NATIONAL RECOGNITION

In 2013, the spotlight continued to shine brightly on U-M and the Department of Internal Medicine. The annual U.S. News & World Report Best Graduate Schools rankings rated the U-M Medical School 8th in the nation among research-based medical schools. U-M also held its rank among medical schools for primary care training, coming in at 8th for the second year in a row. Four U-M specialties ranked in the top 10 including internal medicine at 6th, women’s health and geriatrics at 7th and family medicine at 8th. U-M Medical School graduates also continue to be rated highly by the directors of residency programs nationwide.

EXCELLENCE: ABOVE AND BEYOND

Our 2013 was a very fruitful, as well as challenging year. We are still adjusting to the effects of implementing the Mi-Chart electronic medical records system and continue to face external pressures from decreases in funding for research and education. Yet, I am more optimistic than ever about our Department of Internal Medicine due to our “excellence.” That is why I have chosen it as the theme of this year’s report. We continue to go above and beyond in everything that we do.

We attract and support fantastic faculty, and have a wonderful staff that shows a lot of ingenuity to keep us moving forward. Our philanthropic activities continue to rise. There are now more than 50 professorships and other support is growing. We recruit top-notch residents and fellows for our department and divisions — some of the best classes in the country (page 25). We continue to be innovative and competitive in research and in clinical care.

RESEARCH THAT LEADS THE WAY

Research from our faculty is transforming health care. They are publishing their findings in the best journals in the world and receiving impressive amounts of competitive grants. The work of some our finest faculty and recruits is featured in the research section (page 30).
IMPROVING PATIENT CARE
Our focus on clinical improvements and expansion continues to grow. Renovations to the third floor of Taubman Center to better handle patient flow were completed this year. It is now more integrated with the new Transplant Multidisciplinary Clinic on the first floor (page 58) and our new Northville site will be opening in July 2014 (page 60).

We opened an Acute Care for Elders unit at St. Joseph Mercy Hospital that is being run by faculty from our Geriatric and Palliative Medicine Division (page 62). We have continued to develop important programs such as Transcatheter Aortic Valve Replacements in the Division of Cardiovascular Medicine (see page 78). We are also undertaking several new initiatives to address the future challenges of primary care (page 66).

CLINICAL EXCELLENCE SOCIETY
The Department of Internal Medicine’s Clinical Excellence Society (page 64) inaugurated its first group in 2013. Fourteen new members will be joining them in 2014. We are the only department at U-M to provide this type of recognition for outstanding faculty clinicians.

A HISTORIC PERSPECTIVE
As we approach the bicentennial of the University of Michigan, we have started reflecting back on our accomplishments of the past. In this report, you will see some of them highlighted in our “Tradition of Excellence” features.

The U-M Department of Internal Medicine is a powerhouse for clinical care, research, and education. As healthcare changes around us, we are finding new and better ways to deliver excellent care and develop the next generation of “leaders and best.” It’s going to take fantastic minds, clinical abilities and appropriate facilities to continue to enhance quality of care while keeping costs down and handling increasing volumes. Many of the stories in this year’s report describe how we’re preparing for the future, developing new paths, promoting collaboration and evaluating processes to provide patient care that continues to go above and beyond.
We experienced a slight decrease in the growth of our clinical programs in 2013. Our amount of ambulatory care and specialty care visits both on- and off-site were lower than previous years due to the adjustment period required for our new electronic medical records system. Our outpatient facilities in Ann Arbor (Briarwood and Domino’s Farms) and Livonia and Brighton continue to perform well, our new efforts to establish facilities in the Northville area are near completion. In addition, we have been implementing and exploring several other approaches that will enable us to meet the rapidly increasing demand for patient care.

**CONTINUED EXPANSION**

The construction of a new $39 million health center in Northville Township, at the intersection of Seven Mile Road and Haggerty Road, near our existing Livonia Center for Specialty Care, is running on schedule. This facility will include 100,000 square feet of clinical and diagnostic space dedicated to caring for adults and children. We are also planning to invest in expanding and renovating our Brighton and West Ann Arbor clinics soon.

**Hospital Admissions**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations Cases</td>
<td>15,441</td>
<td>15,923</td>
<td>16,320</td>
<td>16,353</td>
<td>15,976</td>
</tr>
<tr>
<td>Discharges</td>
<td>+3,403</td>
<td>+2,516</td>
<td>+2,872</td>
<td>+3,743</td>
<td>+3,749</td>
</tr>
<tr>
<td></td>
<td>18,904</td>
<td>18,439</td>
<td>19,192</td>
<td>20,096</td>
<td>19,725</td>
</tr>
</tbody>
</table>
Our efforts to renovate, reorganize and revitalize Taubman Center after the outpatient clinics for women, newborns, and children moved to the new C.S. Mott Children’s Hospital and Von Voigtlander Women’s Hospital were completed this year. Nearly 30,000 square feet of space was transformed to better serve our patients (page 58). This was a stellar effort made possible by our department project planning team and the flexibility and cooperation of faculty and staff. The Transplant Center also allowed us to use their space during this transition. As a result, we can proudly report that not one day of clinic was missed during the entire 13-month renovation period.

**MI-CHART IMPLEMENTATION**
We are still adjusting and integrating Mi-Chart, our electronic medical records system, at UMHS. It is being introduced into our inpatient areas in June 2014. Once established and fully integrated into our system this new approach is expected to help improve overall processes and streamline our workflow.

**REORGANIZED AMBULATORY CARE UNITS**
We also reorganized our ambulatory care units so each specialty clinic is more linked and integrated with its own division in 2013 and also decentralized call operations. Both of these changes have made our units more customer-friendly and more efficient overall. This has resulted in increased satisfaction among the units, patients and first-time callers.

The Department of Internal Medicine’s deep commitment to patient care excellence is demonstrated through our many thoughtful efforts to evaluate, transform and innovate our clinical programs — helping them to stand out as “leaders and best” in Michigan and the nation.
The total number of Department of Internal Medicine faculty remained relatively stable during 2013 with the balance shifting slightly toward a higher percentage of clinical faculty. The chart below breaks down that growth by year and by faculty type.

**FACULTY PROMOTIONS**

Our department had a record number of promotions in 2013. Out of our more than 680 faculty — 61 received promotions that became effective September 1, 2013. The large number reflects the high level of academic achievement of our faculty and the recognition they receive for it. The high success rate of our candidates for promotion is also a direct effect of the skill and dedication of the staff in our faculty affairs office who coordinate all of the materials sent to the Dean and the Provost.

**RECRUITMENT AND RETENTION**

The recruitment and retention of a diverse
faculty continues to be a priority of the Department of Internal Medicine. We are working with several initiatives that develop strategies to recruit the best faculty candidates from all demographic groups.

One of them is the Committee on Strategies and Tactics for Recruiting to Improve Diversity and Excellence (STRIDE) offered through the university’s ADVANCE Program. STRIDE provides information and advice about practices that will maximize the likelihood that diverse, well-qualified candidates for faculty positions will be identified, and, if selected for offers, recruited, retained, and promoted at the University of Michigan. Originally designed for use in faculty recruitment, our department has also begun using these practices during the resident and fellow selection process as well.

LEADERSHIP TRAINING
The U-M Medical School and Health System Human Resources have recently partnered with Linkage, Inc. to offer the Linkage Leadership Institute. This world-class program includes interactive and aligned development programs, leveraging a dynamic mix of concepts, activities, practical tools, self-assessments, case studies and team learning. It is designed for senior leadership such as division chiefs, section heads, program or medical directors and chairs. To date, 20 faculty leaders from the Department of Internal Medicine have participated in these workshops.

