

colleagues

in care

BRINGING RESEARCH INTO PRACTICE
SUMMER 2016

19%

of the U.S. population
will develop
nonalcoholic fatty
liver disease

3–9%

of reported adverse
drug reactions relate
to drug-induced
liver injury

24%

of women in the U.S.
are affected by
pelvic floor
dysfunction

4.5%

of the U.S. population will
be diagnosed with colon
and rectal cancer

5–10%

of those undergoing
ERCP will develop
pancreatitis

11%

of people worldwide
are affected by IBS

20%

of people in the U.S.
are affected by
gastrointestinal diseases
every year



HEALTH SYSTEM
UNIVERSITY OF MICHIGAN

colleagues in care



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Solving the Puzzle of IBS: A New Standard of Care Emerges

COVER
Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder, with worldwide prevalence rates of about 11 percent.

Reference: Canavan, C.; West, J.; Card, T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol.* 2014; 6: 71-80

<http://umcic.org>



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Colorectal Cancer in Younger Patients Not as Uncommon as Thought

COVER
Lifetime Risk of Developing Cancer: Approximately 4.5 percent of men and women will be diagnosed with colon and rectal cancer at some point during their lifetime, based on 2010-2012 data.

Reference: National Cancer Institute. SEER Stat Facts Sheet: Colon and Rectum Cancer. <http://seer.cancer.gov/statfacts/html/colorect.html>

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Research Uncovers Causes of Drug-Induced Liver Injury

COVER
Worldwide, the estimated global annual incidence rate of drug-induced liver injury (DILI) is 13.9-24.0 per 100,000 inhabitants, and DILI accounts for an estimated 3-9 percent of all adverse drug reactions reported to health authorities.

Reference: Drug-Induced Liver Injury Network. <http://www.dilin.org/for-researchers/dilin-overview/>. Updated September 2011. Aithal, G.P., et al. *Br Med J* 1999; 319: 1541-5. Friis, H.; Andreasen, P.B. *J Intern Med* 1992; 232: 133-138. Dossing, M.; Anderson, P.B. *Scan J Gastroenterol* 1982; 17, 205-211.

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Michigan Bowel Control Program Offers a Pioneering Approach

COVER
Nearly 24 percent of U.S. women are affected with one or more pelvic floor disorders, report researchers funded by the National Institutes of Health.

Reference: National Institutes of Health. *Pelvic Floor Disorders: NICHD Research Information*. Lawrence, J.M.; Lukacz, E.S.; Nager, C.W.; Hsu, J.W.; Luber, K.M. (2008). Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. *Obstetrics & Gynecology*, 111(3), 678-685. Sept 2013. <https://www.nichd.nih.gov/health/topics/pelvicfloor/researchinfo/Pages/default.aspx>

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Strategies Emerge for Preventing Post-ERCP Pancreatitis

COVER
Endoscopic retrograde cholangiopancreatography (ERCP) is associated with a 5 to 10 percent risk of pancreatitis.

Reference: The National Pancreas Foundation. *ERCP and Pancreatic Disease*. Ulrich, C.D.; Martin, S.P. <https://www.pancreasfoundation.org/ercp-endoscopic-retrograde-cholangiopancreatography/>

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Research Focuses on Genetic Diagnostic and Therapeutic Approaches to NAFLD

COVER:
In the U.S. population, the prevalence rates of hepatic steatosis and non-alcoholic fatty liver disease (NAFLD) are 21.4 percent and 19.0 percent, respectively.

Reference: *Am J Epidemiol.* 2013 Jul 1;178(1):38-45. doi: 10.1093/aje/kws448. Epub 2013 May 23.



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Imaging Technology and Molecular Probes Advance Gastrointestinal Therapy

COVER
Twenty percent of people in the U.S. are affected by gastrointestinal diseases every year.

Reference: Everhart, J.E.; Ruhl, C.E. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology* 2009;136:376-386.



SOLVING THE PUZZLE OF IBS: A NEW STANDARD OF CARE EMERGES

Successful management of irritable bowel syndrome (IBS) requires a comprehensive approach to care that combines the expertise of multiple health care professionals who specialize in dietary and behavioral counseling, in addition to medical treatments and pharmaceutical therapies.

"Over the last five years, we have identified and assembled the puzzle pieces that allow us to offer a more holistic approach to patients with IBS," said William D. Chey, MD, who is a widely known expert on IBS.

That means thinking critically about how diet, lifestyle, and behavior might interact to bring about the symptoms of IBS. "We consider how we might offer interventions for each of those components of care to really maximize the benefit of medical treatments for patients with IBS," he said.

"If you asked any of the gastroenterologists at the University of Michigan five years ago, diet and behavior would have been very low on their list of priorities," Dr. Chey said. "Now, our gastroenterologists say they can't imagine how we did it before we had these assets in place. It has really been a transformation in care over the past five years, and we're extremely proud of that."

Successful long-term management of IBS, it turns out, is a multidisciplinary affair.

PUZZLE PIECE A: EXPERT DIETARY COUNSELING

For many patients, symptoms of IBS are triggered by what they eat, and increasingly, physicians are recognizing the critical role of diet in managing the symptoms of IBS. Unfortunately, few physicians are trained to provide nutritional counseling.

"The reality is most gastroenterologists receive little to no training in nutrition or the practical elements of administering diet therapies for patients with IBS," Dr. Chey said.

Emerging evidence suggests diets free of gluten and diets low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols—commonly known as the low-FODMAP diet—can be beneficial for patients with IBS. The low-FODMAP diet, in particular, is a fairly complicated diet, Dr. Chey noted. Patients following this diet require the assistance of professional nutrition specialists.

"I think most physicians right now are trying to manage diet by giving patients a sheet of paper with a list of foods to eliminate, and that's simply inadequate," he said. "Diets are definitely more comprehensive and complicated than can be conveyed with a sheet of paper—even potentially dangerous if not administered in a medically responsible way."

As a result, many diets do not work as well in clinical practice as evidence from clinical trials might suggest, he noted. In order to achieve similar results, diets need to be administered by experts who understand gastrointestinal (GI) nutrition and know how to help patients incorporate dietary changes into their daily routines, he said.

"One of the problems right now is there aren't that many trained GI dietitians around. There are dietitians, but they're not specially trained in gastroenterology," Dr. Chey said.

