have developed a new experimental treatment for IPF that stopped the progression of fibrosis in mice and preserved their lung function. Treatment inhibits the activity of an enzyme called NOX4, which U-M scientists discovered is key to the formation of fibrotic scar tissue in the lungs and other organs. The researchers plan to develop the treatment for future testing in human patients. —SP

MORE ON THE WEB



Dialogue between a dendritic cell (orange) and self-reactive T cells (tan) is interrupted by a regulatory T cell (green).

WESLEY TANNER

Understanding Immune Response

What keeps aggressive immune system T cells from attacking the body's own cells? Part of the answer, according to Ruma Banerjee, Ph.D., the Vincent Massey Collegiate Professor of Biological Chemistry, is in the chemical environment between the cells. A new study from Banerjee's research team found that regulatory T cells can change this environment in ways that either cool down or ramp up the immune response. Understanding how this mechanism works could lead to new treatments for autoimmune diseases, such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis and lupus. —SP

MORE ON THE WEB

In the Clinic

Diagnosing the Diagnostics

New findings on radiation exposure from imaging tests


Brahmajee Nallamothu

THE STANDARD PROCEDURE FOR physicians when diagnosing illness is to confirm its presence with state-of-the-art tests. In today's technologically advanced world of medicine, those tests often include imaging studies that utilize radiation. Now, after a recent study on the levels of exposure to radiation from such tests in the U.S., a change in protocols may be needed.

"We decided to research this topic because of the rise in medical imaging," says Brahmajee K. Nallamothu, M.D. (Fellowship 2004), an author of the study who is a U-M associate professor of internal medicine and a staff cardiologist at the VA Ann Arbor Healthcare System. As a clinical researcher, Nallamothu recognized the need to examine the use of these tests on patients throughout their lifetime.

"Rarely do patients undergo a single examination," he says. "If you have chest pain, for example, it's likely that you're going to get more than one test, such as a stress test and possibly a cardiac catheterization. We approached the research by asking: If a single test in one person has a certain associated risk and is raising concerns, how many of these tests are occurring or being repeated in the same patient over longer periods of time?"

"There are a number of studies showing that many physicians aren't even aware of this issue," adds Reza Fazel (M.D. 2001, Residency 2004), lead author of the study and a cardiologist at Emory University. The study also included colleagues at Yale, Columbia, Mayo and Johns Hopkins, and was published in the *New England Journal of Medicine* in August.

In the study, nearly 1 million adults age 18-64 from five health care markets across the U.S. were identified from UnitedHealthcare claims data. The utilization data from this group from 2005-07 was used to estimate cumulative effective doses of radiation from imaging procedures. Exposures were estimated using the concept of effective dose, which is expressed in millisieverts and reflects how harmful a given exposure is to the body.

Computed tomography (CT) scans were among the procedures exposing patients to the largest amounts of radiation. CT scans constituted only 16 percent of all procedures, but accounted for nearly 50 percent of the total exposure to patients.

Even before this study, the U-M was leading the charge to improve safety by justifying the use of each procedure, seeking alternative methods that might be safer, and minimizing radiation exposure during imaging.

Fazel and Nallamothu recommend that patients take an active role in reducing their risk by understanding why their physician is recommending a procedure, asking if there are safer alternatives, and requesting that the facility providing the imaging be certified for safe operating procedures.

Nallamothu stresses that imaging tests are a vital, lifesaving part of medical care. "Our study isn't about eliminating imaging tests," he says. "It's about using them better — that is, only when necessary and in the best manner possible to reduce the risks to patients." —NICK CHARLES

MORE ON THE WEB

SCOTT SODERBERG, U-M PHOTO SERVICES

A New View of the Safest Hospitals for Surgery

A NEW U-M STUDY OVERTURNS A LONG-HELD CONVENTION THAT THE safest hospitals are those with the lowest complication rates. The study found that after major surgery, complications happen in about one out of six patients, a rate that remained fairly consistent among the 186 participating hospitals. It was what happened after the complication that mattered.

