

Division of Digestive Diseases

David Geffen School of Medicine at UCLA

Summer 2010 Newsletter

Georgia Frontiere

A Pioneer and a Generous Spirit



Georgia Frontiere

As the first woman to own a National Football League franchise, Georgia Frontiere was a pioneer in the worlds of sports and business. But to the countless individuals who were touched by her philanthropic works, Mrs. Frontiere was someone else – a generous spirit devoted to helping others, often with little fanfare. And to the two children she raised, she was a devoted mother whose lessons on the importance of philanthropy continue to loom large.

“Our mother taught us that it was our responsibility to give back in whatever way we can, and she set a great example,” says Dale (Chip) Rosenbloom.

When Mrs. Frontiere passed away in 2008 after battling breast cancer, Mr. Rosenbloom and his wife Kathleen, along with Mrs. Frontiere’s daughter Lucia Rodriguez and her husband Guadalupe, established the Georgia Frontiere Memorial

Fund to benefit research, education, and patient care in the UCLA Division of Digestive Diseases. “We received incredible support from the doctors in the Division during her illness,” Mr. Rosenbloom explains, “and we wanted to create a lasting memorial that would help others.”

The generosity and spirit of giving that was a hallmark of Mrs. Frontiere’s life endures in the lives of her children. Among other charitable causes, the Rosenbloom and Rodriguez families are strong supporters of the Division, and their ongoing support continues to have a big impact on its programs.

“We are so appreciative of the memory of Mrs. Frontiere and of the friendship and support of these two families,” says Eric Esrailian, M.D., M.P.H., Assistant

Our mother taught us that it was our responsibility to give back in whatever way we can, and she set a great example.

Professor and Chief of Development for the Division, as well as a family friend who delivered a eulogy at Mrs. Frontiere’s funeral. “With so many patients in need of critical care and at very uncertain times in their lives, the Frontiere Fund has gone

Fighting the Growing Problem of Obesity

Amid an epidemic of obesity in the United States, metabolic syndrome – a cluster of conditions that includes excess body fat, high blood pressure, high blood sugar, and high cholesterol – has emerged as a major health concern. Believed to affect as many as one in three Americans, metabolic syndrome is considered a herald for some of the leading causes of death: diabetes, heart disease, and stroke.

The liver is the workhorse organ for metabolism. It is responsible for transforming the food we eat into energy and other building blocks for the rest of the body, protecting us from toxins, and controlling the synthesis of particles that carry “good” and “bad” cholesterol in the bloodstream. Thus, it’s no surprise that metabolic syndrome is also closely associated with chronic liver disease – and the growing obesity problem suggests that the number of people at risk will soar in the near future. There is no treatment for metabolic syndrome. Even losing weight, for example, is not a guarantee that the destruction that has begun in the liver will cease.

Understanding how metabolic syndrome causes liver disease in the

From the Division Chief

UCLA Division of
Digestive Diseases
David Geffen School of
Medicine at UCLA
Gary Gitnick, M.D.

When Neil Armstrong stepped onto the moon, the world was mesmerized. Thanks to television, this first step opened up the imaginations of millions – inspiring them to wonder about the possibilities of what humans can accomplish when they set their minds on a goal.

Jonas Salk, Louis Pasteur, and Marie Curie are just a few of the many luminaries who brought their passion to our world of science and healthcare. Through their dedication, and with the support of many around them, they made discoveries that had a profound impact on the lives of millions, if not billions, worldwide.

Today, the UCLA Division of Digestive Diseases continues to carry a banner of imagination, discovery, and dedication. We continue to strive to make the world a better place and to improve the quality of healthcare and life around us. And like the scientific leaders who came before, we continue our efforts, thanks in no small part to the support of so many dedicated physician-scientists and their staffs and the public and private funding that allows them to transfer what is in their imagination into reality.