"One of the things that needs to happen on a national level to improve the quality of care for patients with IBS is to train a population of dietitians that have expertise in GI disorders, and to have them work closely with gastroenterologists to administer dietary interventions in a medically responsible way," he added.

This is just one of the many areas where the University of Michigan sets itself apart: the Division of Gastroenterology has the equivalent of four GI dietitians—two full-time GI dietitians at University Hospital and others who assist in caring for patients at offsite facilities that are part of the University of Michigan Health System.

"I think most physicians right now are trying to manage diet by giving patients a sheet of paper with a list of foods to eliminate, and that's simply inadequate."

—WILLIAM D. CHEY, MD

LOW-FODMAP DIET

MEATS

AVOID

Chorizo
Sausages
Processed meat

ENJOY

Beef
Chicken
Lamb
Pork
Turkey
Seafood



DAIRY AND EGGS

AVOID

Milk
Sour cream
Yogurt
Cream cheese
Ice cream

ENJOY

Lactose-free milk
Lactose-free yogurt
Butter
Cheese
Eggs



**BEHAVIORAL THERAPIES FOUND
INSTRUMENTAL FOR IBS MANAGEMENT**



The Behavioral Health Program at the University of Michigan offers patients with GI disorders an opportunity to address symptoms with a specially trained GI psychologist.

Megan Riehl, PsyD, is a clinical health psychologist at the University of Michigan, and the state's only psychologist with a specific focus on GI disorders. IBS

is the most common GI illness that brings patients to her clinic. "About 65 percent of patients present with IBS or a functional bowel disorder," she said.

Typically, patients are referred to Dr. Riehl by a gastroenterologist who may have exhausted medical treatment options and/or believes a patient would benefit from stress and anxiety management techniques. Increasingly, behavioral therapy is becoming routine in the treatment of patients with IBS. "As more patients become aware of the GI behavioral health service, more of them are asking their gastroenterologists for a referral to the program," Dr. Riehl said.

Behavioral therapy is personalized for each patient, but in general, therapy is designed to help patients deal with the "uncontrollable" and "unpredictable" aspects of IBS. Patients learn relaxation and stress management techniques they can apply to everyday life stressors.

"My goal is to help patients learn to cope effectively and efficiently with worries that can interfere with social, occupational, and family life," Dr. Riehl said.

GUT-DIRECTED THERAPIES

Most often, behavioral therapy for patients with IBS involves interventions based on cognitive-behavioral therapy (CBT), a short-term, collaborative treatment that is focused on a patient's current problems.

"CBT involves helping patients find new ways of thinking and behaving to help in managing stressful situations," Dr. Riehl explained. For example, patients with IBS may experience anxiety-provoking thoughts such as, "Where will a bathroom be if I need it?", "What if I'm having symptoms before a big exam or presentation?", or "How will I ever be intimate with a partner?" CBT teaches patients how to manage emotional responses to these potentially stress-inducing situations.

"My goal is to aid patients in self-management strategies that benefit GI health, emotional well-being, and overall quality of life," Dr. Riehl said. "People learn tools to create long-term change, without remaining in treatment for long periods of time. It's very rewarding."



PUZZLE PIECE B: FOCUSED BEHAVIORAL THERAPY

Just as diet has come into focus as an essential aspect of treatment for IBS, so have behavior and lifestyle. The way in which an individual responds to stress can greatly affect symptoms of IBS.

"There are certainly some things that gastroenterologists can recommend to try to facilitate changes in lifestyle or behavior," Dr. Chey said. For example, yoga or a regular exercise plan can be very helpful in managing stressors that can lead to the symptoms of IBS, he noted.

But as in the case of diet, many gastroenterologists are not trained to provide more advanced behavioral counseling to patients with IBS. For example, cognitive-behavioral therapy, hypnosis and interpersonal psychotherapy can be very beneficial for patients with IBS. But these therapies require specialized training—even more specialized than many clinical psychologists are equipped to offer.

PUZZLE PIECE C: MEDICATIONS AND RESEARCH

"Medications still play the really important role," Dr. Chey noted.

Therapy for IBS is symptom-driven, depending on a patient's needs. "For patients with mild or moderate IBS symptoms, sometimes all they need is a little bit of medication, such as an over-the-counter antidiarrheal or antispasmodic on an as-needed basis, and they'll do just fine. Patients with more severe IBS symptoms will almost always need one or more medications," Dr. Chey said.

Notably, Dr. Chey's group has been involved in some capacity in the research that led to the FDA approval of all five prescription drugs indicated for the treatment of IBS in the United States.

Because of its dedication to research, patients at the University of Michigan have the opportunity to participate in ongoing IBS clinical trials, such as those involving the low-FODMAP diet and an upcoming trial of prebiotics in patients with IBS.

Building on this foundation in GI nutrition and behavioral therapy, a new effort—the Digestive Disorders Nutrition and Lifestyle Program—will bring together the diverse elements necessary to provide support in nutrition and behavior, as well as "vertically integrate research from the bench to the bedside," Dr. Chey said. "So we're not only providing excellent quality of care for patients, we're also striving to make discoveries that will transform the role of diet and behavior and how they interact with medications to maximize benefit for patients with IBS and other functional disorders." **M**



FOR COMMUNITY GASTROENTEROLOGISTS

The Division of Gastroenterology at the University of Michigan emphasizes a holistic approach to IBS treatment that incorporates modifications in diet, behavior, and lifestyle in the management of symptoms of IBS.

When a diagnosis of IBS has been confirmed, consider the following approaches to treatment:

- Are symptoms triggered or exacerbated by diet? Consider a referral to a dietitian with specialized training in the treatment of GI disorders.
- Are symptoms triggered or exacerbated by stress or a mood disorder? Consider a referral to a behavioral therapist with specialized training in the treatment of GI disorders.
- How frequent and severe are symptoms? Are symptoms comprised mainly of diarrhea, constipation, or both? Consider using medications that target the relevant symptoms in combination with strategies that address diet, lifestyle, and behavior.
- Are symptoms severe and/or medically refractory? Consider a referral to a tertiary referral center.