"The general assumption has been that high-mortality hospitals simply have higher complications rates," says John D. Birkmeyer, M.D., the George D. Zuidema Professor of Surgery and chair of surgical outcomes research at the Medical School. Birkmeyer, along with lead author Amir Ghaferi, M.D., a surgical resident, and Assistant Professor of Surgery Justin Dimick, M.D., found that low-mortality hospitals are those with teams that are most proficient in rescuing patients from potentially catastrophic complications. Despite similar patterns in complications, patients treated at high-mortality hospitals were nearly twice as likely to die after a serious post-surgical complication.

The study used data on 84,730 patients undergoing general and vascular surgery at hospitals participating in the American College of Surgeons National Surgical Quality Improvement Program. The mortality rate varied dramatically, from 3.5 percent at the best hospitals to 6.9 percent at the very high-mortality hospitals. Birkmeyer says the study shows that "Rather than focusing only on what the surgeon does in the operating room, we need to focus on what's happening on the wards and in the intensive care unit afterward." —RK

MORE ON THE WEB

SCOTT SODERBERG, U-M PHOTO SERVICES

Health Briefs

When tissue or blood type incompatibilities prevent a willing friend or family member from donating a kidney to a transplant patient, new U-M software seeks to match that pair with other pairs in the same situation. The match enables the donor from the first pair to donate to the recipient from the second pair, and the donor from the second pair to donate to the recipient from the first pair.

MORE ON THE WEB

Cheerleading is the leading cause of catastrophic injury among young female athletes today, according to Amy Miller Bohn, M.D., assistant professor of family medicine. Data show that injury rates rose from nearly 5,000 in 1980 to close to 28,000 in recent years. Bohn says cheerleading is now a competitive sport with increased difficulty and risk for serious injury, and that more safety measures and supervision are needed.

MORE ON THE WEB

Medical School researchers will lead a $10.25 million collaboration among 15 academic medical centers and the Nephcure and Halpin foundations to study rare kidney diseases that lead to kidney failure and the need for dialysis. Known collectively as nephrotic syndrome, the diseases, while rare, contribute to nearly 12 percent of kidney failures at an annual cost of more than $3 billion. —RK

MORE ON THE WEB

In the School

Dear Doctor ...

Students' innovation models process

Andrew Lin and Aaron Farberg

IT BEGAN AS AN IDEA BETWEEN two first-year medical students; it ended up a disarmingly simple innovation to patient-physician communication.

Introduced to patients early in their medical education through the Family Centered Experience, which matches students with patient-families for a two-year period, Andrew Lin, from Los Angeles, and Aaron Farberg, from Chicago, quickly recognized what so many of us experience: questions that patients want to ask their doctors often occur to them after the physician has moved on — or don't occur to them at all.

"When people are dealing with chronic disease in particular," says Farberg, "it's a lot to take in and difficult to think of everything, including what questions to ask."

What if, the two wondered, patients were provided with the means to write down questions, and maybe even prompted with questions typical to many patients' situations? Questions like, what tests are planned for today? What medications will I be on?

"We took our idea to Dean Woolliscroft during one of his open office hours sessions," says Lin. The dean suggested they seek the guidance of hospitalists Scott Flanders, M.D., and Chris Kim, M.D. (Residency 2004).

Encouraged and mentored by Flanders and Kim on logistics and process, Lin and Farberg began modeling a prototype — cutting paper into squares, experimenting with fonts, making trips to Kinko's, often into the small hours of the night. Flanders and Kim urged the students to apply for one of the Medical School's Fostering Innovations Grants, which encourage innovative solutions and improvements in the Health System.

Farberg and Lin's project was funded.

They interviewed patients. They spoke with stakeholders — nurses, physicians, housekeeping staff whose responsibility it would be to place the items when preparing rooms for new patients. They held focus groups. "We didn't want to harm the chain of communications," Farberg says, "so we carefully sought and listened to input from hospital staff and patients, and watched out for any negatives." They also sought the counsel of the Health System's marketing and communications staff, who directed them to U-M Printing Services so they wouldn't have to wield paper-cutters anymore.

The students produced 1,000 notepads they call Dear Doctor Notes, shrink-wrapped with companion pens, and conducted a pilot program lasting more than two months in the general medicine and cardiac units, with control groups in each.

Anecdotal feedback indicates high satisfaction among patients who used the notes. Lin and Farberg are gathering patient survey data and hope to publish the results of their study in a medical education journal, and perhaps present at a national conference. Ultimately, they'd like to see the concept spread throughout the hospitals, and to outpatient clinics as well. "It helps patients chart their own care," says Farberg. "Family members and friends will sometimes leave questions, too."