With this in mind, I introduce to you, within the pages of our Division's summer newsletter, several physician-scientists whose research is shaping the world of science and healthcare around us: Dr. Simon Beaven, who studies metabolic syndrome, a condition that affects more than 1-billion people worldwide; Dr. Francisco Durazo, who will make you think twice about the vitamin supplements and common over-the-counter medicines found in our homes; Dr. Brennan Spiegel, who is helping physicians be better "listeners" to their patients; and Dr. Enrique Rozengurt, under whose leadership we near the 40th anniversary

of CURE (Center for Ulcer Research and Education) – an achievement reflective of this program's success and of the Division's national leadership in this field.

Joining this group of outstanding UCLA physician-scientists – some of whom have been featured in previous editions of our newsletter – whose contributions are of particular note are Drs. Emeran Mayer, Lin Chang, and Kirsten Tillisch in brain-gut interactions; Dr. Nori Kasahara in gene therapy; Dr. Spiegel's work in outcome assessments and healthcare policy; Drs. Harry Pothoulakis and Jennifer Choi in irritable bowel disease; and Dr. Peter Anton in mucosal immunology.

As the Division continues to move ahead, particularly in this challenging economic climate, we look forward to telling you more about the progress of these specialists' exciting work in this and upcoming issues of the newsletter. For now, I close by saying how grateful we remain to our friends and the public entities who continue to support these very worthwhile scientific endeavors. You are very much true partners in this progress and success. ■

Are Prescription Drugs Damaging Your Liver?

Drug-induced liver injury – an adverse reaction to prescribed or over-the-counter medications, including herbal and dietary supplements – is one of the most common causes of acute liver failure in the United States, accounting for more than one in eight cases. Often unintentional and unexpected, it typically requires hospitalization and sometimes can be cured only through life-saving liver transplantation.

Much is not understood about the causes of these incidents or how to diagnose them, but a large, multi-center study that includes the UCLA Division of Digestive Diseases aims to find answers. The National Institutes

of Health (NIH)-funded Drug Induced Liver Injury Network (DILIN), a consortium that includes five clinical

Dr. Durazo notes that the most common cause of drug-induced liver injury in the United States is from an

The most common cause of drug-induced liver injury in the United States is from an accidental overdose of acetaminophen – a mainstay in the medicine cabinets of many American households.

sites, is headed at UCLA by Francisco Durazo, M.D., Associate Professor in the Division who has long studied the issue of drug-induced liver damage, also known as hepatotoxicity.

accidental overdose of acetaminophen – a mainstay in the medicine cabinets of many American households. When used at recommended levels, the drug

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is safe, but because acetaminophen is found in more than 100 pharmaceutical products – from over-the-counter cold formulas and tablets for aches and fever to prescription pain medications – some people unknowingly take too much. “This is what we call a therapeutic misadventure,” Dr. Durazo explains.

While acetaminophen-induced hepatotoxicity has been well-studied, many other causes have not. The DILIN is establishing a comprehensive registry of all types of hepatotoxicity cases in an effort to learn more about clinical, genetic, environmental, and immunological risk factors. The study, which began in 2003 and was recently renewed by the NIH, recruits patients with suspected drug-induced liver injury and collects biological samples for analysis.

“If we can find a common signature

to regulate supplements, Dr. Durazo notes. As a result, many of the products, particularly those for weight-loss, are believed to increase the risk for liver toxicity.

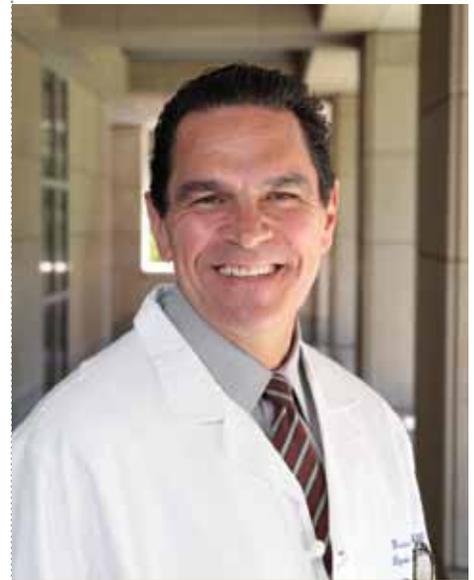
As part of its work, the DILIN is using biological samples to conduct studies designed to determine if individuals can have genetic predispositions to developing drug-induced liver injury. In addition, Dr. Durazo and colleagues are using the repository as a way to improve the ability of doctors to diagnose the problem. “Right now, this is a diagnosis of exclusion,” Dr. Durazo explains. “There are no tests we can conduct to determine that the patient has suffered drug-induced liver injury – not even a biopsy. With this study, we hope to design a new method for assessing causality.”