GRAINS : low-FODMAP

AVOID

Wheat (gluten)
Barley
Bran cereals
Rye
Semolina

ENJOY

Gluten-free baked goods
Brown rice
Oatmeal
Quinoa
Corn tortilla



FRUITS : low-FODMAP

AVOID

Apples
Avocado
Cherries
Grapefruit
Peaches

ENJOY

Bananas
Blueberries
Cantaloupe
Grapes
Lemon



CONDIMENTS : low-FODMAP

AVOID

Honey
Jam
Pesto sauce
Relish
Stock cubes

ENJOY

Mustard and Ketchup
Barbecue sauce
Chocolate
Mayonnaise
Peanut butter



For more information on
the low-FODMAP Diet,
visit: **umcic.org**

MORGAN'S STORY

Morgan Blenkhorn missed high school several times because of symptoms that doctors said were related to irritable bowel syndrome (IBS).

"Anything I would eat, I would get sick," she said. "I was nauseous; I would have headaches, stomachaches; I had diarrhea and I was just ill all day, every day."

Morgan's symptoms started a few months after a severe food poisoning incident in 2010 during her junior year of high school. She endured pain, particularly while dancing and playing soccer. She eventually turned to apples and honey for relief, but they only made her symptoms worse.

"It was really hard having to come home from school being sick all the time, waking up sick, and trying to go to school and act like everything was fine," she said.

A CHANCE MEETING BEARS FRUIT

Over the next three years, several doctors told her she was exhibiting IBS symptoms and gave her probiotics for treatment. But a chance meeting on an airplane between her father and gastroenterologist William Chey, MD, would lead to a series of interviews, tests, and a final diagnosis from the University of Michigan's gastroenterology and dietitian team.

Her first visit to the University of Michigan was in 2013, during the fall of her sophomore year of college. She had several blood tests done before meeting with Dr. Chey. Upon her first appointment with him, she was promptly told what to expect: a fructose test, a lactose test, more blood tests, and an endoscopy.

According to Morgan, Dr. Chey went above and beyond preliminary tests to find the root of the problem. The test that changed it all, she said, was the fructose test, which consisted of a fructose mixture, water, and a breath test. A few weeks after her appointment, Dr. Chey spoke with Morgan and her family and told them the diagnosis: fructose intolerance.

"We all cried," Morgan said.

FINALLY, CONTROL ...

This experience was unlike any other for Morgan. The team's gastroenterologists were briefed on her case and knew exactly how to address her issues. The dietitian they referred her to mapped out a zero-fructose eating plan that catered to her vegetarian diet and her love for veggies, pasta, and curry.

"They listened to my specific wants, not just me as a patient but me as Morgan," she said.

After being diagnosed with fructose intolerance, Morgan now plans out her own meals and has full control of her symptoms. She continues to dance and play sports. Last summer, she was even able to study abroad in the Netherlands.

"It was beautiful, life-changing, something I didn't think I'd ever be able to do before because I couldn't sit in a car for two hours without having to pull over," she said. "Biking 10 miles to work and backpacking alone through Germany was something I thought I'd never be able to do because I was so sick."

Morgan is finishing up her fourth year at Grand Valley State University in Allendale, Michigan, with another year left to complete her special education degree. She still checks in with Dr. Chey every once in a while. For now, she hopes to be accepted into Grand Valley's Consortium for Overseas Student Teaching program in Ireland this summer.

LEGUMES : low-FODMAP

AVOID

Kidney beans
Lima beans
Butter beans
Black beans
Split peas
Soy beans

ENJOY

Chick peas
Lentils



VEGETABLES : low-FODMAP

AVOID

Garlic
Onions
Cauliflower
Celery
Mushrooms

ENJOY

Carrots
Green beans
Lettuce
Bell peppers
Squash

For more information visit: umcic.org





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Elena M. Stoffel, MD, MPH

COLORECTAL CANCER IN YOUNGER PATIENTS NOT AS UNCOMMON AS THOUGHT

DON'T IGNORE SYMPTOMS

Clinicians should consider colorectal cancer as a possible diagnosis when a younger patient presents with symptoms of intestinal bleeding, anemia, or a change in bowel habits.

Research spearheaded at the University of Michigan Comprehensive Cancer Center (UMCCC) found that 10 percent of patients with colorectal cancer were under age 50, and young individuals were more likely to be diagnosed at advanced stages compared with older patients. The results that Samantha Hendren, MD, associate professor of surgery at the University of Michigan Medical School, and her team culled from the Surveillance, Epidemiology, and End Results (SEER) database and published in the journal *Cancer* (2016;122:929-934) suggest clinicians should consider colon cancer as a possible diagnosis when a patient presents with symptoms of intestinal bleeding, anemia, or a change in bowel habits.

"While colorectal cancer incidence is decreasing overall, thanks to routine screening in individuals age 50 and older, it's on the rise in younger patients," said Elena Stoffel, MD, assistant professor of internal medicine and a gastroenterologist at the UMCCC, who was not involved in the *Cancer* paper.

The SEER findings are important for gastroenterologists and other clinicians to remember: "Don't forget about the possibility of a colorectal cancer diagnosis in young patients," she added. "It's important to keep colon cancer on the radar rather than dismissing bleeding or other symptoms as hemorrhoids."

"Don't forget about the possibility of a colorectal cancer diagnosis in young patients."

—ELENA STOFFEL, MD



Samantha Hendren, MD

IDENTIFYING HIGHER-RISK PATIENTS

The reasons for the increase in colorectal cancer cases among young people are unknown. Incidence is highest among blacks who develop tumors at younger ages, when compared with non-Hispanic whites. In a paper under review, Dr. Stoffel and her colleagues examined the SEER data on outcomes for colorectal cancer patients under 50, and found the survival rate for blacks was lower at every stage of the disease and particularly striking among individuals with stage II cancers.

"While differences in treatment may play a role in racial disparities of outcomes, we have to consider there may be genetic factors that influence cancer risk and outcomes that haven't been accounted for," said Dr. Stoffel, who also runs the University of Michigan's Cancer Genetics Clinic. "The current algorithms used for colorectal cancer risk assessment don't account for race. So, we're working to find a better way to assess people's cancer risk."