U-M'S NEW PRESIDENT
In July 2014, Mark S. Schlissel, MD, PhD, will begin serving as the 14th president of the University of Michigan. He is the first medical doctor to lead the university and will hold appointments in the Departments of Internal Medicine and Microbiology & Immunology.

ASSOCIATE CHAIR FOR QUALITY AND INNOVATION
The Department of Internal Medicine has created a new leadership position of Associate Chair for Quality and Innovation. The development of this new role demonstrates the commitment of our department to find new and better ways to employ our collective talents to optimize all aspects of medical care.

This year, our annual report is highlighting “excellence” in the Department of Internal Medicine. Throughout these pages you will see this excellence is manifested in our faculty in many ways — through teaching, research and patient care. You will also see it reflected in the number of individuals who have been inducted into honorary societies (page 84) and received awards. The esteem held for internal medicine at Michigan is driven by our faculty. It is our people, our intellectual capital, that truly brings this department and its excellence to life.
The VA Ann Arbor Healthcare System (VAAAHS) continued to experience a significant increase in both outpatient and inpatient activity in 2013. There was a 2 percent increase in total inpatients and an 8 percent increase in outpatient visits. Through numerous ongoing initiatives and efforts, we’ve been able to decrease our readmission rates and lengths of stay for patients this past year.

**FACILITY IMPROVEMENT UPDATES**

To improve the situation for short-term stays, an observation unit with eight beds opened in July 2012. Our new 28-bed telemetry unit opened on our 6th floor in fall 2013 (see photo at right). We also opened a new state-of-the-art emergency room that combines our urgent and emergency care into one. There are also plans to expand our hematology/oncology outpatient clinic.

**TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) PROGRAM**

We recently received approval to implement a TAVR Program at VAAAHS. It is being led by Paul Michael Grossman, MD, an associate professor from the Division of Cardiovascular Medicine and director of the cardiac catheterization laboratory at the VAAAHS. We are only the second VA site approved to offer this less-invasive option for patients with severe aortic stenosis.

**LUNG CANCER SCREENING PROJECT**

Two associate professors from the Division of Hematology/Oncology Nithya Ramnath, MD, and Kemp Cease, MD, MBA, have been awarded a Lung Cancer Screening Project at the VAAAHS. We are one of eight VAs chosen nationally to spearhead this three-year project. Its goal is to determine the impact of systematically implementing lung cancer screening in VHA facilities. The data generated will inform a national plan for implementation in VAs across the U.S.

**VA INITIATIVES**

Our Specialty Care Access Network—Extension of Community Healthcare Outcomes (SCAN-ECHO) program continues to expand. Directed
by Grace Su, MD, a professor from the Division of Gastroenterology, it is now leading the nation in the number of veteran patients with liver disease served. Using telehealth video technology, VA primary care providers can evaluate and treat veterans in rural and underserved areas — without the cost and inconvenience of the patient traveling to Ann Arbor. We recently saw our 400th patient in the VA Liver Clinic. Other SCAN-ECHO clinics offered now include cardiology, endocrinology, endoscopy, nephrology and IBD.

**NEW FACULTY**

Greg Clines, MD, PhD, has joined the Metabolism, Endocrinology & Diabetes Division as an assistant professor. Dr. Clines’ primary research interest is in the endocrinology of bone metastasis. His research lab is located at the VA. He is launching a metabolic bone disease clinical practice at U-M.

**CENTER OF INNOVATION**

VAAAHS’s Center for Clinical Management Research which just celebrated its 35th year and is led by Eve Kerr, MD, MPH, a professor from the Division of General Medicine, was named one of 19 new VA Centers of Innovation (COINs) by VA’s Office of Research and Development.

The purpose of a VA COIN is to foster more timely and relevant research to address the needs of key stakeholders, including patients and providers, as well as the leaders and managers of healthcare systems. This unique approach to research requires effective partnerships with these stakeholders to ensure the research addresses the most critical questions and has the greatest possible impact on healthcare practices, VHA policies, and most importantly, healthcare quality and outcomes for veterans.

After 18 years as Associate Chair for VA Programs and 28 years with the U-M Department of Internal Medicine and Division of Gastroenterology, Richard H. Moseley, MD is retiring from the VA in mid-May 2014. He will be a professor emeritus at U-M and is joining a private gastroenterology practice in Boulder, Colo.

As part of the nation’s largest integrated health care delivery, the VAAAHS continues to improve our facilities and find new and better ways to meet veteran’s health care needs. While there are a lot of unknowns facing the future of healthcare, our dedicated faculty and staff members are well-prepared for the future and taking research innovation and internal collaboration to new levels.
While the cuts in federal research funding have had a tremendous impact on research across the country, the Department of Internal Medicine is continuing to support and inspire basic and translational research excellence. The department has made an unprecedented commitment to bridge research funding if faculty grants lapse. This program has been critical in maintaining research laboratories within the department. The department has also partnered with the medical school and the central campus in several new research initiatives:

**FAST FORWARD**
The University of Michigan Health System’s (UMHS) Strategic Research Initiative is backed by a long-term commitment of more than $100 million from the U-M Medical School. This initiative was designed to leverage existing areas of research strength to advance the research mission of UMHS by fostering innovative, ground-breaking science. The Department of Internal Medicine is an important partner in this initiative.

A program known as FastForward was initiated as part of the Strategic Research Initiative. This past year, the Host Microbiome Initiative was selected by the program to proceed with its plans to build research infrastructure for microbiome research at U-M. This initiative is led by Vince Young, MD, PhD, from the Infectious Diseases Division of Internal Medicine and Harry Mobley, chairman of the Department of Microbiology & Immunology.

The Host Microbiome Initiative is building on the existing strengths at U-M in the areas of microbial pathogenesis and microbiome research. It currently has more than 50 faculty members from 12 departments participating in microbial research in human health. The department of Internal Medicine is the largest participant among departments and has made significant financial commitments to this initiative.

Another project, the Protein Folding Diseases (PFD) Initiative, was also selected by FastForward. This group is connecting diverse campus-wide expertise on disorders of abnormal protein accumulation and perturbations in “protein quality control.”
Faculty participants include Peter Arvan, MD, PhD, from the Division of Metabolism, Endocrinology & Diabetes.

A better understanding of disease mechanisms and more effective therapies is needed for nearly all PFD disorders. The programs developed by the PFD Initiative will accelerate the path to new mechanistic insights and improved treatments for these diseases.

**U-M MTRAC FOR LIFE SCIENCES**

The U-M Medical School, the Office of Technology Transfer, and the Office of the Vice President for Research announced in February 2013 that the Michigan Economic Development Corporation awarded $2.4 million to the Medical School to help fund a U-M Michigan Translational Research and Commercialization for Life Sciences Program (U-M MTRAC).

Three projects developed by Department of Internal Medicine faculty were approved for MTRAC funding and the department participates by cost sharing with the medical school and central campus in funding these approved projects.

**MCUBED**

MCubed, a two-year seed-funding program U-M created to empower interdisciplinary teams of faculty to pursue new initiatives, funded 42 projects from the Department of Internal Medicine in 2013. This program is helping to minimize the time between idea conception and successful research results by providing startup funds for novel, high-risk and transformative research projects.