The most common cause of drug-induced liver injury in the United States is from an accidental overdose of acetaminophen – a mainstay in the medicine cabinets of many American households.

for these cases in terms of clinical features as well as outcomes, it would improve our ability to prevent or predict liver injury and would enable us to do a better job diagnosing it,” Dr. Durazo says.

The consortium is looking not just at prescribed medications but at dietary and herbal supplements – an aspect of hepatotoxicity that Dr. Durazo has studied. “Supplements are a big problem right now because they are not well-regulated,” he explains. The Dietary Supplement Health and Education Act of 1994 limits the federal Food and Drug Administration’s ability

Dr. Durazo believes taking such a comprehensive approach to learning about hepatotoxicity provides the best opportunity yet to curb the problem. “This is very prevalent – and because of the difficulty in diagnosing it, it often goes undetected,” he says. “Hepatotoxicity is the most common reason for removing a drug from the market or changing its labeling, and that step is only for licensed drugs; there are many unregulated supplements with hepatotoxicity that remain on the market. This problem is important, and we hope to make a difference with this study.” ■



Dr. Francisco Durazo

Honorable Mention

Francisco Durazo, M.D., Associate Professor in the Division, recently had two papers accepted for publication on the treatment of anastomotic strictures with maximal stenting following liver transplantation. Dr. Durazo was the senior author and performed all of the procedures for both papers, which were accepted for publication in the March and June issues of the journal *Gastrointestinal Endoscopy*.



Dr. Joseph Reeve, Ph.D.

Joseph Reeve, Ph.D., Professor in the Division, has received a grant from the National Institutes of Health to study the feeding patterns of a molecular form of cholecystokinin, a peptide found in the upper intestine. Dr. Reeve showed that CCK-58, isolated and characterized by his lab in 1982, decreased meal size. His laboratory also has characterized an agent that could be given as a pill to release cholecystokinin in the body, which could be an effective tool for reduction of daily food intake – and, thus, a potentially effective treatment for obesity.

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a long way in helping make a tangible difference in the areas of patient treatment, research, and education.”

As owner of the Rams for three decades – first in Los Angeles and since 1995 in St. Louis- Mrs. Frontiere was also active in a number of philanthropic endeavors. Her St. Louis Rams Foundation contributed more than \$5 million to charities in the St. Louis area. Mrs. Frontiere was also a major donor to the Los Angeles-based Fulfillment Fund, an organization that provides low-income students with the support necessary to graduate from high school and go on to college. She was also strongly committed to supporting retired NFL players and was a devout patron of the arts.

But perhaps her greatest philanthropic passion was helping children with cancer and other life-threatening diseases. During the more than five months she spent being treated at UCLA at the end of her life, Mrs. Frontiere kept photographs near her hospital bed of the sick children with whom she had become close. “Those kids were her heroes,” says Mrs. Rodriguez. “She garnered strength from them, as well as from knowing that she had the love of her family along with the best medical care.”

After Mrs. Frontiere passed away, Mr. Rosenbloom and Mrs. Rodriguez assumed majority ownership of the Rams and communicated their intention to continue their mother’s high level of community engagement. At her first news conference, Mrs. Rodriguez announced the formation of “Team Georgia” to participate in the Komen St. Louis Race for the Cure, one of the world’s largest breast cancer fundraising walks.

Although spending time in the hospital with a loved one in the final months of life is a trying experience for any family, the Rosenblooms and the Rodriguezes are thankful for the outstanding care Mrs. Frontiere received from the doctors and staff. “Any large hospital, no matter how good it is, can be daunting,” says Mr. Rosenbloom, who in addition to his role with the Rams works in the film industry. “Dr. [Gary] Gitnick [chief of

the Division], Dr. Esrailian, and the other members of the team were outstanding resources who did so much for our mother and to make all of us comfortable as we dealt with her illness. They were advocates as well as caregivers.”

