

## In the Lab

# Circle Trumps Square

## Unique pattern-recognition software aids pathologists in identifying digital features

**FROM MUSIC TO MEDICAL RECORDS,** digital technology is revolutionizing nearly every corner of society — and the field of pathology is no exception. Whole slide imaging, for example, can transform a single tissue slide into an image 200,000 pixels wide and 100,000 high — or about 50-100 times larger than a high-resolution beachscape one might set as a desktop background.

U-M pathologists Ulysses Balis, M.D., and Jason Hipp, M.D., Ph.D., were not only confronting questions about how to sift through such an overwhelming cascade of data, but how to harness its potential in ways that would be undreamed of using traditional methods.

Enter SIVQ. Spatially Invariant Vector Quantization is a unique pattern-matching software designed by Balis, Hipp and their collaborators. The program can quickly and accurately identify features within a digital picture, far exceeding what the human eye can do unaided.

With a few clicks, the algorithm can recognize microorganisms, separate tumors from background tissue, or identify cell types unique to a particular diagnosis — such as the cherry-red nucleoli of Reed-Sternberg cells associated with Hodgkin's lymphoma. It can also be used to rapidly calculate the area of an irregularly shaped feature or to eliminate the slow and painstaking tallying of tiny elements.

"Three things set SIVQ apart from other pattern-matching programs,"

says Balis, director of the Division of Pathology Informatics at the U-M Medical School and associate professor of pathology. "It's extremely flexible, requires minimal training to operate, and it's based around the circle rather than the traditional square."

While the difference between a circle and a square may not sound like much, when it comes to pattern matching,

it's fairly revolutionary. Circles have continuous symmetry. Unlike a square, if you rotate a circle 45 degrees, the shape remains the same. So as the program searches an image for a particular pattern, its rings also spin like a combination lock, checking every possible degree of rotation.

"What that means is that it will efficiently find the image no matter how it's rotated or even flipped, like in a mirror," says Hipp, a pathology informatics fellow. "That's good because in pathology, human cells don't line up all nice and neat. They can face any direction."



Jason Hipp and Ulysses Balis

The tool is flexible enough to be used across many disciplines of medicine — recently, a Harvard pathology fellow used SIVQ to analyze gunshot wounds in autopsy photos — but its potential doesn't stop there. In their first article on SIVQ, published last year in the *Journal of Pathology Informatics*, the researchers showed how the software was able to home in on parked helicopters in a satellite photo of Baghdad, Iraq. (It can even find Waldo in a *Where's Waldo?* picture.)

While Hipp and Balis believe SIVQ is a potential “game changer” for pathologists, it's meant to augment rather than replace human capabilities.

“By eventually bringing a tool like this into the clinical workflow, we can provide a higher level of expertise that is distributed more widely, and lower the rate at which findings get overlooked by even the most skilled and diligent pathologists,” Balis says. —IAN DEMSKY

## Stem Cell Line Placed on NIH Registry

**THE UNIVERSITY OF MICHIGAN'S FIRST HUMAN EMBRYONIC STEM CELL** line has been placed on the National Institutes of Health's registry, making the cells available for federally funded research. It is the first of the stem cell lines derived at the U-M to become part of the registry.

The line, known as UM4-6, is a genetically normal line, derived in October 2010 from a cluster of about 30 cells removed from a donated 5-day-old embryo roughly the size of the period at the end of this sentence. That embryo was created for reproduction but was no longer needed for that purpose and was therefore about to be discarded.

“This is significant, because acceptance of these cells on the registry demonstrates our attention to details of proper oversight, consenting, and following of NIH guidelines established in 2009,” says Gary Smith, Ph.D., who derived the line and also is co-director of the U-M Consortium for Stem Cell Therapies, part of the A. Alfred Taubman Medical Research Institute. The U-M is among only a handful of U.S. universities creating human embryonic stem cell lines. There are only 147 stem cell lines available on the registry.

A. Alfred Taubman, founder and chair of U-M's Taubman Institute, called the registry placement a tremendous step for stem cell research. “We hope it is the first of many lines that the University of Michigan can contribute to the global efforts to improve human health,” he says. —MM



## Alliance to Accelerate Search for New Therapies

### LEADERS FROM THE U-M

Medical School and MedImmune, the global biologics arm of AstraZeneca, have signed a new agreement to work together on a broad range of projects. The three-year strategic collaboration will bring scientists from one of the nation's top medical research institutions together with scientists from one of the world's leading developers of biologic therapies.