During this difficult funding environment, the Department of Internal Medicine is making significant investments in research and promoting innovative new approaches to collaboration with other areas of the university allowing our basic and translational research programs to continue to make important breakthroughs in patient care.
The Department of Internal Medicine’s clinical research programs continue to flourish and improve patient care around the world. We have been finding new ways to work both smarter and better at home while our collaborations with China through the Joint Institute are starting to pay off through increased recognition and funding.

**CENTRAL IRB APPROVALS**
Some exciting news from this past year is that U-M clinical researchers can now use central institutional review boards (IRB) for industry sponsored clinical trials. This approach is more efficient and will help our faculty to be more competitive and provide our patients with more opportunities and access to promising new treatments.

**MBECT PLATFORM INTRODUCED**
The Michigan Budget Enrollment Calendar Tool was upgraded at the U-M Medical School to provide research study teams with one point of data entry for building a clinical research budget, billing calendar, Michigan Clinical Research Unit schedule of events, and for submitting and tracking subject enrollment. Now that this system is integrated into MiChart, our electronic health record system, it is starting to help minimize billing errors and allow research teams to track milestones and payments.

**JOINT INSTITUTE UPDATES**
The Joint Institute for Clinical and Translational Research (JI), the University of Michigan Health System’s partnership with the Peking University Health Science Center (PUHSC) in Beijing, China, held its Third Annual Symposium in Beijing in fall 2013. Since its launch in 2010, the JI has made many accomplishments in just three short years:
- Six projects are actively enrolling patients; ~9,000 patients enrolled to date
- Six peer-reviewed articles have been published
- Two external grants have been secured
- Six new projects were awarded in September 2013, expanding the JI research projects to cardiac surgery, neurology, radiology, and renal disease
- Training & exchange programs have been established and are enjoying success: Two fellows, funded by the Fogarty NIH Global Health Research Training Grant, have...
been trained at PUHSC; more than 30 MD students, residents/fellows, scholars/faculty have been cross-trained at the two institutions

**FUNDING FOR JI PROJECTS**

The JI was created to provide an important springboard for new collaborations and projects to eventually get external funding. This has recently paid off for two of our projects so far:

Through an investigator-initiated grant funded by the Collaborative Science Research & Operations, Global Development & Medical Affairs Division of the Bristol-Myers Squibb Company, my colleague Professor Wei Lai, MD, PhD, and I were recently awarded $1.46 million in support to continue our Hepatitis C Virus project.

A one-year pilot study led by Margaret Gyetko, MD, from the Division of Pulmonary and Critical Care Medicine exploring how the respiratory microbiome is affected by known contributors to chronic obstructive pulmonary disease has received $600,000 from the National Heart, Lung and Blood Institute. It comes as a direct result of work that began in 2010 through the JI.

The Department of Internal Medicine’s clinical research programs continued to make great advances in 2013. Streamlining the approval process, opening up new sources of funding, and establishing new partnerships enable our faculty to bring new treatments and new answers to our patients faster.

![Margaret Gyetko, MD (right) and Bei He, MD, are leading a multi-country microbiome study through the JI.](image)
DEPARTMENT OF INTERNAL MEDICINE DIVISION CHIEFS

Front row (left to right): James Baldwin, MD (Allergy & Clinical Immunology Interim Chief); David Fox, MD (Rheumatology); David Pinsky, MD (Cardiovascular Medicine); Laurence McMahon, Jr., MD, MPH (General Medicine); Powel Kazanjian, MD (Infectious Diseases)

Back row (left to right): Raymond Yung, MB, ChB (Geriatric & Palliative Medicine); Peter Arvan, MD, PhD (Metabolism, Endocrinology & Diabetes); Chung Owyang, MD (Gastroenterology); Theodore Standiford, MD (Pulmonary & Critical Care Medicine Interim Chief); John Carethers, MD (Chair of Internal Medicine); Eric Fearon, MD, PhD (Molecular Medicine & Genetics); Kathleen Cooney, MD (Hematology & Oncology); and Frank Brosius III, MD (Nephrology)
DEPARTMENT OF INTERNAL MEDICINE ASSOCIATE CHAIRS

Left to right: Benjamin L. Margolis, MD (Basic & Translational Research); Timothy J. Laing, MD (Clinical Programs); Cyril Grum, MD (Undergraduate Medical Education); John Del Valle, MD (Graduate Medical Education); John Carethers, MD (Chair of Internal Medicine); Richard H. Simon, MD (Faculty Affairs); Richard H. Moseley, MD (VA Programs); Anna S. F. Lok, MBBS, MD (Clinical Research); and Musty Habhab (Chief Department Administrator)
Back row (left to right): John Carethers, MD, Chair of Internal Medicine; John Coatney, MD; and James Reinhart, MD.
Front row (left to right): Melissa Roberts, MD; Jamie Votava, MD; and Rajesh Patel, MD, MPH.
2013 DEPARTMENT OF INTERNAL MEDICINE AWARDS

THE DR. JACOB P. DEERHAKE COMMUNITY SERVICE AWARD
Jeanne Rittschof, MD

THE H. MARVIN POLLARD AWARD FOR OUTSTANDING TEACHING OF RESIDENTS
Michael Lukela, MD

THE EXCELLENCE IN CONTINUITY GENERAL INTERNAL MEDICINE TEACHING AWARD
Jennifer Nastelin, MD

THE JOHN G. FROHNA AWARD FOR OUTSTANDING TEACHING IN MEDICINE-PEDIATRICS
Jason Kahn, MD

THE JEROME W. CONN AWARD FOR EXCELLENCE IN RESEARCH
Jack Iwashyna, MD

THE PAUL DE KRUIF LIFETIME ACHIEVEMENT AWARD
Timothy Nostrant, MD

THE CHAIRMAN’S AWARD FOR OUTSTANDING SERVICE
David Pinsky, MD

THE RICHARD JUDGE AWARD FOR EXCELLENCE IN MEDICAL STUDENT TEACHING
Anthony Courey, MD

SPECIAL RECOGNITION FOR CONTRIBUTIONS TO THE MEDICAL STUDENT TEACHING PROGRAM AWARD
Andrew Odden, MD

SPECIAL RECOGNITION FOR CONTRIBUTIONS TO THE HOUSE OFFICER TEACHING PROGRAM AWARD
Hari Conjeevaram, MD
EDUCATION
PREPARING STUDENTS TO LEAD IN A CHANGING HEALTH CARE ENVIRONMENT
U-M MEDICAL SCHOOL IS TRANSFORMING THE TRAINING OF TOMORROW’S DOCTORS

When the University of Michigan Medical School (UMMS) was founded in 1850 it was immediately considered a leader in American academic medicine. U-M was the very first medical school to build a university hospital for physician instruction. It was also one of the first schools to change the role of student from passive observer to active participant through lab instructions and clerkships. Now, the school is taking those efforts to a new level, after being awarded a $1.1 million grant from the American Medical Association (AMA).

The AMA launched the “Accelerating Change in Medical Education” competition in 2013 to find new ways to bridge the growing gap between the way physicians are trained and the future needs of the health care system. In an outstanding show of interest, 82 percent of the nation’s 141 accredited medical schools submitted proposals for these grants — a strong sign that medical schools are eager to implement the transformative changes needed to respond to the evolving medical environment.

UMMS was one of only 11 medical schools selected as winners by the AMA and plans on using the funds to create a more flexible curriculum for medical students that will prepare them to lead change in health care in the dynamic global environment,” explains Cyril Grum, MD, the Department of Internal Medicine’s senior associate chair for undergraduate medical programs.