Both Mr. Rosenbloom and Mrs. Rodriguez say the support of their spouses – during their mother’s illness as well as in the decision to establish the memorial fund – was remarkable. “When you have a sick parent, without that support of your spouse it can be overwhelming,” says Mr. Rosenbloom. “During trying times, people either rise to the challenge or they don’t. In our cases, Kathleen and Lupe both did and continue to do so.” Adds Mrs. Rodriguez, “We thought we had a close family before, but this brought us even closer.”

Support also came from friends of the families as well as others whose lives were touched by Mrs. Frontiere, many of whom donated to the fund after the Rosenbloom and Rodriguez families requested donations in lieu of flowers. “We wanted to keep our mother’s memory alive, which was very easy to do because she was loved by so many people,” says Mrs. Rodriguez. “To receive contributions to the memorial fund in her name, along with personal notes and phone calls from so many people, is very comforting when you lose someone you love.”

“We know that the Division of Digestive Diseases at UCLA will be at the forefront as medicine develops better treatments and cures for some of these devastating illnesses,” says Mr. Rosenbloom. “We hope that this fund in our mother’s name will make a difference in the important work the Division is doing. This is a way to honor her memory at the institution that did heroic things to make her last days as good as they could be under the circumstances.”

Georgia Frontiere’s memory is indeed honored through the Georgia Frontiere Memorial Fund. But more than that, it is honored by the way her children and their families continue to live and breathe the life lessons she conveyed through her words and deeds. ■

CURE Nears the BIG 4-0 – and Going Strong!

The annual meeting of the CURE: Digestive Diseases Research Center is always an important event. But the 2010 meeting, held April 9 at the UCLA Faculty Center, was particularly notable, coming shortly after the successful renewal of the fifth cycle of the CURE center grant by the National Institutes of Health (NIH). When the cycle is completed, at the end of 2014, CURE will have reached the ripe age of 40.

“For a center to be funded continuously by the NIH for 40 years is a remarkable achievement and is a testimony to the excellence of the center’s work over the last four decades,” says Enrique Rozengurt, D.V.M., Ph.D., Professor in the UCLA Division of Digestive Diseases and director of CURE.

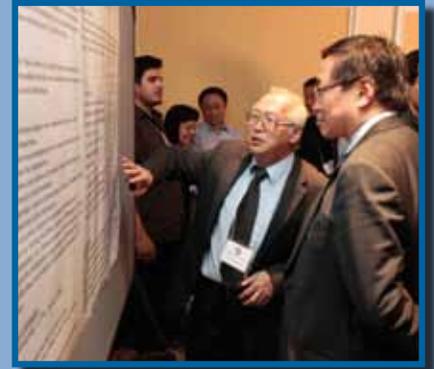
The meeting for CURE, which administers much of the research of the Division, brings together a wide-ranging group of investigators from the UCLA community to hear presentations on the latest findings of CURE researchers, participate in poster sessions, and network with researchers from across campus.

This year’s meeting was divided into three sessions of talks. A morning session focusing primarily on human studies. Speakers included Lin Chang, M.D., Kirsten Tillisch, M.D., Brennan Spiegel, M.D. and James Farrell, M.D. The clinical session was followed by a second morning session in which the focus was translational research aiming to turn laboratory findings into clinical therapies. Lectures were delivered by Charalabos “Harry” Pothoulakis, M.D., and Robert Coffey, M.D., a CURE External Advisory Board Member. In the afternoon, the emphasis was on basic science research, with presentations by Simon Beaven, M.D., Ph.D., Hon Wai Koon, Ph.D., Sylvie Bradesi, Ph.D., and Osvaldo Rey, Ph.D. Between the morning and afternoon, an extended poster session was held. “It allows

the young investigators to display their research,” Dr. Rozengurt says. “Among other things, it’s a unique opportunity for these young scientists to interact with the distinguished scientists who serve on the center’s advisory board.”

