Bringing research into practice

COPD treatment
Liver transplant
Vulvodynia Prevalence
Prostate Cancer Prevention

GAME CHANGER

U-M led team makes computer-aided tissue analysis better, faster and simpler

ALSO:
COPD Treatment
Liver Transplant
Vulvodynia Prevalence
Prostate Cancer Prevention
Prostate cancer surviving side effects

Prostate cancer histories, including signs of recurrence, counseling for sexual health recovery for individuals and couples, penile and pelvic floor rehabilitation, prostate cancer screening and lifestyle recommendations.

To ensure continuity of care, a treatment summary and survivorship care plan are sent to the patient, his primary care physician and the physician who referred the patient to the program.

Prostate cancer survivorship care — specifically sexual health and penile rehabilitation consults — is also available through the U-M Department of Urology to patients who have received cancer treatment elsewhere.

On the cover: Ulysses Balis, M.D., (right) and Jason Hipp, M.D., Ph.D., (left) of the U-M Division of Pathology Informatics, developed Spatially-Invariant Vector Quantization, a new technique that can pinpoint cancer cells and other critical features from digital images made from tissue slides.

As a member of the Prostate Cancer Survivorship Clinic team, social worker and certified sex therapist Daniela Wittmann offers couples strategies for coping with the sexual side effects of surgery.

PROSTATE CANCER

SURVIVING SIDE EFFECTS

The U-M Comprehensive Cancer Center has developed a Prostate Cancer Survivorship Clinic to provide patients with strategies to address the urinary and sexual side effects of treatment. Patients referred to the clinic begin survivorship visits after they complete cancer treatment.

During a visit, patients meet with a nurse practitioner and sexual health therapist with extensive education and training in the care of prostate cancer patients. They receive a comprehensive health exam followed by open discussion about topics of concern related to their individual prostate cancer histories, including signs of recurrence, counseling for sexual health recovery for individuals and couples, penile and pelvic floor rehabilitation, prostate cancer screening and lifestyle recommendations.

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Prostate cancer survivorship care — specifically sexual health and penile rehabilitation consults — is also available through the U-M Department of Urology to patients who have received cancer treatment elsewhere.

M-LINE For more information or to refer a patient to the clinic, call M-LINE at 800-962-3555.
**Chronic GVHD Clinic Offers New Hope**

About 50 percent of blood and marrow transplant patients develop some form of chronic graft-versus-host disease (GVHD). Chronic GVHD typically develops within the first year post-transplant, but the disease can continue for years. Some of the most common manifestations include skin rashes, dry mouth and irritated eyes. Some patients can become quite debilitated when organs such as the lungs are affected.

UM has recently launched a new comprehensive chronic GVHD clinic offering patients and their families new options and hope.

“This is a survivorship clinic,” says Carrie Kitko, M.D., assistant professor in pediatrics and communicable diseases. “Our goal is to restore normalcy for adults and children with chronic GVHD so they can go back to work or school and live normal lives again.”

The clinic offers patients a comprehensive evaluation, discussion of potential treatment options and access to clinical trials based upon the clinic’s research. Because this potentially fatal disease can target just about any area of the body, almost all fields of medicine are part of the clinic.

“This allows us to offer a multidisciplinary approach to treatment that gives patients individualized care designed specifically for them and their symptoms,” says Daniel Couriel, M.D., professor of internal medicine and clinical director of the adult blood and marrow transplant program.

Among several innovative GVHD treatments, UM physicians have extensive experience using extracorporeal photopheresis (ECP). The University of Michigan’s ECP program is one of the largest in the country and performs more than 150 treatments on affected patients every month.

**EPILEPSY**

**Stopping Seizures with Surgery**

John Ligerakis was told he had to learn to live with the seizures that disrupted his life. “As time went on, I could count on having a seizure every day,” the 35-year-old says. “We tried medication after medication, but none of them worked and each of them had different side effects.”

“Epilepsy absolutely ruins the quality of someone’s life,” says Simon Glynn, M.D., assistant professor of neurology and a member of the Epilepsy Surgery program at UM, which has one of the nation’s largest and most comprehensive epilepsy programs.

After having surgery at UM, Ligerakis has been seizure-free for six years. But only about one or two out of 100 people who are eligible for epilepsy surgery ever make it to the operating room, says Oren Sagher, M.D., professor of neurosurgery at UM.