The resulting new curriculum will connect students directly with U-M’s clinical settings from the beginning of their training. There will be a focus on the development of leadership skills and professional identity, with the opportunity to unify the learning that happens in both medical school and residency training.

As UMMS leaders, including many from the Department of Internal Medicine such as UMMS Dean James Woolliscroft, MD, Joseph Kolars, MD, the senior associate dean for education and global initiatives, and Rajesh Mangrulkar, MD, the associate dean...
for medical student education, develop and launch the new curriculum, they will take part in an AMA-led consortium of the other funded medical schools to ensure that best practices and innovations can be shared.

“We need to bring medical education into the 21st century and directly redesign education to address the needs that our patients and their communities express. This will involve building knowledge and skills in data-driven, team-based health care, grounded in science and quality, and informed by ethical, social and patient-centric factors,” says Mangrulkar, who is the principal investigator on the proposal. “Our new curriculum will ensure we produce doctors who will be ready to lead changes in different aspects of health care that will have an impact on patients and their communities.”

A FLEXIBLE APPROACH
Over the next five years, as the curricular model is designed and phased in, the U-M medical student learning experience will become increasingly flexible, competency-based and oriented to the student’s interests, learning styles and abilities. Students will progress through aspects of the program at different rates, allowing them to master one phase before proceeding to the next.

A critical component of the curriculum will be the creation of the "M-Home," a learning community that each student will be assigned to for his or her entire medical school career, connecting them to a team of faculty mentors, advisors and clinical care settings that will foster their professional development.

This new curriculum will also expose learners to various specialties within medicine earlier, so they can make more informed choices about residency paths and other training or research paths they might wish to explore.

“Providing more flexibility and clinical experiences will help each student to develop their full potential and interests,” says Grum.

The proposal provides students the opportunity to develop leadership and change management skills, applying them in critical fields such as Quality and Safety, Global Health and Health Disparities, and Bioethics.

The new curriculum will also integrate the science and clinical practice portions of training during the first two years of medical school, far earlier than is done currently. In addition, the program will incorporate medical students into the inter-professional care teams at the U-M Hospitals & Health Centers and the VA Ann Arbor Healthcare System.

Central to the flexibility of the curriculum will be the measurement and tracking of achievement of medical student milestones through outcomes assessment, important both for U-M and other schools that might wish to emulate the approach. The AMA hopes by the end of this five-year initiative that these undergraduate medical education improvements will have been tested, refined and adopted as mainstream options and will enable the next generation of physicians to maintain the tradition of professional and clinical excellence within the health care system of the future.
At the beginning of the twentieth century, the U-M Medical School led efforts to revise and improve medical curricula by doubling the length of the program for the MD degree and by integrating clinical rotations into every student’s course of study.

In the 1950s through the 1960s, there were sweeping changes to U-M’s medical curriculum. Students now had early clinical contact with patients and were introduced to an interdepartmental course in the neurosciences.

The late 1960s was an era of increased clinical training in the first two predominantly basic science years of medical school. The U-M, along with many medical schools across the country, adopted an interdepartmental Introduction to Clinical Medicine course that would remain a staple of the first two years. U-M also introduced senior year subinternships, which are still part of the advanced clinical curriculum.

U-M also pioneered one of the first comprehensive clinical skills examinations, designed to ensure that students were not only knowledgeable, but could also apply their knowledge and skills to patient care settings on day one of their internship. This examination format has been adopted by nearly all schools and is now a centerpiece for the national board examinations for all U.S. senior medical students.
The U-M Medical School honored some of its most-esteemed educators with induction into the League of Educational Excellence — established in 2013 to celebrate our faculty who have a passion for sharing their extensive knowledge through the instruction of students in classrooms, laboratories, and hospitals and health centers.

Many of the nearly 100 members of the first league class have been lauded previously for their teaching as recipients of the Kaiser-Permanente Awards for Excellence in Teaching or the Lifetime Achievement Award in Medical Education through the Dean’s Awards Program; department chairs nominated others. All inductees received a special medallion commemorating their membership in the inaugural class.

Please join us in congratulating the first internal medicine faculty members inducted into the League of Educational Excellence — a group committed to preparing the next generation of Michigan physicians and scientists.

Sandro K. Cinti, MD  
John Del Valle, MD  
Kim A. Eagle, MD  
N. Cary Engleberg, MD, DTM&H  
Paul L. Fine, MD  
Roger J. Grekin, MD  
Cyril M. Grum, MD  
Carol A. Kauffman, MD  
Arno K. Kumagai, MD  
Robert W. Lash, MD  
Mark McQuillan, MD  
Gilbert S. Omenn, MD, PhD  
Sanjay K. Saint, MD, MPH  
Michael J. Shea, MD  
Thomas H. Sisson, MD  
Rebecca W. Van Dyke, MD
2013 EDUCATION + TEACHING AWARDS

STUDENT AWARDS
William Dodd Robinson Award
Owen Albin
Eli G. Rochelson Memorial Award
Laura Phelps

FACULTY AND HOUSE OFFICER TEACHING AWARDS
Galens Medical Society Bronze Beeper Awards
Joshua Levenson, MD
Special Recognition for Contributions to the Medical Student Teaching Program
Andrew Odden, MD
Special Recognition for Contributions to the House Officer Teaching Program
Hari Conjeevaram, MD
Medical School Community Service Award
Robert C. Hyzy, MD

DEPARTMENT OF INTERNAL MEDICINE SENIOR SCHOLARSHIPS
The Department of Internal Medicine Senior Scholarship honors senior medical students whose academic achievement epitomizes the tradition of excellence in internal medicine, encourages students to pursue their dreams by lessening the financial constraints of their chosen path in internal medicine, and honors the faculty who train them. These scholarships are possible due to the contributions of faculty and are based solely on academic achievement. This was a banner year for students going into internal medicine with a record number of scholarships ($7,000 each) being given.

2013 SENIOR SCHOLARSHIP RECIPIENTS
Owen Albin
Peter Bosch
Jessica Golbus
Corey Lager
Kathleen Murphy
Claire Northway
Laura Phelps

James Woolliscroft, MD, Dean
Margaret Gyetko, MD, Senior Associate Dean for Faculty and Faculty Development
Joseph Kolars, MD, Senior Associate Dean for Education and Global Initiatives
David A. Spahlinger, MD, Senior Associate Dean for Clinical Affairs
Rajesh Mangrulkar, MD, Associate Dean for Medical Student Education
Steven Gay, MD, MS, Assistant Dean for Admissions
Monica Lypson, MD, Assistant Dean for Graduate Medical Education
Eric Young, MD, Assistant Dean for VAMC
Roger Grekin, MD, Curriculum Director for the first two years
Cyril Grum, MD, Curriculum Director for third and fourth years
Robert Lash, MD, Director, Clinical Foundations of Medicine
Arno Kumagai, MD, Director, Social and Behavioral Issues in Medicine
Seetha Monrad, MD, Director, Feedback on Clinical Skills
This past year was marked by the continued strong growth and caliber of internal medicine residency candidates and new opportunities.

The Department of Internal Medicine Residency Program received a total of 2,919 medicine and 306 combined medicine-pediatrics applications, an increase of 303 from last interview season. “Normally, we experience a growth of 100-150 applications each year. To see that it more than doubled in 2013 shows the extremely competitive demand for our program, an increase in interest in internal medicine and the national shortage of residency spots due to the increase in new medical schools may in part explain the growth,” explains John Del Valle, MD, the Department of Internal Medicine’s senior associate chair for graduate medical education and the director of the residency program.