Afternoon highlights also included an address by A. Eugene Washington, M.D., M.Sc., the recently appointed Vice Chancellor for the UCLA Health Sciences and Dean of the David Geffen School of Medicine at UCLA, who outlined his vision for the medical school. That address was followed by a “State of CURE” presentation delivered by Dr. Rozengurt, leading into the John H. Walsh Memorial Lecture, given each year in honor of the distinguished scientist and previous Director of CURE who passed away in 2000. This year’s lecture was delivered by Timothy C. Wang, M.D., the Dorothy L. and Daniel H. Silberberg Professor of Medicine at Columbia University.

CURE was originally funded in 1974. The focus in the initial years was on resolving a major problem at the time: peptic ulcer. Since then, CURE’s scope has broadened to encompass all aspects of GI function and diseases. The center continues to have strong leadership – Dr. Rozengurt is himself a pioneer in the area of cell growth regulation and one of the most widely cited researchers in his field (with more than 25,000 citations in scientific literature, source ISI). ■



◀ A. Eugene Washington, M.D., M.Sc., Vice Chancellor, UCLA Health Sciences, Dean, David Geffen School of Medicine at UCLA.



▲ Enrique Rozengurt, D.V.M., Ph.D.

◀ Timothy C. Wang, M.D.



Simon W. Beaven, M.D.

Believed to affect as many as one in three Americans, metabolic syndrome is considered a herald for some of the leading causes of death: diabetes, heart disease, and stroke.

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earliest stages and the process by which it can progress to the end stages of cirrhosis and liver cancer could lead to novel treatments for this extremely common condition. That focus inspires the pursuits of Simon W. Beaven, M.D., Ph.D., Assistant Professor in the UCLA Division of Digestive Diseases. His research explores how alterations of fat and cholesterol metabolism promote liver damage. “Essentially, we are looking at how fatty liver contributes to insulin resistance and liver injury in order to find new pathways to treat patients with metabolic syndrome,” Dr. Beaven explains.

It is estimated that one-third of Americans have excess fat in their liver – roughly the same proportion who are obese and who present with abnormal liver tests. But Dr. Beaven notes that these groups do not perfectly overlap. Among the fundamental questions addressed by his lab: What are the relationships between a fatty liver insulin resistance / diabetes, and chronic liver damage? To study this concept, Dr. Beaven investigates an important metabolic sensor for cholesterol, the liver X receptor (LXR). Of particular interest is the question of how cholesterol and fat metabolism drive and exacerbate the liver’s wound-healing response. Metabolic syndrome provides a chronic injury stimulus to the liver, and in response, the liver generates scar tissue – a process known as fibrosis – that can ultimately lead to cirrhosis, the need for liver transplantation, and a dramatically reduced expected lifespan.

When Dr. Beaven was in medical school at UC San Francisco, he became fascinated with liver diseases while training under Dr. Scott Friedman, currently Chief of Hepatology at the Mt. Sinai School of Medicine in New York and recent President of the American Association for the Study of Liver Diseases (AASLD). Dr. Friedman is widely known for identifying the cell within the liver that is responsible for generating scar tissue during chronic liver injury: the hepatic stellate cell. At UCLA, Dr. Beaven completed his clinical

fellowship in Gastroenterology and received his Ph.D. training with Dr. Peter Tontonoz, an investigator in the Howard Hughes Medical Institute. Dr. Tontonoz is internationally known for his discovery of the gene that creates fat (PPAR) and for insights into the role of cholesterol sensing via LXRs in atherosclerosis. Dr. Beaven will continue to use the tools for studying nutrient metabolism to investigate the biology of the scar-making hepatic stellate cell. Recently, his group made a major discovery with the observation that cholesterol and fat metabolism (through LXR signaling) play a role in the activation of this specialized cell. “This was not something we expected to find, and it has opened up a new field of study – cholesterol metabolism in liver wound healing,” Dr. Beaven explains.