Medical School and MedImmune scientists will cooperate on studies that aim to translate scientific discoveries from the laboratory into new candidates for treating cancer, heart disease, digestive disease, lung disease and diseases caused by inflammation.

The agreement goes beyond the traditional type of academic-industry relationship, in which companies fund projects such as clinical trials, or license patents on discoveries made by university scientists and develop them on their own. In this new type of agreement, scientists from medical schools and industry collaborate closely on projects — while also preserving academic freedom, research integrity and both sides' rights to intellectual property for discoveries. —KG

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## In the School

# In Comfort, with Dignity

## Fellowship trains physicians in palliative medicine and hospice care

### DESPITE MEDICINE'S ABSOLUTE

mission to better human health, there comes a time for many patients with serious illness when a cure is no longer the primary goal. "Palliative medicine is both a way of care, and a philosophy," says Raymond Yung, M.D., chief of the Division of Geriatric and Palliative Medicine in the Department of Internal Medicine. "The main goals become comfort, and

relief of pain and suffering. No matter what we as physicians might hope to do, we have limitations."

Physicians have always worked to ease the pain and suffering of the seriously ill and dying as part of the spectrum of patient care, but that care has traditionally focused on physical symptoms and discomfort. The growing field of palliative medicine and hospice care recognizes that patient needs — and those of family and friends — go far beyond the physical to encompass emotional issues, legal issues, issues of faith and relationships, grieving and mourning.

The Medical School established a fellowship in palliative medicine and hospice care in 2008, which now claims four cohorts of graduates skilled in end-of-life care, including communicating effectively with patients and family. Adam Marks, M.D. (Residency 2012), who completes his fellowship this year, recalls a story that took place during the first month of his internship. An ICU patient with terminal lung cancer was put on a ventilator because of respiratory failure. The family's strong religious beliefs put them at odds with the medical team. "I was totally out of my element," Marks recalls. With the help of the palliative care team, delicate, respectful conversations led to removal of life

support, "and what could have been a very difficult family interaction became a positive experience because of the nature of faith involved." The complexities of palliative medicine led Marks to pursue training, and he chose the U-M because of its strong pediatrics component. This summer Marks will join the Medical School faculty, devoting one-third of his time to pediatrics and two-thirds to palliative medicine. "There are some great clinical mentors here," Marks says, "and an increasing awareness of palliative care. Patients even ask for it using that term now."

The fellowship combines clinical and research experiences, as well as rotations at the VA Ann Arbor Healthcare System, University Hospital, C.S. Mott Children's Hospital and Arbor Hospice. Two of the program's three slots are funded by the VA, where fellows consult and round and are part of a five-bed inpatient palliative medicine unit. Didactic training — lectures, grand rounds, case discussions — contributes to the fellows' experience. Fellowship Director Marcos Montagnini, M.D., an associate professor of internal medicine, says graduates learn to provide care to a "wide range of pediatric and adult patients with life threatening illness. They also complete a scholarly project, such as writing a paper or developing educational materials, relevant to their career path and guided by a mentor."

Yung cites Health System support as critical to establishing "a continuum of care in palliative medicine. A fuller academic structure, which includes research, education and patient care, will help the program grow. I see a gap that needs to be filled." —RICK KRUPINSKI

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Raymond Yung, Marcos Montagnini and Adam Marks



James Woolliscroft

## Dean Appointed to Second Term

**JAMES O. WOOLLISCROFT, M.D.** (Residency 1980), has been reappointed to a second five-year term as dean of the Medical School, beginning July 1, 2012. Woolliscroft served as interim dean for nearly a year prior to his first term, and previously held the post of executive associate dean from 1999-2006. He is an internationally recognized medical educator and has played major roles in medical student, resident and fellow education at the U-M. Woolliscroft was selected in 1996 as the first Josiah Macy Jr. Professor of Medical Education, and in 2001 was named the Lyle C. Roll Professor of Medicine, recognizing his work in enhancing the practice of medicine through education. —RK

## Chairs Appointed to New Departments

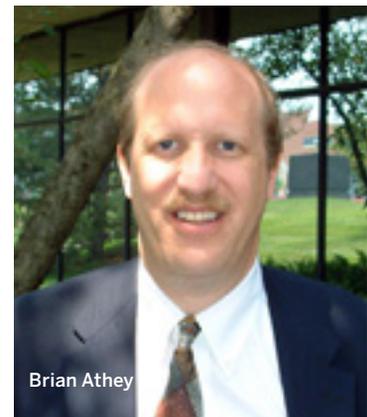
**THE UNIVERSITY OF MICHIGAN REGENTS HAVE APPOINTED CHAIRS TO** oversee the Medical School's two newest departments, which were established in January. Both appointments were effective January 2.