When a focus — or location in the brain that causes the seizures — can be identified, epilepsy surgery is very successful. “What we actually are doing is carving out the area that we think is the cause of these electrical storms and removing it from the brain so it can no longer spark the fire of the seizure,” Sagher says.
U-M led team makes computer-aided tissue analysis better, faster and simpler

Ulysses Balis, M.D., clicks on a helicopter in a digital satellite photo of Baghdad, Iraq. With another click, an algorithm that he and his team designed identifies three more choppers in the image without highlighting any of the buildings, streets, trees or cars.

Balis isn’t playing war games. The director of the Division of Pathology Informatics at the U-M Medical School is demonstrating the extreme flexibility of a software tool aimed at making the detection of abnormalities in cell and tissue samples faster, more accurate and more consistent.
SIVQ TO THE RESCUE
In a medical setting, instead of helicopters, the technique, known as Spatially-Invariant Vector Quantization (SIVQ), can pinpoint cancer cells and other critical features from digital images made from tissue slides.

It’s going to allow us to think about things differently. We’re starting to bridge the gap between qualitative analysis … and quantitative approaches.

Jason Hipp, M.D., Ph.D.

SIVQ isn’t limited to any particular area of medicine. It can readily separate calcifications from malignancies in breast tissue samples, search for and count particular cell types in a bone marrow slide, or quickly identify the cherry-red nucleoli of cells associated with Hodgkin’s disease, according to findings published in the Journal of Pathology Informatics.

“The fact that the algorithm operates effortlessly across domains and length scales, while requiring minimal user training, sets it apart from conventional approaches to image analysis,” Balis says.

The technology — developed in conjunction with researchers at Massachusetts General Hospital and Harvard Medical School — differs from conventional pattern recognition software by basing its core search on a series of concentric, pattern-matching rings, rather than the more typical rectangular or square blocks. This approach takes advantage of the rings’ continuous symmetry, allowing for the recognition of features no matter how they’re rotated or whether they’re reversed, like in a mirror.

“That’s good because in pathology, images of cells and tissue do not have a particular orientation,” Balis says.

THE PATHOLOGY OF PIXELS
In SIVQ, a search starts with the selection of a small area of pixels, known as a vector. The algorithm then compares this circular vector to every part of the image. And at every location, the ring rotates through millions of possibilities in an attempt to find a match in every possible degree of rotation. The program then creates a heat map, shading the image based on the quality of match at every point.

Pathology informatics fellow Jason Hipp, M.D., Ph.D., believes the technology has the potential to be a “game changer” for the field by opening myriad new possibilities for deeper image analysis.

“It’s going to allow us to think about things differently,” says Hipp, also a clinical lecturer in the Department of Pathology. “We’re starting to bridge the gap between the qualitative analysis carried out by trained expert pathologists and the quantitative approaches made possible by advances in imaging technology.”

Still, pathologists shouldn’t be worried that SIVQ will put them out of a job.

“No one is talking about replacing pathologists,” Balis says. “But working in tandem with this technology, the hope is that they will be able to achieve a higher overall level of performance.”

U-M has been seeking licensing partners for the technology.
THE WAITING GAME

Transplant candidates seek best quality livers, even if it means waiting longer
Liver transplantation candidates want to be involved in decisions regarding quality of the donor organ, and many are reluctant to accept organs with a higher risk of failure, according to University of Michigan researchers.

More than 42 percent of patients would choose to remain on the waiting list rather than accept a “lower quality” liver, according to a recent study led by Michael L. Volk, M.D., M.S., published in the journal *Liver Transplantation*. Volk is an assistant professor in U-M’s Department of Internal Medicine, Division of Gastroenterology.

**QUALITY COUNTS**

As of Nov. 30, 2011, the Organ Procurement and Transplantation Network (OPTN) reports that 16,124 candidates are on the waiting list to receive a liver, with only 5,375 deceased donor organs recovered through August. Additionally, there is a large variation in quality of deceased donor livers, due to donor characteristics such as age, cause of death and ischemia time. Previous research has shown that donor characteristics can make the difference between a 20 percent and 40 percent risk of graft failure by three years following transplantation.

“The decision to accept or pass on an organ could mean the difference between life and death for patients with end-stage liver disease.”

Michael L. Volk, M.D., M.S.

“Organ quality is an important issue for all liver transplant candidates, increasingly so, given the aging donor pool and more frequent use of organs that carry a higher risk of failure,” says Volk, who is a hepatology specialist. “The decision to accept or pass on an organ could mean the difference between life and death for patients with...”