Recently, Dr. Beaven received a Career Development Award from the National Institutes of Health to study the role of cholesterol metabolism on stellate cell function during liver fibrosis. A better understanding of how this scarring process occurs could lead to new approaches for slowing or halting the progressive fibrosis that is at the root of all chronic liver diseases, including metabolic syndrome. “One of the Holy Grails in liver research is to find an agent that will stop the scarring and prevent cirrhosis, regardless of the cause of the liver injury,” Dr. Beaven says. “We are hopeful that modulating cholesterol metabolism might lead to such a generalized anti-fibrotic therapy.”

Dr. Beaven points out that there are no proven medications to prevent or treat metabolic syndrome and liver fibrosis. This fact is in stark contrast to other major causes of illness and death – such as atherosclerosis and heart disease, where there are many safe and effective medical interventions. “We have an opportunity to make a major impact in a way that would improve countless lives around the world,” says Dr. Beaven. “That’s very exciting and is the primary reason why I choose to do biomedical research.” ■

The Division of Digestive Diseases Donor Luncheon



Supporters and friends of the Division attended a luncheon last February where Dr. Eric Esrailian spoke on stress, its affects on the body, and what an individual can do to reduce one's stress level.

◀ Ms. Nancy Borun, Dr. Gary Gitnick, Mrs. Ruth Borun, Dr. E. Raymond Borun.

▼ Mrs. Keets Cassar and Mr. Hugh Cassar



(Top Right)- Mr. Brandon Stoddard

(Center Right) Ms. Alyce Woodward

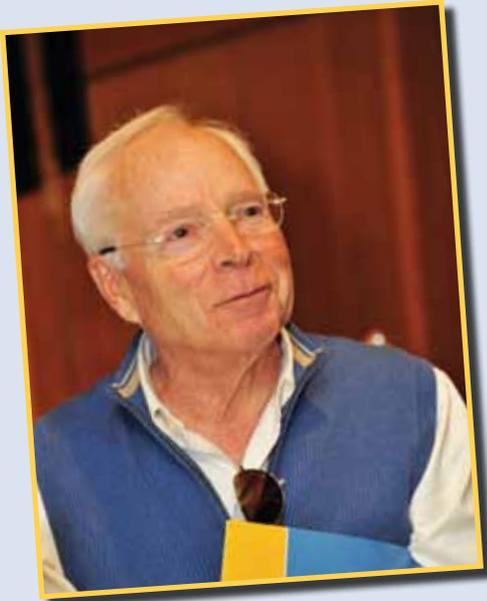
(Bottom right) Mrs. Carol Green and Dr. Harry Green ▶



◀ Ms. Margo Peck

Mrs. Marion Anderson ▶





How Is the Patient (Really) Feeling?

Gastroenterologists, says Brennan Spiegel, M.D., M.P.H., Assistant Professor in the Division of Digestive Diseases, tend to be skilled at learning about their patients' symptoms and using the information to render diagnoses and provide treatments. "But we're probably not as good as we think at truly communicating with patients and understanding what they mean when they talk to us," says Dr. Spiegel.

He is now leading an effort, in collaboration with Dr. Lin Chang, to ensure that the self-reports of patients with gastrointestinal symptoms are both better understood and more of a factor in their care. Dr. Spiegel heads a National Institutes of Health (NIH)-funded study that will develop, validate and distribute a questionnaire designed to quantify patients' GI-symptom-related distress.

The study is part of a larger initiative, the Patient-Reported Outcomes Measurement Information System (PROMIS), which was launched in 2004 to develop tools for accurate and efficient assessments of patients' symptoms and health-related quality of life across a wide variety of chronic diseases and conditions. Part of this initiative brings together different divisions within the Department of Medicine, such as the Division of Rheumatology, whose Dinesh Khanna, M.D., serves as an additional principal investigator of this research.

The questionnaires, publicly available and administered online, can be completed by patients in any number of settings, including the waiting room of their doctors' offices. With sophisticated software that asks follow-up questions based on responses, in minutes patients' quality of life can be objectively

measured.

"The idea is to come up with structured and rigorous techniques for learning how individual patients are experiencing their illness," Dr. Spiegel explains. "We will end up with something that serves like a vital sign, so that in addition to the usual things gastroenterologists would measure – blood pressure, heart rate, temperature, they will be able to obtain a PROMIS score that they can immediately compare with other people who have the disease

The idea is to come up with structured and rigorous techniques for learning how individual patients are experiencing their illness," Dr. Spiegel explains.

to better grasp how severe the illness is."