Edward Bove, M.D., was named chair of the Department of Cardiac Surgery. Bove is the Helen F. and Marvin M. Kirsh Professor of Cardiac Surgery; he and the pediatric surgical team at the U-M Congenital Heart Center have revolutionized surgical approaches to congenital heart defects. Bove completed a general surgery residency at the U-M in 1976 and another in thoracic surgery in 1977. He joined the U-M faculty in 1985. Heart programs at the U-M Cardiovascular Center and C.S. Mott Children's Hospital are consistently ranked among the best in the nation, and U-M physicians perform more than 2,000 heart operations each year.

Brian D. Athey, Ph.D., was appointed chair of the Department of Computational Medicine and Bioinformatics, two related applied fields which rely on an interdisciplinary research culture and underpin the future of biological and biomedical research. The new department builds upon the success of the U-M Center for Computational Medicine and Bioinformatics, created as a campus-wide center in 2005, and consists of the center, the Bioinformatics Graduate Program, the Bioinformatics Analysis Core, and the National Center for Integrative Biomedical Informatics. Trained as a biophysicist, Athey received his doctorate in cellular and molecular biology from the U-M in 1990 and in addition to his role as chair, will remain a professor of psychiatry and of internal medicine in the Medical School. —RK



Edward Bove



Brian Athey

## In the Clinic

# Hope for Patients with Hepatitis C

## New drug combinations suppress virus

**THE MOST COMMON FORM OF** the hepatitis C virus in the United States and worldwide — known as genotype 1 — also remains the most difficult to treat. Hepatitis C infects the liver and can lead to cirrhosis and liver cancer; an estimated 170 million people around the globe are infected. Although there is no vaccine to prevent hepatitis C, it is a potentially curable disease. A recent U-M study added to that potential with a new combination of investigational drugs that suppressed hepatitis C genotype 1 in a high percentage of patients who hadn't responded to previous treatment.

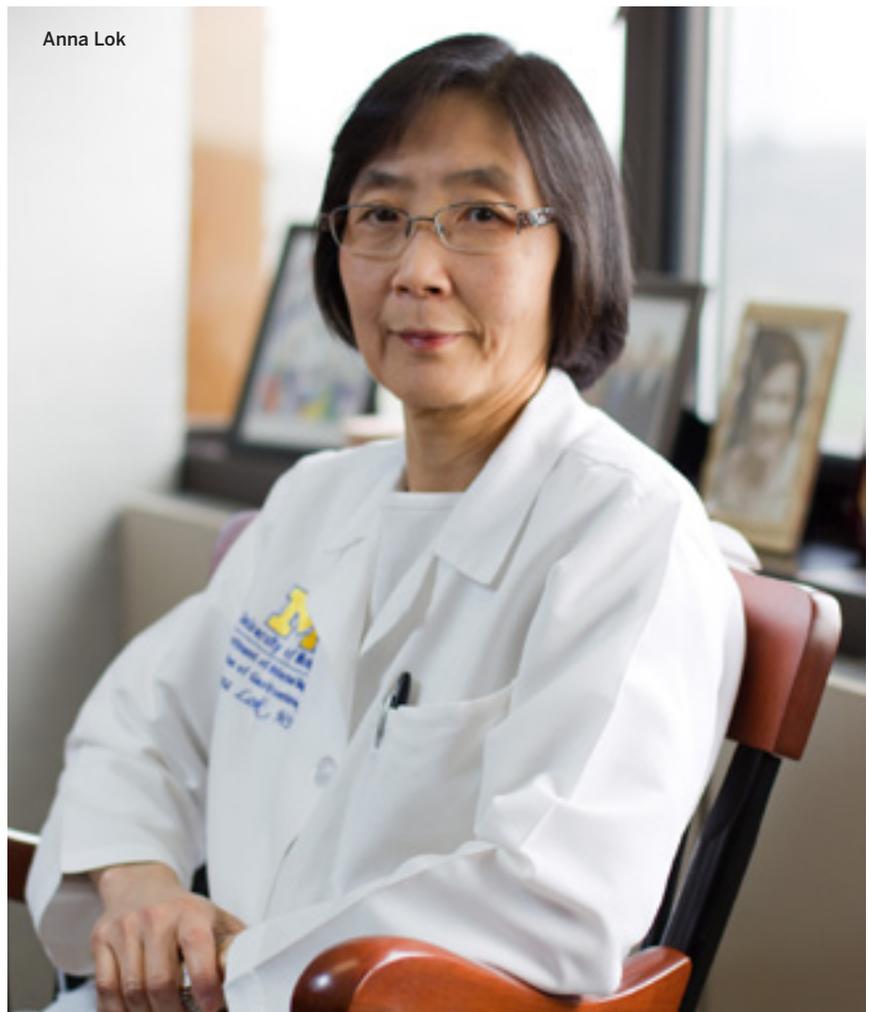
Two antiviral agents, known as PEG-interferon alfa and ribavirin, are typically used to treat this form of hepatitis C. The U-M study, published January 19 in the *New England Journal of Medicine*, focused on patients with hepatitis C genotype 1 who had not responded to treatment with these drugs.