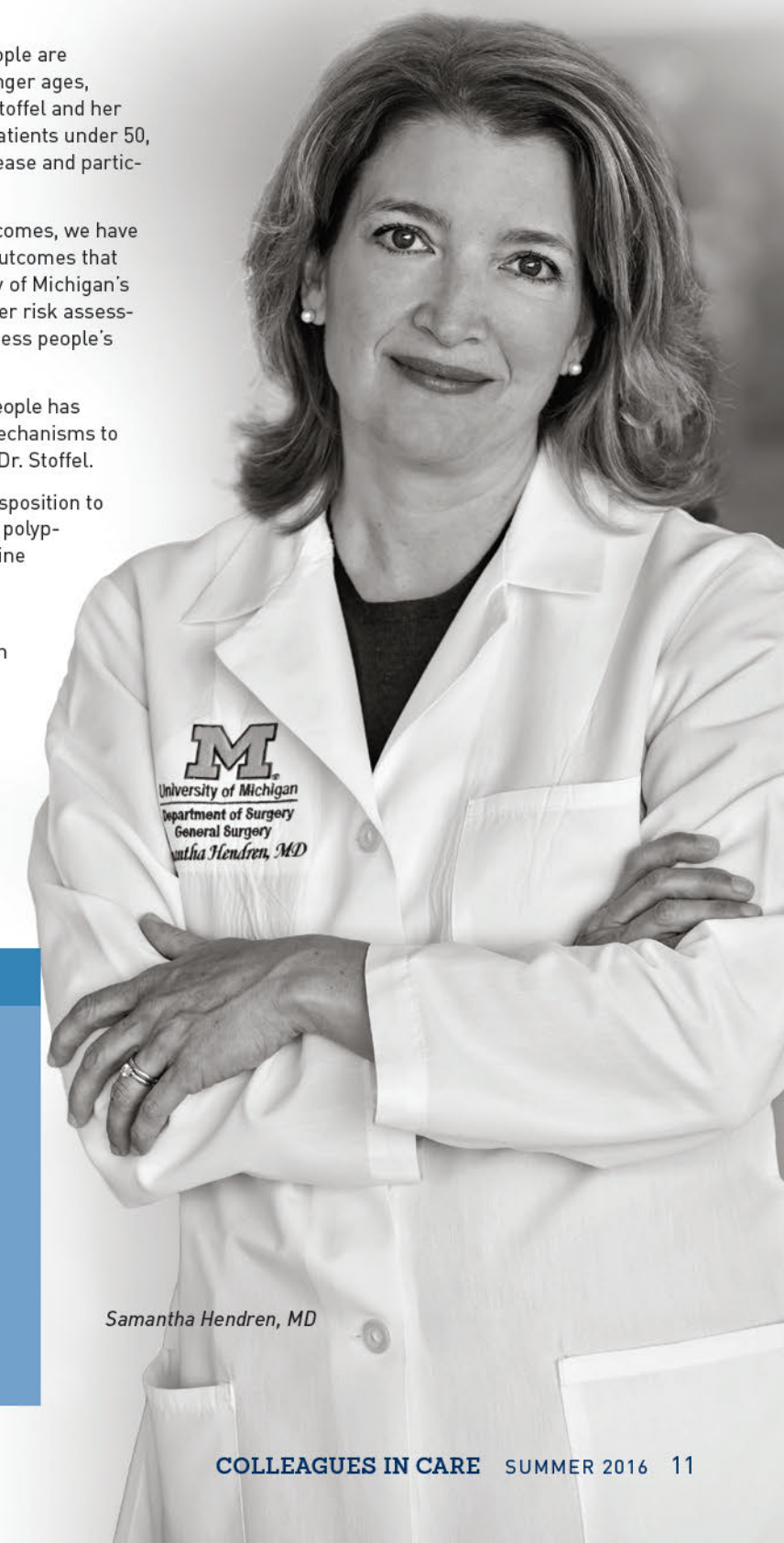
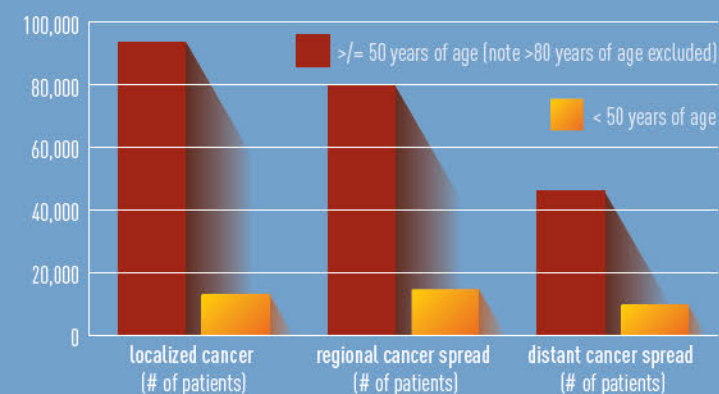
"There's also an observable trend that the rise in colon cancer in young people has tracked alongside the rise in obesity, but we haven't identified specific mechanisms to explain how obesity might increase risk for polyps or colon cancer," said Dr. Stoffel.

"There are a number of genetic conditions associated with inherited predisposition to colon cancer, including familial adenomatous polyposis, MYH-associated polyposis, and Lynch syndrome," Dr. Stoffel said. "Individuals who carry germline mutations associated with hereditary cancer syndromes tend to develop colorectal polyps at young ages, so they should be screened early."

It is important to remember that 70 percent of colorectal cancers occur in people with no known predisposition or obvious risk factors. Thus, there may be genetic and environmental components to colorectal cancer risk that researchers have yet to identify.

Lowering the recommended age for colorectal cancer screening for everyone is not the answer; however, University of Michigan researchers continue to research ways of identifying patients at higher risk who would benefit from early screening. **M**

10% of patients with colorectal cancer were under 50 years of age



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RESEARCH UNCOVERS CAUSES OF DRUG-INDUCED LIVER INJURY

“We’re trying to figure out why selected patients who take a drug that is considered safe and medically helpful in the majority of people will get DILI.”

— ROBERT J. FONTANA, MD

Significant adverse events that pose risks to patients treated with specific drugs are usually identified in preapproval clinical trials, but relatively rare complications can go undetected.

One such rare complication is drug-induced liver injury (DILI), and physicians at the University of Michigan are at the forefront of ongoing research designed to identify drugs that carry this risk, as well as genetic or other factors that may predispose patients to this complication.

“Unfortunately, there is often a big disconnect between the results of preclinical and clinical trials and what happens in patients who use these drugs in clinical practice,” said Robert J. Fontana, MD, medical director of liver transplantation at the University of Michigan Health System. Dr. Fontana has been leading research in DILI at the University of Michigan for more than 15 years.