Candidate applications were reviewed by the program directors. A total of 518 medicine and 101 medicine-pediatrics candidates were extended invitations to interview with the

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Medicine-Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Applications</td>
<td>Invited to Interview</td>
</tr>
<tr>
<td>2,919</td>
<td>306</td>
</tr>
<tr>
<td>518</td>
<td>101</td>
</tr>
<tr>
<td>409</td>
<td>79</td>
</tr>
</tbody>
</table>

John Del Valle, MD
program on 16 different recruitment days. In addition to the program directors, more than 200 teaching faculty interviewed 409 medicine and 79 medicine-pediatrics candidates during this time.

All of this led to the selection of 42 new medicine residents and eight new medicine-pediatrics residents who were finally revealed on Match Day in March 2013.

**NEW PRIMARY CARE TRACK**

To help meet the nation’s growing need for primary care physicians, the Department of Internal Medicine Residency Program has initiated a primary care track to allow residents even more options as they solidify their career paths. This new track, which begins in July 2014, is funded by U-M Hospital and adds two new positions to the program increasing the total number of medicine residents to 44. It will focus on providing expanded exposure to ambulatory care rotations and interactions with primary care mentors. Residents will participate in multiple dedicated month-long continuity/ambulatory clinic rotations, and get the opportunity to experience primary care in multiple settings. There will be a focus on the principles of the patient-centered medical home and developing a portfolio of ambulatory care experiences in multiple areas such as women’s health and the musculoskeletal system.

**NEW ROLES**

Associate Residency Program Director Vikas Parekh, MD took on the new role of UMHS medical director for care management and clinical effectiveness on November 1st, 2013. He is gradually phasing out of his role with the residency program through June 2014. In his new role, Dr. Parekh is providing a physician’s voice to the hospital’s reorganization of discharge planning, social work and related services to improve care coordination and transitions of care in the hospital. In addition, he will also focus on improving the efficiency and effectiveness of patient care processes in the inpatient setting to ensure the provision of high value care to all our patients.

Sarah Hartley, MD has joined the residency program team as one of the assistant program directors. She is recognized as an outstanding hospitalist as well as a superb educator in both undergraduate and graduate medical education. Sarah now oversees the inpatient component of the Department of Internal Medicine Residency Program.

**GLOBAL FOCUS**

Dr. Del Valle is also leading an initiative for the U-M Medical School that is exploring global health training programs for U-M residents from all fields across the institution. The initiative, still in its early stages, is working toward building a curriculum and global health track for graduate medical education at U-M.
DEPARTMENT OF INTERNAL MEDICINE RESIDENCY PROGRAM LEADERSHIP TEAM

Back row, left to right:
Adam S. Tremblay, MD, Associate Program Director; Michael P. Lukela, MD, Program Director, Medicine-Pediatrics; John Del Valle, MD, Program Director, Senior Associate Chair, Graduate Medical Education; Vikas I. Parekh, MD, Associate Program Director; Subramaniam Pennathur, MD, Associate Program Director

Front row, left to right:
Namita Sachdev, MD, Associate Program Director, Medicine-Pediatrics; Sara Hartley, MD, Assistant Program Director; Cara A. McDonagh, MD, Assistant Program Director

Not pictured:
Anna M. Booher, MD, Assistant Program Director
When it comes to education and learning, it’s not only medical students and residents who have new things to discover. “Many of the best researchers, educators and clinicians often find themselves in new roles where they are tasked with administrative duties and leadership challenges that they’ve never faced before,” says Musty Habhab, the Department of Internal Medicine’s chief administrator.

“We had been using different leadership training programs at U-M and around the country. When Sonya Jacobs, director of faculty development for the medical school, Professor Michelle Heisler, MD, from the Division of General Medicine and I discovered the Linkage Leadership Institute, we were so impressed with their approach we knew we had to bring it to Michigan,” she explains.

The Medical School and Health System Human Resources began partnering with Linkage, Inc. in September 2012 to offer a Leadership Academy that focuses on the development of the individual senior leader. “In an effort to save time for our faculty, we decided to bring the Leadership Academy experiences to U-M twice-a-year instead of sending them to various trainings across the country. To date, there have been five cohorts with 20 faculty members and four administrators who have participated from our department, and more than 200 participants from across the Health System,” says Habhab.

The Medical School and Health System Human Resources began partnering with Linkage, Inc. in September 2012 to offer a Leadership Academy that focuses on the development of the individual senior leader. “In an effort to save time for our faculty, we decided to bring the Leadership Academy experiences to U-M twice-a-year instead of sending them to various trainings across the country. To date, there have been five cohorts with 20 faculty members and four administrators who have participated from our department, and more than 200 participants from across the Health System,” says Habhab.

The Leadership Academy program is an accelerated four-day immersive learning experience that draws on the leader’s 360 leadership and personality assessment data and includes one-on-one feedback/coaching. The curriculum focuses on three major themes; Leading Self, Leading Others and Leading for Results. The first two days concentrate on the self and teams and the last two days on the organization — specifically leading/managing change and driving results.

“The Leadership Academy has been extremely well received by our department participants. We strongly encourage our faculty and staff in leadership roles to take advantage of having this valuable resource right here at U-M,” she adds.
The Department of Internal Medicine Office of Development has started conducting philanthropy workshops for faculty to raise awareness about the importance of their role in fundraising efforts and to help them feel comfortable speaking with potential donors and grateful patients. As internal medicine physicians, faculty are well positioned to help these individuals understand why the department is worthy of their support and to explain some of our programs and funding priorities. In particular, they can talk knowledgeably about the vision for the department and their own area of expertise.

Some of the topics included in the workshops include how to discuss philanthropy with patients, explaining ways to give and when to make referrals to the development team.

In line with these efforts, Kim A. Eagle, MD, the Albion Walter Hewlett Professor of Internal Medicine, a director of the Frankel Cardiovascular Center, and professor of health management and policy in the School of Public Health, was recently named faculty director of philanthropy for the U-M Health System Office of Development.

In addition to his other clinical and leadership roles within UMHS, Dr. Eagle will be providing executive leadership for development training programs, conducting educational sessions for physicians and helping connect the development program with a broad spectrum of faculty as UMHS embarks on the Victors for Michigan campaign and the challenge of meeting its largest campaign goal in history.

Dr. Eagle’s passion and commitment to philanthropy have inspired significant philanthropic support for the health system. He has a long history of working with grateful patients, introducing them to programs and connecting them with their areas of interest.

**MEDICINE NEEDS VICTORS**

More than 46,000 donors have already contributed to the U-M Health System’s Victors for Michigan campaign to support medical research, patient care and medical education. With its $1 billion goal, it is the Health System’s most ambitious fundraising effort ever, and is a significant portion of the $4 billion university-wide Victors for Michigan fundraising campaign that kicked off in November 2013.
RESEARCH
Professor **David Ginsburg**, MD, from the Division of Molecular Medicine & Genetics, is passionate about his role as a physician-scientist. Board certified in internal medicine, clinical genetics, hematology and oncology, Ginsburg has spent his career uncovering the molecular underpinning of bleeding and clotting disorders. The progress he’s made wouldn’t have been possible, he says, without the interplay between his clinical and laboratory perspectives.

In many ways, the proof is in the pudding. His lab has identified the complex genetic contributors to several target diseases and has offered insight into how the environment can trigger their onset. And thanks to an eagerness to follow his research wherever it leads, Ginsburg has also shed light on a fundamental mechanism of protein transfer within cells and how bacteria become specialized to invade certain species.