"The two recently approved hepatitis C drugs — telaprevir and boceprevir — combined with PEG-interferon alfa and ribavirin have limited success in patients who have not responded to previous treatment with PEG-interferon alfa and ribavirin," says Anna S. Lok, M.D., the Alice Lohrman Andrews Research Professor of Hepatology, director of clinical hepatology, and lead author of the study. A new combination regimen to increase response rates in that population was the goal of the phase 2 clinical trial conducted by Lok and colleagues, including scientists from Bristol-Myers Squibb, which funded the study.

Patients were given a combination of two investigational direct-acting antiviral agents (daclatasvir and asunaprevir) alone, or with PEG-interferon alfa-2a and ribavirin. All of the patients saw their hepatitis C viral load drop rapidly, Lok says.

Of the 10 patients who were given the four-drug treatment, all had sustained

virologic response at the end of treatment and at 12 weeks after stopping treatment. Sustained virologic response means there is no hepatitis C virus detected in a patient's blood after treatment is stopped, and research has shown later relapse to be rare. Four of the 11 patients who were given only the



two direct-acting antiviral agents also achieved sustained virologic response.

Lok finds the high rate of sustained virologic response in patients who received the four-drug regimen “very exciting,” and although just 36 percent of patients given only the two direct-acting antiviral agents achieved sustained virologic response, Lok is encouraged by those results as well. “This is the first study to show that sustained virologic response can be achieved without the use of interferon or ribavirin,” Lok says. “These data are very encouraging because PEG-interferon alfa and ribavirin are associated with many side effects, and many patients with hepatitis C choose not to receive treatment for fear they cannot tolerate those drugs.”

The results suggest that further research into combinations of direct-acting antiviral agents should be encouraged, Lok says, but she also cautions about selecting the right combination of direct-acting antiviral agents in studies of interferon-free regimens. “In this study, all seven patients who received only two direct-acting antiviral agents and did not achieve sustained virologic response had emergence of drug resistance variants to both drugs,” she says.

Hepatitis C is transmitted through direct contact with infected blood and blood products. Up to 80 percent of those infected with hepatitis C will become chronically infected and, of those, 20 percent will develop cirrhosis. Up to 25 percent of patients with cirrhosis of the liver may progress to liver cancer.  
—MARY MASSON/RICK KRUPINSKI

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## Pathology On-Site, Fewer Second Breast Cancer Operations

**NEARLY ONE IN THREE WOMEN WHO** have breast cancer surgery will need to return to the operating room for additional surgery after the tumor is evaluated by a pathologist. But a service that began two years ago at the University of Michigan Comprehensive Cancer Center cuts that number drastically by having pathologists on-site in the operating suite to assess tumors and lymph nodes immediately after removal. The surgeon and patient remain in the operating room until the results are known, and any additional surgery can be done immediately.

A study evaluating 271 patients treated eight months before the program began and 278 treated eight months after showed that the new process decreased the number of second operations needed by 64 percent, to one of every 10 women. Patients must return to the operating room for two primary reasons: to remove additional tissue

when the cancer cells are too close to the margin of tissue removed, and, in some cases, to remove additional lymph nodes if the initial sentinel lymph node biopsy tests positive for cancer.

“The frequent need for second surgeries represents a tremendous burden for patients,” says lead study author Michael S. Sabel, M.D., associate professor of surgery in the Medical School. “Additional surgeries can result in worse cosmetic outcomes and increased complication rates.” Not only is the on-site pathology service beneficial for patients, “but it reduced the costs of caring for patients with breast cancer,” Sabel adds.