“When you have clinical trials of 1,000 to 2,000 patients, you may not see an adverse event that occurs in only 1 of 10,000 or 1 of 100,000 treated patients,” he said. “So we’re trying to figure out why selected patients who take a drug that is considered safe and medically helpful in the majority of people will get DILI.”

RARE BUT SIGNIFICANT

Research conducted by Dr. Fontana’s team suggests the incidence of DILI is approximately 15 events per 100,000 in the general population. Although rare, these events are hardly insignificant. Indeed, they can result in significant morbidity and mortality, particularly as one of the leading causes of acute liver failure in the United States, and have proven to be “important barriers to new drug development and marketing.”

This is why the research initiative called the Drug-Induced Liver Injury Network (DILIN), an ongoing multicenter trial funded by the National Institutes of Health, has generated great interest in the health care community. Patients experiencing DILI may suffer from chronic liver disease and may ultimately require a liver transplant. Based on the team’s research, DILI seems to indiscriminately affect children and adults of various demographic groups equally.

According to Dr. Fontana, the DILIN registry already includes more than 1,600 patients (300 of whom are from the University of Michigan system). Using this registry, the team has identified trends in DILI in the United States over a 10-year period. In a paper published in *Gastroenterology* (2015;148:1340-1352.e7), they found dozens of drugs associated with a fairly high incidence of DILI, and drugs in the antimicrobial class, particularly amoxicillin-clavulanate (Augmentin, Beecham Pharmaceuticals) and isoniazid, were among the leaders.

“Amoxicillin-clavulanate is prescribed to millions of patients each year,” Dr. Fontana said. “It is a very commonly used antibiotic, with a good spectrum of activity that is very efficacious. Unfortunately, it is also the number one cause of DILI, although most patients recover. Isoniazid, of course, is less commonly used, but it is prescribed frequently to health care workers who may have been exposed to tuberculosis, and right now there is no alternative choice.”

ALSO SUSPECT: SUPPLEMENTS

The use of dietary and herbal supplements has also been associated with a relatively high incidence of DILI. These supplements are not subject to FDA testing requirements and are often used without the supervision and direction of health care professionals.

“We’re not suggesting that people stop using these drugs or supplements,” he said. “We merely want physicians to include the potential for DILI in their risk-benefit analysis. Now, when doctors see patients with unexplained liver injury, we want them to ask what medications or supplements the patients are taking as part of their evaluation.”

According to Dr. Fontana, the ultimate goal of DILIN is to identify genetic polymorphisms that may put certain patients at increased risk for DILI. He and his team have been collecting DNA and other biological samples from patients in the DILIN registry, hoping to find differences between people developing DILI and the general population. Although they have yet to identify common risk factors among DILI patients—such as age, gender, and race—the team has begun to identify some genetic risk factors that are drug-specific, and hopes to present its findings in the near future.

“We really see this as a vital part of the precision medicine movement,” Dr. Fontana said. “Most precision medicine has been geared toward efficacy, but we’re looking at it from a ‘do no harm’ or safety perspective. If we can identify a genetic risk factor for DILI and confirm it through a blood test, we can ultimately determine if one drug is a better option for one patient than another. We can use the latest molecular techniques to develop blood tests to improve the overall safety of the practice of medicine.”

Meanwhile, patients coming to the health system for a variety of health conditions—from neurological disorders to heart diseases to infectious diseases to pediatrics—are now having any drug treatment evaluated with regard to the risk for DILI, with patients and their families being educated about these risks. Dr. Fontana has established the Michigan Hepatotoxicity Network to help educate physicians throughout the state and communicate the latest research findings.

“Because I’ve been doing this research for so long, there is a growing awareness of DILI in our medical center,” he said. “If patients who come here experience toxicity, our physicians now notice it more quickly and intervene more quickly, and as a result, I think patient outcomes are improving.”



Above: Dr. Fontana and Dr. Brian Nedeau, an internal medicine resident, examine a patient for physical signs of chronic liver disease.



ERIC'S STORY

A CASE OF DRUG-INDUCED LIVER DAMAGE

In 2009, a 45-year-old otherwise healthy male patient presented to an emergency department in Kalamazoo with the typical symptoms of pneumonia. The emergency department physicians prescribed high-dose azithromycin (Zithromax, Pfizer), known colloquially as a "Z-Pak," which the patient took for the prescribed five-day treatment period.

Azithromycin has proved effective for the treatment of bacterial infections, and unsurprisingly, the patient's pneumonia improved over the course of therapy. However, unfortunately, the patient began to experience other troubling symptoms, including upper abdominal pain, nausea, and dark-colored urine.

"I started feeling better right away with my pneumonia, but within about two weeks I started feeling more ill every day," recalled Eric Barth. "It's like what the fast-talking voice-over says in the commercials, 'Be careful for a yellowing of the skin and eyes, as this can be the signs of a serious infection.' It turns out, in my case, that's what it was."

Barth visited his primary care physician, and blood tests revealed that his liver values were high. According to Dr. Fontana, Barth was experiencing the hallmark symptoms of drug-induced liver injury (DILI). Research performed in Dr. Fontana's clinic has revealed that azithromycin use, in a relatively small subset of patients, can lead to DILI. Indeed, it is one of a long list of drugs in the antimicrobial class associated with liver-related adverse events.

Barth was referred to Dr. Fontana and ultimately diagnosed with cholestatic hepatitis. He has been receiving treatment for the condition, which is chronic, with an immunosuppressant for the past six years now, and his condition is in remission, Dr. Fontana said.

"It was clear Dr. Fontana had so much experience with my condition, through his research and the liver injury network," Barth said. "There was always a real sense of reassurance from him that I would get better. And that was a huge help in my recovery. It's kind of cool to know, too, that my experience is informing the ongoing research."

"The message here isn't that people who need antibiotics like azithromycin shouldn't take them because of the risks," Dr. Fontana added. "These drugs have been proven safe and effective for the majority of patients. However, as physicians we should consider the possibility of liver damage in some patients and warn all patients of these risks. We should advise them of how to recognize the symptoms and what to do if they experience them."

NOVEL TECHNOLOGY ENABLES LESS INVASIVE DIAGNOSTIC APPROACH

Long-needle biopsy has long been used for the diagnosis of cirrhosis and other liver diseases, although it is not without complications. This is an invasive procedure and takes several hours to perform. Patients can also experience pain and, in rare instances, bleeding following the procedure, the latter of which may require admission to the hospital for overnight observation.