His work has been well-recognized by his peers. He has been inducted into the National Academy of Sciences, held a prestigious National Institute of Health Merit Award, has received many of medicine’s highest honors and boasts not one, but two, named professorships at U-M. He’s the James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics, and the Warner-Lambert/Parke-Davis Professor of Medicine.

**THE GENETICS OF BLEEDING DISORDERS**

The central question for Ginsburg’s lab has always been how our bodies maintain the delicate balance between bleeding and clotting. He began his career by cloning the gene for von Willebrand factor (VWF), a blood-clotting protein that helps glue platelets to the wall of injured blood vessels to control bleeding.

Too little or dysfunctional VWF causes von Willebrand disease, the most common inherited bleeding disorder. The disease has several subtypes, and Ginsburg’s lab has identified mutations in the VWF gene responsible for many of them.
But what’s interesting from a genetic standpoint is how much variability there is in the severity of patients’ bleeding even when they share the same VWF gene mutation. It became clear to Ginsburg that this variability had to be the result of additional “modifier” genes. His lab has identified seven such genes in laboratory mice and is looking for the correlates in humans that affect disease severity and contribute to the wide variation in VWF levels among normal people.

Hoping to address this, Ginsburg launched a large human study. “We decided to look at young, healthy people because age-related factors like atherosclerosis can affect VWF,” says Ginsburg. “We wanted to avoid these confounders and have a direct look at the genes responsible for VWF levels. We also wanted to look at siblings since they share half their DNA. Where better to collect a large cohort of young, healthy volunteers than a place like U-M?”

Though they’re looking at many factors in these blood samples, in 2013 the group published their finding that an area on chromosome 2 accounted for almost 20 percent of the variation in VWF levels among the study participants. This finding, which was not detected in traditional genome-wide association studies, was made possible by exploring the sibling relationships.

The reason for this, Ginsburg suggests, is because there may be many variants of this gene, each of which is rare individually but sufficiently common in aggregate to be detected through a sibling study. His group is now sequencing the region in the hopes of zeroing in on the gene — and, in the process, enriching our understanding of the genetic basis of this disease.

**TOO MUCH CLOTTING**

The flip side of von Willebrand disease happens when instead of too little of this or other clotting factors, you get too much of a good thing. Ginsburg’s lab has helped shed light on this issue, too.

One example is thrombotic thrombocytopenic purpura (TTP), a disorder in which young, healthy people suddenly develop clots in blood vessels throughout the body. Mortality is about 20 percent with plasma exchange and was as high as 80 percent before the use of this treatment, often within two days of diagnosis.

Ginsburg was able to identify the gene involved in a rare inherited form of this condition and discovered a connection to his longtime study subject, VWF. “We found that all these patients had a mutation in the gene coding for the ADAMTS13 protein,” says Ginsburg. “ADAMTS13 is an enzyme that trims down VWF molecules so they’re not so big and sticky.” Without it, the oversized VWF causes platelets to plug vessels.

But as interesting as this finding was, Ginsburg’s team took it further. They were intrigued by the fact that, like von Willebrand disease, TTP could take a different trajectory in patients with the same mutation. “Some patients will have clotting problems from birth and require treatment right away,” says Ginsburg. “Others won’t have symptoms until they’re five or six. Still others make it into...”
their 30s before their first episode. There’s clearly more going on. Having a defect in this gene is necessary but not sufficient to get the disease.”

Modifier genes, he suspects, are one factor. But his group was also able to identify another. They showed in mice that a bacterial toxin, called shiga toxin, could initiate TTP in the context of this mutation. “If we give this toxin to mice who are missing ADAMTS13, we could immediately trigger what looked like TTP,” says Ginsburg. “It suggests that certain types of infections can help explain why people with this mutation get TTP at different times.”

**PATHOGEN SPECIFICITY**

Another bacteria-related project led Ginsburg’s team somewhat off their beaten track. In the process, it provided new insight into how bacteria become adapted to specific species — and how we might use this information to undermine them.

In this case, his lab was examining a protein produced by group A streptococci that can dissolve blood clots. “We’ve known since the ’50s that these bacteria, which cause strep throat and other infections, make an enzyme called streptokinase that breaks down blood clots,” says Ginsburg. “We also know that these bacteria are quite species-specific. The strep that affects humans only affects humans; the strep that affects horses only affects horses, and so on.” Through an elegant series of experiments, Ginsburg and his collaborators showed how these two bits of knowledge fit together.

When bacteria invade the body, one of our defenses is to form a clot, corralling the invaders at the site of infection. Bacteria are able to break free by using our bodies’ own anti-clotting mechanisms against us. Their streptokinase activates a clot-buster we produce naturally, called plasminogen. Ginsburg’s lab showed that this process is one reason bacteria are so adapted to their hosts. The streptokinase produced by bacteria that infect humans only activates human plasminogen; it doesn’t affect plasminogen from other species. “The bacteria developed this protein to help them invade,” says Ginsburg. “Over time, our plasminogen became resistant to it, so they mutated to keep up with us. This arms race is how you end up with bacteria that only infect humans,” he says.

By creating transgenic mice that expressed the gene for human plasminogen, Ginsburg’s lab got human-specific strains to infect the animals. They now hope to use these models to beat strep at its game. They’ve screened some 300,000 chemicals to identify those that can turn off the production of streptokinase. Several of these compounds succeeded in saving the mice from fatal infections. “One of the advantages to this approach — just shutting off genes bacteria use to attack us instead of actually killing them,” says Ginsburg, “is that it might not select as much for antibiotic resistance.”

**BREAKTHROUGHS IN PROTEIN TRANSPORT**

Ginsburg says he is continually amazed where following his research trail will lead. Looking into the cause of a puzzling bleeding disorder,
he was once again drawn into unexpected territory.

As its name implies, combined factor V and VIII deficiency is a disease in which two clotting proteins, factors V and VIII, are severely reduced in the bloodstream — to as little as 5 percent of normal. By studying families with the condition, Ginsburg’s lab was able to track down two genes responsible. They also discovered the genes’ unexpected function. Rather than impacting factors V or VIII directly, these genes coded for two proteins that, together, formed a complex called a “cargo receptor” that plays a key role in shuttling the factors out of the cell. When the shuttle was broken, so to speak, few of these factors reached the bloodstream, and patients had trouble clotting.

Ginsburg became fascinated by this protein-transport machinery and teamed up with Randy Schekman, PhD, a University of California, Berkeley cell biologist who won the 2013 Nobel Prize for defining the protein-transport machinery in yeast. The pair joined forces to examine the mammalian versions of these proteins, and Ginsburg’s lab developed knockout mouse models to test the effect of removing them.

The results were surprising. While blocking some of these proteins was incompatible with life, blocking one of them, SEC24A, created healthy animals with extremely low levels of cholesterol. These findings, published in eLife in 2013, suggest that SEC24A is a necessary part of the machinery that shuttles PCSK9, a key regulator of cholesterol, out of the cell. Without SEC24A, too little PCSK9 leaves the cell, and the mice have low cholesterol.

While drugs are now being formulated to inhibit PCSK9 directly, Ginsburg says that SEC24A might offer another target. Treatments like this could provide alternatives to statins for patients who cannot tolerate them or for whom they do not provide sufficient effect.
Understanding Microbes: An Ecological Approach
Thomas Schmidt, PhD

On first blush, it might seem odd to find Professor Thomas Schmidt, PhD, sharing an appointment between the Departments of Ecology & Evolutionary Biology and Internal Medicine. And his is, in fact, the first such appointment in the university’s history.