"Doctors say it holds them more accountable," Lin says. "The questions are there. They have to answer them."

Nurses report they're paging physicians less frequently with patient questions, thanks to the notepads. Now in their second year, the enterprising duo is quick to credit the support they got along the way. "It wasn't just us," Lin says. "We couldn't have done it without so many helpful people directing us to the next step." —RICK KRUPINSKI

Questions? E-mail Farberg and Lin at deardoctor@umich.edu.

SCOTT GALVIN, U-M PHOTO SERVICES

County, U-M Create Autopsy Partnership

IN AN ALLIANCE THAT'S RARE IN THE UNITED STATES, THE U-M morgue has been doubled in size and capacity, and all of Washtenaw County's autopsies will now be performed in the renovated facility — effectively doubling the educational opportunities for medical students to participate or observe. The county contributed to the cost of renovations, and the chief medical examiner has moved his office to the medical campus. The partnership centralizes the county's efforts to improve death investigations, and furthers the U-M's goal of establishing an academic center of excellence in forensic pathology. —RK

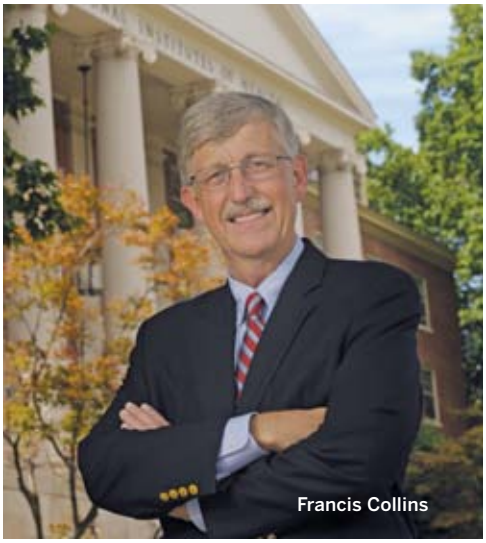
Former Faculty Member Heads NIH

FRANCIS S. COLLINS, M.D., PH.D., FORMER FACULTY MEMBER IN THE departments of Internal Medicine and Human Genetics and pioneering leader of the Human Genome Project, was sworn in as director of the National Institutes of Health on August 17. The NIH funds research at its 27 institutes and centers, as well as at universities nationwide.

Collins was on the faculty of the Medical School from 1984 to 2003. While at the U-M, he identified the gene for cystic fibrosis and discovered the genes for neurofibromatosis and Huntington's disease. He also co-authored the definitive medical genetics text, *Principles of Medical Genetics*.

During a leave of absence from the U-M, Collins led the Human Genome Project — which mapped and sequenced all human DNA — to successful completion in 2003. Data resulting from the project continue to fuel many avenues of biological and medical science. He became director of the National Center for Human Genome Research in 1993, and of its successor, the National Human Genome Research Institute, in 1997, retiring in 2008. In 2007, he was awarded the Presidential Medal of Freedom.

Collins never lost his ties with the Medical School, returning each year to help teach genetics and, in 2000, to deliver the commencement address. —RK



Francis Collins

LEFT: NATIONAL INSTITUTES OF HEALTH; RIGHT: MARY MASSON

New Leader for School's Largest Department

John Carethers

NATIONALLY RECOGNIZED gastroenterologist and Detroit native John M. Carethers, M.D., is the new leader of the Medical School's Department of Internal Medicine. Chief of gastroenterology at the University of California, San Diego, and director of UCSD's NIH Digestive Disease Research Development Center since 2004, Carethers began his U-M appointment November 1.

As chair, Carethers will oversee 585 faculty members in 12 divisions, and the department's research, education, clinical care and development efforts. He heads one of the nation's leading internal medicine departments, one that ranks fourth in NIH grant funding.

Carethers is respected among top gastroenterologists for his study of colorectal cancers, particularly among African-Americans. He earned his medical degree from Wayne State University in Detroit, and completed a residency in internal medicine at Massachusetts General Hospital in Boston and, in 1995, a fellowship at the U-M. —RK

MORE ON THE WEB