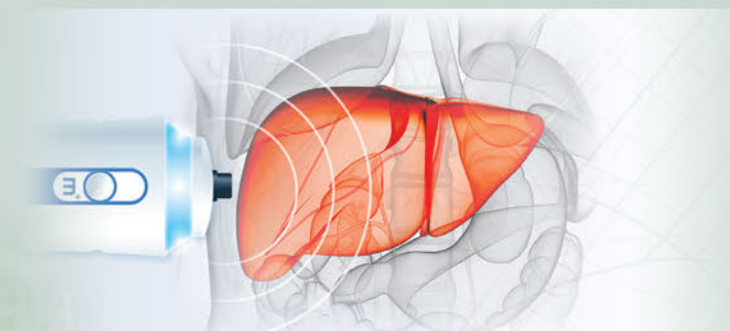
Now, a new technology has the potential to make diagnosis of cirrhosis, chronic hepatitis C, and perhaps fatty liver disease easier for physicians and patients alike. The device is called FibroScan (Echosens), and the University of Michigan Health System is one of the few centers in the state to offer it.

"This is a simple, noninvasive procedure that enables us to assess the amount of scar tissue in the liver in a matter of minutes," explained Dr. Fontana. "It's really a nice point-of-care test that allows us to get the information right there in the exam room."

The FDA approved FibroScan for use in diagnostics in 2014. According to Dr. Fontana, the device is similar to an ultrasound system in that it uses radiofrequency waves to capture a visual image of the surface of the liver. During assessment, which takes approximately five minutes, an ultrasound probe is positioned just beneath a patient's right rib cage for approximately "10 gentle touches," Dr. Fontana said.

"The liver is close to the surface of the skin, so effectively this device takes advantage of that," said Dr. Fontana. "We can use it to get an accurate picture of the amount of scar tissue in the liver, or the stiffness of the liver."

Dr. Fontana and his team are currently using FibroScan for the preliminary diagnosis of liver disease, and as a result are now performing biopsies on fewer patients, usually only to confirm a diagnosis. Physicians who suspect their patients may have liver disease can refer them directly to Dr. Fontana's clinic for the test only—without them needing to be evaluated by clinic physicians beforehand.



FibroScan®

MICHIGAN BOWEL CONTROL PROGRAM OFFERS A PIONEERING APPROACH

Patients with severe defecation disorders or pelvic floor dysfunctions require care spanning multiple medical specialties, which is why the Michigan Bowel Control Program (MBCP) exists.

“There are very few programs nationally that allow patients to get a comprehensive and integrated care plan from people who—we like to believe—are national experts in the care of patients with severe constipation and fecal incontinence,” said William D. Chey, MD, director of medical services at MBCP, and Timothy T. Nostrant professor of gastroenterology at the University of Michigan.

Dr. Chey, along with Dee Fenner, MD, director of surgical services at MBCP, leads a program that prides itself on delivering highly coordinated, holistic patient care. Patients receive a combination of medical and surgical services, and nutrition and lifestyle counseling from a team of health care professionals that includes gastroenterologists, urogynecologists, colorectal surgeons, physical medicine and rehabilitation providers, physical therapists, nutritionists, and psychologists.

“In 2005, when we started this program, gastroenterologists, urogynecologists, and colorectal surgeons were all completely siloed,” Dr. Chey explained.

Over a decade ago, Dr. Chey, Dr. Fenner, and Emina Huang, MD, then a colorectal surgeon at the University of Michigan, established MBCP, with the vision of providing truly multidisciplinary patient care. “We thought we could do things a whole lot better if we saw patients together and developed integrated care plans,” Dr. Chey said.

CHRONIC CONDITIONS REQUIRE DEDICATED FOLLOW-UP

If the success of their original idea can be measured by the growth of the program, then consider the team members visionaries.

“The first year we saw about 50 new patient referrals, and they were almost all from within the university,” Dr. Chey recalled. “Last year, we saw more than 500 new patient referrals, and we continue to grow on an annual basis.” The word is definitely out about the excellence of the program, with some patients traveling thousands of miles to be treated at MBCP.

“A key message we stress to patients is that these are chronic conditions,” Dr. Fenner noted. “Patients need to think about them as they would other chronic conditions, such as diabetes. The key is that we maintain contact; we don’t just send the patient out and then have them come back three months later,” Dr. Fenner said. Key to the program’s success is its careful attention to follow-up care. MBCP has a dedicated nurse concierge team that assists in the implementation of care plans, shepherds patients through their journey at MBCP, and provides follow-up care that is essential to positive patient outcomes.

CONTINUING RESEARCH

Dr. Chey cited innovative research as another feature that sets MBCP apart from other programs. For example, Dr. Fenner played an integral role in clinical trials of the novel TOPAS (Astora Women’s Health) minimally invasive surgical procedure that is under evaluation for fecal incontinence in women. Additionally, her team has just begun using an FDA-approved modification of the Eclipse System (Pelvalon).

Dr. Chey, along with University of Michigan gastroenterologist Stacy Menees, MD, is currently leading a randomized controlled trial comparing dietary fiber supplementation with a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) for the treatment of fecal incontinence. He also has designed a glove-based manometry system, for which he holds a patent, that is being tested in clinical trials as a low-cost alternative to anorectal manometry for the evaluation of anal sphincter function. “At MBCP, we’re trying to grow beyond providing excellent care,” Dr. Chey said. “We’re trying to learn from the care we deliver, to create novel ways of understanding why patients suffer from the symptoms that they do, and to improve upon the excellent care we are currently able to deliver.”



WILLIAM D. CHEY, MD



DEE FENNER, MD



EMINA HUANG, MD

“In 2005, when we started this program, gastroenterologists, urogynecologists, and colorectal surgeons were all completely siloed.”

—WILLIAM D. CHEY, MD

Using a model of the pelvis, Dr. Fenner, with nurse Anne Mcleod, helps a patient understand the relationship between constipation and pelvic organ prolapse.



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University of Michigan
Von Voigtlander Women's Hospital
Department of Obstetrics & Gynecology
Division of Gynecology
Dee E. Fenner, MD



STRATEGIES EMERGE FOR PREVENTING POST-ERCP PANCREATITIS

University of Michigan Health System researchers guided by James M. Scheiman, MD, professor of internal medicine and GI lead in the hospital's Multidisciplinary Pancreatic Cancer Destination Program, have been actively engaged in studies designed to identify ways to improve the standard of care in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP).