But his position is a superb opportunity, he says. It allows him to bring the same techniques he helped pioneer to study complex communities of microorganisms in settings as diverse as the open ocean, termite hindguts and terrestrial ecosystems to similarly complex communities on and within the human body.

In fact, Schmidt was recruited to U-M in 2013 from a 20-year run at Michigan State to lead the Center for Microbial Systems, a campus-wide effort to explore the interactions among bacteria, archaea, viruses, fungi and other microorganisms in these various environments. This center, though broader in scope, is complementary to the medical school’s Host Microbiome Initiative, which focuses specifically on the role the body’s microbial communities play in health and disease. He hopes the two groups will enrich each other, sharing tools, techniques, perspectives and insights.

His position is designed to help him bridge disciplines likely to be key players in this effort. His primary appointment blends the ecology perspective from the College of Literature, Science & the Arts with a medical orientation through the Division of Infectious Diseases. Schmidt also holds appointments in the Departments of Microbiology & Immunology and Civil & Environmental Engineering.

To understand the value he brings to the study of microbes generally and those involved in health specifically, it helps to trace his career, which mirrors the evolution of the microbial ecology field itself.

Community Matters
Ironically for someone who has built a career around the complex interrelationships among microbes, Schmidt began his graduate work bewitched by the simplicity of the single cell. “When I took my first microbiology course,
the world finally made sense to me,” says Schmidt. “People gravitate to different levels of complexity, and for me there seemed such a cohesiveness to life at the single-cell level.”

As he went on, that simplicity quickly broke down. “It was a bit of an illusion,” he says. “These single-cell organisms don’t live alone; they’re in communities. To understand them, you have to see them as members of more complex systems.”

Not only can microbes behave differently depending on who their neighbors are, the whole community’s function is dependent on its constituent parts. Microbial systems are known for producing “emergent properties” — properties that bubble up from the complex interactions among its members, which would be hard to predict by studying any of them in isolation. An analogy in the animal world is termites, says Schmidt. One wouldn’t predict the building of elaborate nests by examining individuals, but it happens naturally when they’re in a group.

DEVELOPING TOOLS
Though Schmidt was interested in these interactions, the tools to study them weren’t yet available. “Microbiology at the time meant isolating organisms from the environment and studying them in pure culture,” he says. So he contented himself with studying unusual microbes — luminescent bacteria and organisms that thrived on toxic gas.

Then, within a few years, Schmidt heard a microbial ecologist’s rallying cry. Professor Norman Pace, PhD, then at Indiana University, suggested that researchers need not limit themselves to studying organisms they could culture. Instead, they could go into the environment, grab a sample, and analyze the DNA to learn what was there.

Taking a second postdoc in Pace’s lab, Schmidt began working to help develop the technique. “Using a framework laid down by University of Illinois microbiologist Carl Woese, we zoomed in on a gene that every organism on earth has, which encodes for one of the ribosomal RNAs,” says Schmidt. “By comparing this sequence from different organisms, you can say how closely related two organisms are. Ultimately, we can map the biological universe.”

Among the challenges was getting the sequence for just that gene from every organism within a complex mixture. “I thought we could do it in six months,” says Schmidt. “It took three years.”

But the work paid off — the technique unveiled the diversity around them. They began identifying the genetic fingerprints of microbes never before cultured — many of which were found to be surprisingly common.

RESEARCH AGENDA
With this tool in hand, Schmidt set up his own lab around a broad question: What determines the structure and function of a microbial community? His current niche is looking at two angles of this. First, how do
oxygen levels shape a community’s structure and function? And, second, how does an environment selectively favor microbes built for either power or efficiency?

In terms of oxygen, Schmidt is interested in something researchers have rarely considered. "Microbiologists have traditionally studied microbes either under ambient atmosphere — 20 percent oxygen — or with absolutely no oxygen," he says. "I think the majority of microbes live somewhere in between."

He’s now looking at low oxygen levels in two environments: terrestrial ecosystems and the human gut.

Scientists have long considered the gut an oxygen-free environment. However, Schmidt points out, oxygen diffuses into the gastrointestinal tract, and microbes living against the lining are at constant low levels of it.

To study microbial communities under these conditions, Schmidt has set up a laboratory for advanced cultivation, which he’s making available to the broader U-M community. He’s also working with Associate Professor Thomas Wang, MD, PhD, from the Division of Gastroenterology and the Departments of Biomedical and Mechanical Engineering, to employ a specially equipped endoscope that can measure oxygen concentrations within the body.

Though he only arrived at U-M in mid-2013, Schmidt and his team have already shown that low-oxygen environments do shape the gut microbiome. "If we go to cultivate organisms from the GI tract," he says, "we recover species under low oxygen that we don’t get under the other two conditions."

His goal going forward is to test the idea that oxygen concentrations are key in determining which organisms are most competitive in a given environment. One hypothesis is that inflammation — as is present in disease, from cancer to inflammatory bowel disease — actually disturbs oxygen concentrations, allowing the growth of atypical microbes.

Schmidt’s second focus area is how microbes’ capacity for either power or efficiency determines their relative numbers in an environment. "For the human gut, pathogens are often the power organisms," says Schmidt. "They invade the system and grow explosively. Those that are more efficient in converting resources into progeny are probably the key players in a healthy microbiome. They likely help stabilize the community and resist invasion."

He’s recently found a genetic marker for power versus efficiency in the bacterial world. "We can now look at bacterial genomes and make a strong prediction as to whether these organisms will be most competitive under conditions where growth rate or efficiency is selected for," he says.

This is important because it provides clues as to the role newly identified organisms might play within a community. In addition,
by comparing the relative populations of organisms predisposed to one trait or the other, researchers can deduce the selective pressures at play in a particular environment. Through work like this, one can imagine puzzling out how things like diet, medication, stress, and disease might impact the gut’s microbiome and how we might better manage this critical microbial community.

**BROADER IMPACT**
The ability to work side by side with colleagues in the medical school to test his ideas in a host microbiome is part of the reason Schmidt decided to return to his undergraduate alma mater. He already had several collaborators at U-M, among them, Vincent Young, MD, PhD, associate professor in the Division of Infectious Diseases and the Department of Microbiology & Immunology. The two began working together while they were both at Michigan State — Schmidt instructing Young in his methods, and Young introducing Schmidt to his milieu, the gut.

While Young co-directs the Host Microbiome Initiative, Schmidt will spearhead the campus-wide Center for Microbial Systems. "The opportunity to do this pushed things over the top for me," says Schmidt.

To learn more about the Center for Microbial Systems, please see its website: microbe.med.umich.edu.

"Everything is in place here for a world-class center. There’s so much expertise. U-M did a cluster hire in microbial ecology not long ago that added six people to this pool — microbial ecologists in different departments across the university. We just needed someone to connect the people and resources. My unique appointment will help me do that.”
Battling Graft vs. Host Disease in Bone Marrow Transplant

Pavan Reddy, MD

Internal Medicine Professor Pavan Reddy, MD, got into studying graft vs. host disease (GVHD), a potentially life-threatening complication of bone marrow transplant, through a desire to “treat medicine’s hardest diseases.” He certainly hit the mark.