Michael L. Volk, M.D., M.S., led research on patient preferences about donor livers.

**Your connection**

Stacy M. Brand, M.B.A., works with referring physicians for the U-M Transplant Center and is your resource for feedback and information. Brand also partners with outside organizations like Gift of Life Michigan and works on U-M’s continuing medical education (CME) programs and other events, including:

- “Advanced Liver Disease and Liver Transplantation Update 2012,” which is set for May 4, 2012, at the Novi Crowne Plaza hotel.
- The Gift of Life on the Minority Organ Tissue Transplant Education Program (MOTTEP)’s third annual Kountz Callender Drew Transplant Symposium. The event is designed for both healthcare professionals and community members and will be at U-M on March 30.

For more information on either event or about the U-M Transplant Center, contact Brand at 734-615-0832 or slipson@umich.edu.
end-stage liver disease. Communication of the risks versus benefits of accepting a ‘lower quality’ organ is critical, and understanding patient views on the subject is essential for physicians caring for transplant candidates.”

**RISK ASSESSMENT**

Volk’s research showed that patients are reluctant to accept higher-risk organs. Of those who participated in the survey conducted by his team, 58 percent would only accept organs with a 25 percent (or less) risk of graft failure and 18 percent would only accept the lowest possible risk of 19 percent at three years following transplantation. Risk tolerance was increased by presenting organ quality as “average quality” rather than “best quality” and by providing feedback about the implications of these preferences on the likelihood of receiving a transplant.

Additionally, 83 percent of candidates were found to prefer an equal or dominant role in deciding whether to accept a higher-risk organ. This finding is striking given that, in most transplant centers, patient involvement in these decisions is minimal.

“Up until now, it has not been clear how much patients want to be involved in this complicated decision,” says Volk. “Furthermore, explaining the intricacies of this topic to sick patients is easier said than done. Our findings offer transplant physicians some useful guidelines for how to counsel transplant candidates on issues of organ quality.”

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**RESULTS** Read the study reported in *Liver Transplantation* at Colleagues in Care Online at [med.umich.edu/cic](http://med.umich.edu/cic).

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**About the U-M liver transplant program**

Since the inception of UM’s liver transplant program in 1985, more than 1,800 transplants have been performed by UM teams. Patients transplanted at the University of Michigan are jointly managed by dedicated transplant surgeons and medical liver specialists. All members of the team — including nurses, coordinators and social workers — have advanced training and expertise in liver disease and liver transplantation.

UM has offered adult-to-child living donor liver transplantation since 1996 and reduced-size liver transplantation (“splits”) since 1988. UM currently considers living donor liver transplantation for children and small adults who are too ill to wait for a deceased donor graft.

In addition to transplant, UM also provides multidisciplinary, cutting-edge treatment for patients with serious liver disease including hilar cholangiocarcinoma (cancer of the biliary tree), primary liver cancer or complications of cirrhosis.

To discuss a patient case or potential referral, call M-LINE at 1-800-962-3555 and ask to speak to one of our liver transplant specialists. Or, send an email to Robert J. Fontana, M.D., medical director of liver transplantation, at rfontana@med.umich.edu or Shawn Pelletier, M.D., surgical director of liver transplantation, at spelleti@med.umich.edu.
Adding azithromycin to the usual treatment regimen for chronic obstructive pulmonary disease (COPD) can reduce acute exacerbations and improve quality of life, according to a recent clinical trial funded by the National Heart, Lung, and Blood Institute (NHLBI).

The U-M Health System and VA Ann Arbor Healthcare System, under the direction of lung specialists Fernando Martinez, M.D., M.S., and Jeffrey Curtis, M.D., were among 10 centers involved in the large-scale clinical trial. Martinez and his colleagues at U-M provided key preliminary data supporting antibiotic treatment and were involved in the trial’s design.

The findings were published in August in the *New England Journal of Medicine*.

“These promising results with azithromycin may help us reduce the burden of COPD exacerbations and improve the lives of patients at risk of these acute attacks,” says Susan Shurin, M.D., acting director of the NHLBI.

The study participants who took 250 mg of azithromycin daily for a year in addition to their usual care averaged 1.48 acute COPD exacerbations annually, compared to 1.83 exacerbations for a similar number receiving usual care. Participants taking azithromycin also responded more favorably on questionnaires that asked them to assess their breathing ability and overall well-being.