In 2012, the team published the results of a groundbreaking study in *The New England Journal of Medicine* (2012;366:1414-1422) that found indomethacin administered rectally was a highly effective approach to prevent post-ERCP pancreatitis (PEP).

An analysis of that trial further suggested that indomethacin was more effective and more cost-effective for preventing PEP than pancreatic duct stents or a combination of the two (*The American Journal of Gastroenterology* 2013;108:410-415). This has led to an increased use of the drug—a less-invasive approach—at University of Michigan and elsewhere. Dr. Scheiman noted the insertion of prophylactic pancreatic duct stents, an approach used in patients considered to be at high risk for complications after ERCP, can be difficult, and injury to the pancreatic orifice is a possibility.

INDOMETHACIN AND PANCREATIC DUCT STENTS

Dr. Scheiman and his team are seeking to build on these findings with new research into whether the use of stents further reduces the risk for PEP in ERCP patients who also are receiving indomethacin prophylaxis, and to explore why there is significant interindividual variability in patient response to ERCP. Ultimately, the primary goal is to develop a method for identifying and pretreating patients at increased risk for postprocedural complications.

"ERCP is the most dangerous procedure we do as gastroenterologists," Dr. Scheiman explained. "Our initial research led to more widespread use of indomethacin in our institution and nationally, and has helped patients tremendously. Now, we are trying to understand why patients get pancreatitis following ERCP and how to best reduce this risk. Our group is committed to groundbreaking research in this area, and to training gastroenterologists at an extraordinarily high skill level to practice state-of-the-art ERCP."

Pursuant to this goal, Dr. Scheiman served as one of the co-authors of a paper published in the *American Journal of Gastroenterology* (2015;110:48-59) that proposed metrics for assessing quality and efficiency in training programs for endoscopic procedures such as ERCP and endoscopic ultrasound (EUS). In addition, Dr. Scheiman's team is collaborating with University of Michigan biomedical engineering faculty in National Institutes of Health-funded research on the potential for characterization of pancreatic tissue using optical spectroscopy. They hope the technology will assist in the "differentiation of various pancreatic diseases," Dr. Scheiman explained, and in better patient selection for procedures such as ERCP and EUS, ultimately making these procedures safer.

"We have been involved in studying the process by which we learn these various endoscopic procedures and are involved in an ongoing study that assesses training programs nationally," Dr. Scheiman said.

"Our in-depth understanding of the risks and benefits of invasive procedures involving the pancreas has really helped us target the safest and most-effective approach to diagnosing patients with pancreatic disease. Because we have high-quality, less-risky alternatives such as EUS, we've been able to use these approaches to make sure ERCP is the right procedure to do and, if it is, we've pioneered approaches to make that procedure safer." **M**

"ERCP is the most dangerous procedure we do as gastroenterologists."

—JAMES M. SCHEIMAN, MD



RESEARCH FOCUSES ON GENETIC DIAGNOSTIC AND THERAPEUTIC APPROACHES TO NAFLD



Nonalcoholic fatty liver disease (NAFLD), now estimated to be the most common form of liver disease in the United States and worldwide, is expected to be the primary cause for liver transplantation by the end of the decade.

However, regardless of its pervasiveness, there are many unknowns surrounding the disease. Elevations in liver enzymes may indicate NAFLD; however, the accuracy of such tests is poor, and the standard procedure for diagnosis, liver biopsy, is aggressive. Further, the condition can manifest from a plethora of factors, and initial symptoms, including abdominal pain and fatigue, are indistinct, if expressed at all.

As a result, many individuals with NAFLD are initially oblivious to even having it, until it advances to something much more serious, such as cirrhosis or liver failure. Additionally, there are inadequate treatments for the disease, so patients are frequently left without viable options, even if diagnosed early and accurately.

Because of these difficulties, Elizabeth K. Speliotes, MD, PhD, MPH, assistant professor of internal medicine, computational medicine and bioinformatics at the University of Michigan Health System, hopes to uncover the disease's actual pervasiveness and risk, in addition to identifying effective treatments through genetic research.

NAFLD AND OBESITY GENES DIFFER

In working with the Genetics of Obesity-Related Liver Disease Consortium, Dr. Speliotes' team has identified five genetic loci associated with NAFLD. Using a group of approximately 7,000 people, the investigators calculated liver fat based on CT scans and carried out related genome-wide association analyses to recognize genetic patterns related to fatty liver. They then performed genetic analyses of people with NAFLD.

One noteworthy finding was that genes related to NAFLD are different from those associated with obesity.


"Obesity was one of my first interests and, in part, what drove me to study fatty liver disease," Dr. Speliotes said. "Ultimately, I do think they are linked. But in terms of genetics, it looks like the main drivers of obesity are more neurologically based, whereas the drivers that seem to be causing fatty liver disease are more lipid- and glucose-based. That changes how we think about these diseases."

Dr. Speliotes' team also is exploring the relationship between NAFLD-related genes and environmental factors.

"Our studies suggest that approximately 25 to 30 percent of how much fat is in your liver is due to genetics, and the rest is probably environmental," Dr. Speliotes said. "Some of my patients are the epitome of health. They tell me they work out every day. But it doesn't matter. They still have a lot of fat in their liver."

"We've identified genetic variants that put some individuals at much higher risk for developing fat in the liver, even without being overweight. For example, we've identified one variant that confers a sixfold higher risk for developing scarring and cirrhosis, and another variant that is associated with a twelvefold higher risk for developing liver cancer."

Future studies will be designed to identify new genes related to NAFLD in order to better inform people who are at risk for the disease and to develop more effective treatments.

"Currently, we can make specific recommendations for people who are at risk for developing some types of cancer, for example," Dr. Speliotes said. "But it's only through this kind of research that we're going to be able to make similar recommendations for people with metabolic diseases." 

"Some of my patients are the epitome of health. They tell me they work out every day. But it doesn't matter. They still have a lot of fat in their liver."

—ELIZABETH K. SPELIOTES, MD, PHD, MPH

Top: Dr. Speliotes and Alissa Wall, medical student, open a liquid nitrogen tank containing human liver cell lines, which are used to model human disease.

Left: Dr. Speliotes examines human liver cell lines through a microscope.