The U-M study showed that before the service, 25 percent of patients needed a second operation to remove more tissue, compared to 11 percent after the service began. Among patients with cancerous lymph nodes, 93 percent of them avoided a second operation. —NF

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## In the Clinic

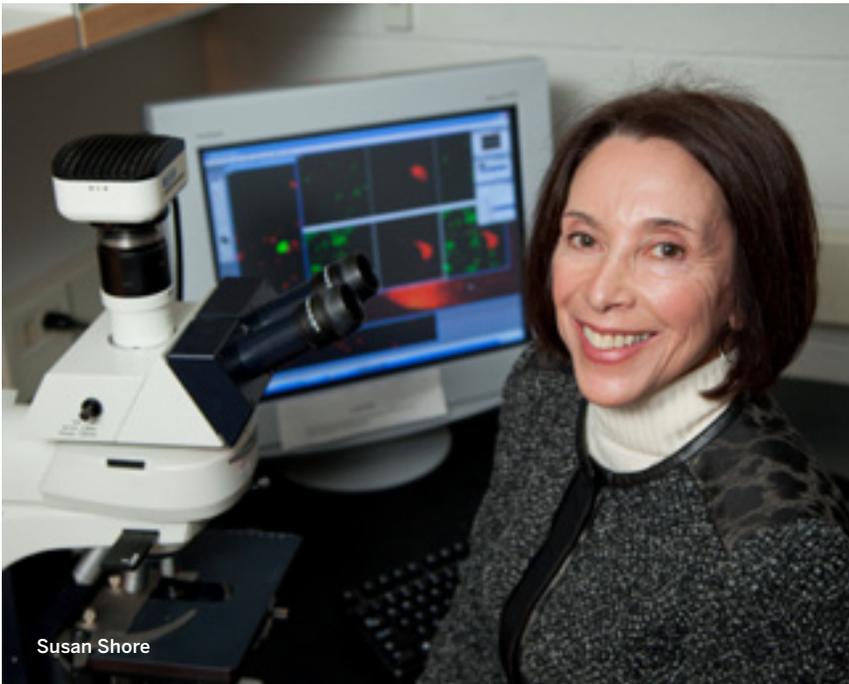
# Tinnitus Tied to Touch-Sensing Nerves

**U-M RESEARCHERS HAVE PREVIOUSLY DEMONSTRATED THAT AFTER HEARING** damage from overexposure to noise, touch-sensing “somatosensory” nerves in the face and neck can become overactive, seeming to overcompensate for the loss of auditory input in a way the brain interprets — or “hears” — as noise that isn’t really there: tinnitus, commonly known as “ringing in the ears.”

Now a new study, published in the February 1 issue of *The Journal of Neuroscience*, has found that somatosensory neurons maintain a high level of activity following exposure to loud noise, even after hearing itself returns to normal.

The findings were made in guinea pigs, but mark an important step toward potential relief for people plagued by tinnitus, says lead investigator Susan E. Shore, Ph.D., of U-M’s Kresge Hearing Research Institute, who also is a professor of otolaryngology and of molecular and integrative physiology at the Medical School.

“The animals that developed tinnitus after a temporary loss in their hearing after loud noise exposure were the ones who had sustained increases in activity in these neural pathways,” Shore says. “In the future it may be possible to treat tinnitus patients by dampening the hyperactivity by reprogramming these auditory-touch circuits in the brain.” —ID



Susan Shore

## Health Briefs

Most parents report that they typically require their child to use a life-saving booster seat, but more than 30 percent say they don’t enforce this rule when their child is riding with another driver, according to child health experts at U-M’s C.S. Mott Children’s Hospital. The study also reports that 45 percent of parents don’t require their children to use a booster if other children in the car do not have one.

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An updated review of data from the Selenium and Vitamin E Cancer Prevention Trial concluded that men who took 400 international units of vitamin E daily had 17 percent more prostate cancers than men who took a placebo. The NIH-funded study involved more than 400 sites in the U.S. and Canada by the Southwest Oncology Group, headquartered at the U-M. Except for skin cancer, prostate cancer is the most common type of cancer among men in the U.S.

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Living in a lower socioeconomic neighborhood was linked with increased pain, pain-related disability and mood disorders for young adults, according to a U-M study — but young black patients faced difficulties with pain management no matter where they lived. The study suggests that physicians may need to be more aware of a patient’s life circumstances and resources when treating their chronic pain. —RK

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