PROMIS has created instruments for measuring patient-reported outcomes on a number of conditions, from anxiety and depression to pain. But Dr. Spiegel's study is the first to adopt the approach for the GI tract. "As a gastroenterologist, I see patients with a variety of GI diseases, and one thing they all have in common is some form of GI distress," he says. "If they didn't have distress of some sort, they wouldn't come to see us in the first place."

Being able to quantify patients' reports on their GI distress is particularly

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Brennan Spiegel, M.D., M.P.H.

Dr. Brennan Spiegel, continued from page 8

important because GI conditions are both highly prevalent and poorly understood, Dr. Spiegel notes. “With pain, for example, we usually think about muscle aches or pain to specific bones,” he says. “But pain of the GI tract is much more complicated. We talk about gut feelings because we experience pain in the gut, but it’s much more difficult to capture in a meaningful way, and there are a lot of gray areas.”

Among other things, the PROMIS tool that Dr. Spiegel and colleagues are developing will make it easier for physicians to obtain patient reports. Rather than having to sit down and take a detailed history, the PROMIS algorithm adjusts the questions based on patient responses to obtain the same information in a much more efficient way.

physicians determining what we think patients are feeling or thinking, we need to go straight to the patients to get that information,” Dr. Spiegel says. The danger in not doing so is illustrated by the different ways patients and their physicians tend to view an illness such as irritable bowel syndrome. “When we measure the relationship between physician-reported severity and patient-reported severity, we often see a complete disconnect – patients say they are doing poorly and their doctors think they are doing okay,” Dr. Spiegel notes. “That means that the illness experience of the patient is not being effectively communicated to the physician.”

Dr. Spiegel says that as medicine has increasingly relied on technology and objective data to arrive at decisions on

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Dr. Spiegel explains that GI distress consists not just of the physical symptoms, but also of emotions and cognitions: how patients feel and think about their symptoms. For example, patients with an external locus of control – a sense that there is nothing they can do to control their illness – might warrant a different treatment approach than those with an internal locus of control, who are more likely to feel they have some control of their outcomes. Emotion and cognition are not typically captured in physician assessments, he says, but will be measured by the PROMIS tool.

“The argument behind patient-reported outcomes is that rather than

diagnosis and treatment, there has been less emphasis on patient reports. “As a scientist, I find it’s easier to interpret data than a patient report,” Dr. Spiegel says. “But that patient report is data too, and we can develop methods to categorize what patients are saying that are as reliable as methods for categorizing physiological findings.” ■

UCLA Health System

Division of Digestive Diseases

405 Hilgard Avenue
100 Medical Plaza, Suite 265
Los Angeles, CA 90095

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U.S. News & World Report's Best Hospital Survey ranks UCLA as the No. 3 hospital and UCLA Division of Digestive Diseases as the Best in the West and top 5 in the country for treatment of digestive disorders.



UCLA Medical Group ranks as one of California's top-performing physician organizations.

Division of Digestive Diseases Alumni:

You're Part of an Elite Group

Since our first class of fellows graduated in 1960, the UCLA Division of Digestive Diseases has prepared hundreds of physicians for careers as leaders in the study and treatment of GI disorders.

Personal relationships are a critical part of any successful career, and graduates of the Division's fellowship program, distinguished in all areas of medicine, are important people to know. Don't lose track of your fellow alumni, or of new developments within the Division. If you have not already sent us your completed information for inclusion in our Alumni Directory, please do so. For information, please call (310) 267-1845.

Gary Gitnick, MD

Chief, Division of Digestive Diseases

Eric Esrailian, MD, MPH

Chief of Development
Section Head, General Gastroenterology

Steve Ramirez

Director of Development

Pam Wilkes

Writer

Ginny King Supple

Contributing Editor/Writer

Michelle Moeck

Graphics/Production

Reed Hutchinson

Photography
Hutchinson PhotoGraphics