Reported side effects during the study were minimal and included slight hearing deficits in a small fraction of participants. More research is needed to determine the long-term effects of the treatment and to identify which group of patients would benefit the most.

“This important research is just one of many efforts — both at U-M and around the country — aimed at helping patients with COPD breathe easier and enjoy a better quality of life,” Martinez says.
Underdiagnosed and Undertreated

25 percent of women have had symptoms of vulvodynia; only 2 percent sought treatment

For many women, chronic vulvar pain is so severe it makes intercourse — and sometimes sitting for long periods of time — painful, if not impossible.

A new U-M study, which surveyed 2,269 women in the metro Detroit area, found that more than 25 percent of women have experienced ongoing vulvar pain at some point in their lives. However, only 2 percent of those women sought treatment for their pain.

For some, vulvar pain may be caused by activities like biking, tampon use or intercourse, and for others it can be a persistent, spontaneous pain that can last for up to 40 years.

Pain ranges from slight discomfort to knife-like pain. Common treatments, including topical creams, are typically directed toward alleviating symptoms and usually only provide partial pain relief.

The study, published in the American Journal of Obstetrics and Gynecology, found that aside from the 9.2 percent of women who reported that they were currently experiencing pain consistent with vulvodynia, an additional 17.9 percent of women reported they have experienced symptoms of vulvodynia in the past.

That factors to more than 318,000 women in southeast Michigan alone.

“What this means for area women is that vulvar pain is common, it has a name, and it can be addressed with their physicians,” says Barbara D. Reed, M.D., M.S.P.H, a professor of family medicine at the U-M Medical School and lead author of the study.

What researchers have found concerning is that of the 2 percent of women who sought treatment for their pain, only 5 percent received a diagnosis of vulvodynia. Many women were misdiagnosed with either yeast infections or estrogen deficiency. The subsequent treatment plans that were recommended did little to alleviate their pain, suggesting misdiagnosis of what was causing their symptoms.

Vulvar pain is common, it has a name, and it can be addressed. — Barbara D. Reed, M.D., M.S.P.H.
ROLE REVERSAL

Trial changes thinking on vitamin E supplements and prostate cancer risk

The largest prostate cancer prevention trial ever undertaken, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), was built on the hypothesis that these supplements could lower a man’s risk of developing prostate cancer. Now, researchers have concluded that vitamin E supplementation actually raised prostate cancer risk for men in the trial.

The finding comes 10 years after the study’s launch by the SWOG clinical trials network based at the University of Michigan Comprehensive Cancer Center. SWOG (formerly the Southwest Oncology Group) is one of the largest cancer clinical trials cooperative groups in the United States.

SELECT enrolled more than 35,000 healthy older men, who were randomly assigned to take daily supplements of vitamin E, selenium, both or placebos.

The study closed early, in 2008, after interim data showed no preventive benefit on any arm. The early data also showed a slight increase in prostate cancer risk among the men who had taken only vitamin E, but the rise was not statistically significant at the time.

Three years of additional data have made that rise in risk even more pronounced and statistically significant. Over a seven-year period, there were 76 prostate cancer diagnoses per 1,000 men on the vitamin E-only arm, compared to 65 diagnoses per 1,000 men on the placebo arm. This represents a 17 percent increase in prostate cancers among men who took 400 International Units of vitamin E daily.

The findings appeared in the Journal of the American Medical Association.

The mechanism driving this increased risk remains a mystery, but researchers are hoping clues can be found among the almost 100,000 samples of blood, toenail clippings and tumors stored from the trial.

“SWOG is soliciting proposals from researchers nationwide to use the SELECT biorepository to help answer the biological question of why vitamin E increased risk instead of decreasing it,” said Laurence Baker, D.O., professor of medicine and pharmacology at the U-M Medical School, study co-author and chair of SWOG.

Funding for the trial came primarily from the National Cancer Institute.

Doctor bio

Laurence Baker, D.O., professor of medicine and pharmacology at the U-M Medical School, study co-author and chair of SWOG, completed his D.O. at the University of Osteopathic Medicine and Surgery in Des Moines and his fellowship in oncology at Wayne State University in Detroit. He joined U-M in 1994. His clinical interests include sarcoma research, clinical trials and new drug development.

ARTICLE Get a link to the Journal of the American Medical Association article on Colleagues in Care Online at med.umich.edu/cic

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