IMAGING TECHNOLOGY AND MOLECULAR PROBES ADVANCE GASTROINTESTINAL THERAPY

“This work alters current diagnostic paradigms because diagnoses can now be made based on microscopic increases in the expression of molecular targets specific to certain diseases rather than on the gross visible appearance of mass lesions.”

—THOMAS D. WANG, MD, PhD

New developments in imaging technology have enabled physicians to identify cancer in its earliest manifestations, which is critical for treatment. In addition, a more thorough understanding of the numerous molecular pathways involved in tumor cell proliferation has allowed physicians to adopt a personalized approach with targeted cancer therapies.

Thomas D. Wang, MD, PhD, associate professor of internal medicine, biomedical engineering, and mechanical engineering, and H. Marvin Pollard collegiate professor of endoscopy research at the University of Michigan Health System, is developing very specific molecular probes to be used in conjunction with new optical imaging to identify precancerous lesions in the gastrointestinal tract.

“We are currently developing peptides that bind to molecular targets expressed in diseases of the biliary tract, colon, esophagus, and liver,” said Dr. Wang, a gastroenterologist whose research has centered on molecular imaging.

PEPTIDE-BASED PROBES

Although most existing targeted cancer therapies are based on monoclonal antibodies that attach to target proteins on the exterior of cancer cells, Dr. Wang is concentrating on peptide-based compounds that are considerably smaller.

“These peptide-based probes provide an attractive alternative for visualizing tissue targets that would otherwise be difficult to penetrate or access,” Dr. Wang said. “This work alters current diagnostic paradigms because diagnoses can now be made based on microscopic increases in the expression of molecular targets specific to certain diseases rather than on the gross visible appearance of mass lesions.”

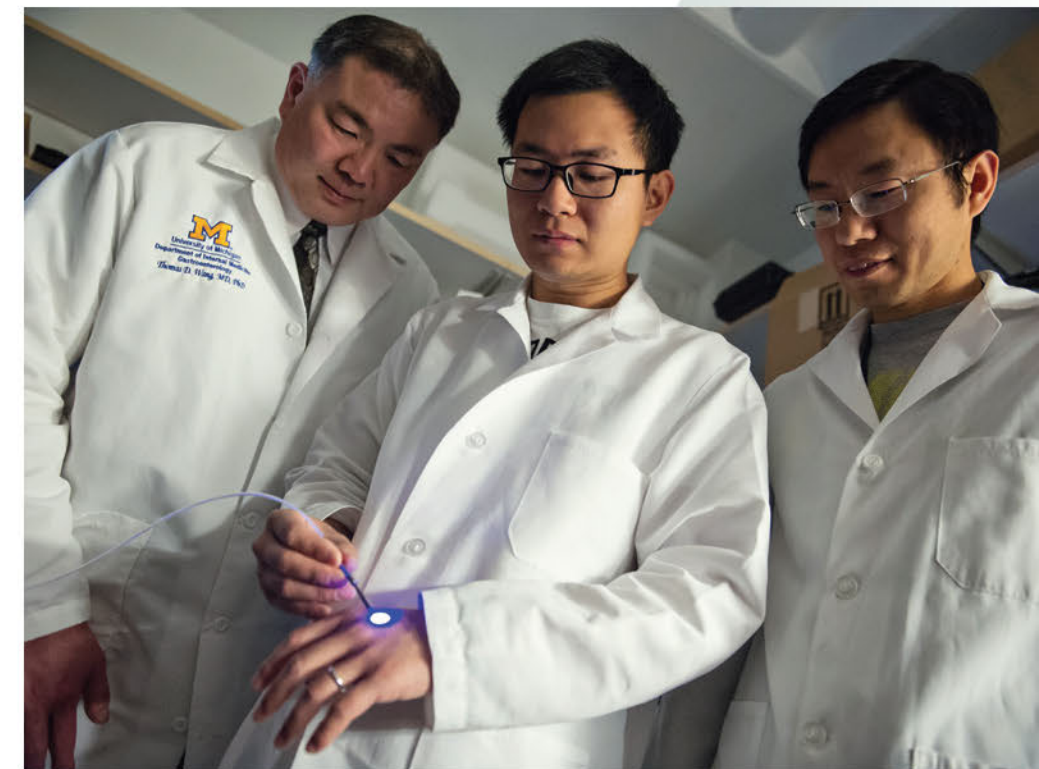
Peptides also are safe for systemic use and are less immunogenic than antibodies. Additionally, peptides can be transformed anatomically to increase stability against proteolytic degradation and can be labeled with fluorophores that will permit imaging several targets at the same time.

Dr. Wang is part of a collaboration that is responsible for “developing novel molecular imaging methodologies to visualize cell surface targets that are either gene amplified and/or highly overexpressed in EAC [esophageal adenocarcinoma],” as compared with Barrett’s esophagus. These cell surfaces will be seen using “highly specific peptides that are fluorescently labeled for real-time endoscopic imaging to rapidly assess esophageal mucosa” for the existence of early neoplasia.

Dr. Wang hopes that with additional research and development of peptide-based probes for molecular imaging, physicians will have a more precise representation of cellular and molecular activities in all areas of the GI tract.

“We have developed novel molecular probes that bind to cell surface targets that are overexpressed in a number of human diseases,” he said. “I expect to find new uses for these molecular probes to detect diseases beyond their original purpose for development.” 

Dr. Wang, Xiyu Duan and Gaoming Li, pictured left to right, work with a laser as part of Dr. Wang’s research.



PHYSICIAN RELATIONS AND OUTREACH PROGRAM



The University of Michigan Health System is pleased to offer a Physician Relations and Outreach Program dedicated to providing personalized service to community-based physicians, including:

- **consultations**
- **education opportunities about the latest treatment options**
- **clinical trials**
- **current news and events**

We are available for on-site meetings in addition to the activities we sponsor at our facilities and in your communities. Our goal is to improve communication and coordination of care for referring physicians and their patients.

MEET **REBECCA CHAMBERLAIN**

Rebecca serves as the Digestive Health and Liver Transplant physician liaison and is available to visit community based physicians' practices. She works with individual practices to understand their patient care needs and shares information on services, treatment options and clinical trials from the many specialty clinics within Digestive Health and Liver Transplant. To contact Rebecca, please call MLINE at **800-962-3555** or email her directly at rjchambe@med.umich.edu