That’s because allogeneic bone marrow transplants — where blood stem cells are used from a genetically nonidentical donor — can be a double-edged sword. While a potent tool for treating cancers like leukemia and lymphoma, the treatment has a dark side. The same immune response that can be harnessed to attack patients’ cancer can turn on their healthy tissue, causing GVHD. In the early days, most transplant recipients died from this complication.

To address this, doctors began using steroids and other immune suppressors to reduce donor cells’ function post-transplant. While the drugs could reduce GVHD, they were a blunt instrument. Their help came at the cost of some of the transplant’s anti-cancer effects and left patients vulnerable to infection. In addition, nearly half of patients still suffer from some degree of GVHD.

Reddy has spent his career trying to disengage the good from the bad effects of bone marrow transplant. And in 2013, several seeds from his decade-long research program began to bear fruit. His lab and their collaborators have succeeded in bringing two promising treatments for GVHD into human trials and have identified two proteins in T cells that may one day offer novel targets for GVHD management.

A Three-pronged Research Approach Yields Hope for GVHD Prevention

Some of Reddy’s success must be attributed to his lab’s multi-level approach to the immunology of bone marrow transplantation. “We work at three levels,” says Reddy, “molecular, cellular, and translational. Our goal is to meld insights from the first two into patient therapies.”
Reddy is uniquely positioned to traverse these levels; he is the Moshe Talpaz MD Professor of Translational Oncology, the co-director of the hematologic malignancies and bone marrow transplant program at the U-M Comprehensive Cancer Center, and associate chief for basic research in the Division of Hematology/Oncology.

His first translational coup is a nearly perfect case study in how these three levels support one another. In this case, the drug availability came first.

“About 10 years ago, a drug came into play for treating certain types of cancer,” says Reddy. “It was a histone deacetylase, or HDAC, inhibitor. A collaborator from University of Colorado, Charles Dinarello, started working with it, not to treat cancer, but in an immunological context, and he asked if I wanted to see how it might regulate the immune response to bone marrow transplant.”

Reddy’s team tested this concept in mice and were surprised by what they found. They were able to mitigate GVHD after bone marrow transplant with very little effect on the anti-cancer response. Their next step was to puzzle out why this was so.

Fortunately, Reddy’s cellular-level work provided some leads as to where they might look for answers. While working on the basic immunology of bone marrow transplant, his lab was starting to get some insight into how the donor and recipient’s immune cells worked together to target cancer.

“We’d identified a type of cell from the patient’s immune system called CD8-positive dendritic cells that seemed to be important for presenting leukemia-specific proteins to the donor T cells after transplant,” says Reddy. “These cells seemed to have a more important role in turning on the anti-tumor effects than in turning on GVHD. This means that you could potentially get more good effects without aggravating the bad effects of the transplant.”

Having identified these host cells as potential players in disentangling GVHD from the transplants’ anti-cancer effects, Reddy decided to explore how HDAC inhibitors affected dendritic cells. What he found was that the drugs work by modifying a transcription factor, STAT3, which activates an enzyme, IDO, which has the effect of calming the dendritic cells — actually changing them from pro- to anti-inflammatory. “These drugs affect many cell types,” says Reddy, “but we were able to show one of the ways they were regulating immune response and reducing GVHD.”

Armed with both animal studies and this new mechanistic insight, Reddy formed a team, led on the clinical side by Sung Choi, MD, assistant professor of pediatrics, to test the drug in humans. The HDAC inhibitor vorinostat was already FDA-approved as a cancer treatment, so the team was able to move briskly into Phase 1 and 2 clinical trials, adding low doses of this drug to the standard post-transplant regimen. Their findings were encouraging.

“The trial showed that we could cut the incidence of GVHD in half. Compared with historical data where about 45 percent of patients ended up getting GVHD, we reduced it to 22 percent.”
“We completed the trial in 2013, and it turned out better than we anticipated,” says Reddy. “A lot of the things we found in the mice seemed to translate into humans. The trial showed that we could cut the incidence of GVHD in half. Compared with historical data where about 45 percent of patients ended up getting GVHD, we reduced it to 22 percent.”

He cautions that the controls in this study were historical; there hasn’t yet been a randomized Phase 3 trial. However, he says, it was gratifying to move from working out biochemical mechanisms in a dish to seeing a promising response in humans.

BASIC RESEARCH YIELDS NEW TARGETS
Another offshoot of Reddy’s molecular-level work may offer entirely new drug targets for GVHD. As his lab was trying to understand how dendritic cells turned on inflammation in a normal immune response, his team became interested in the role microRNAs played in this process. MicroRNAs don’t code for proteins; instead, they fine tune the expression of genes.

Using both bioinformatics and classical molecular biology experiments, Reddy’s team identified one microRNA, miR-142-3p, that regulates a key inflammatory cytokine in the dendritic cells’ immune response.

So Reddy wondered whether this microRNA might play a role in the immune response of T cells, as well. Looking at this led him to two novel proteins, which have never been shown to play a role within T cells, Wapal and Synj1.

Sure enough, when Reddy and his team blocked these proteins in mice, they reduced GVHD.

These are preliminary results, and as yet there are no known compounds that target these proteins, but the team is pressing ahead. They’ve made a knock-out mouse model for the microRNA to see if this will block T-cell production of Wapal, and they plan to study the consequences.

TACKLING RESISTANT GVHD
Reddy’s final advance for 2013 helps chip away at another major GVHD problem — namely, when it doesn’t respond to treatment. “There is a subset of patients who get what’s called steroid-refractory GVHD,” says Reddy. “Their GVHD doesn’t respond to even very high doses of steroid. It’s a serious issue; anywhere from 60 to 90 percent of these patients will die within six months.”

Reddy’s team is working to take advantage of an anti-inflammatory protein called alpha-1-antitrypsin, which occurs naturally in our plasma. “Whenever the body has to fight something off, you have this release of inflammatory cytokines,” says Reddy. “At the same time, the body releases alpha-1-antitrypsin to counterbalance this and prevent the inflammatory response from becoming too exuberant.”
Reddy’s lab had already looked in mice to see whether this protein could dampen the over-exuberant immune response that causes GVHD. It turns out, it did. Not only did more mice survive when given alpha-1-antitrypsin post-transplant, but the treatment seemed to increase the number of regulatory T cells, which appear to play a constructive role in the immune response, while reducing the number of pro-inflammatory effector T cells, a hallmark of GVHD.

Since alpha-1-antitrypsin is already used in humans for other conditions with minimal side effects, Reddy proposed building on his mouse studies with a human trial in steroid-refractory GVHD. Started last year under the clinical direction of Steven Goldstein, MD, associate professor in the Division of Hematology & Oncology, the study’s early results are encouraging. “We’ve treated three patients so far, and two of the three responded,” says Reddy. “It’s too early to say where it will go, but we are thrilled that it was well-tolerated, and we hope the responses pan out. There’s been no standard way to treat GVHD once it’s gone this far, so we’re pleased to have brought this trial forward.”

**SHARING THE CREDIT**

Though keenly aware of the challenges still ahead, Reddy is encouraged by these recent breakthroughs, and he’s eager to share the credit. This work is only possible, he says, with a great laboratory team and the collaboration of colleagues across the globe, around the country, and of course at U-M. Reddy’s research is routinely supported by several members of his division, including Research Investigator Yaping Sun, MD, PhD, and the cancer center’s clinical bone marrow transplant team: Steven Goldstein, MD; Professor Daniel Couriel, MD; and Assistant Professors Attaphol Pawarode, MD, John Magenau, MD, and Mary Riwes, DO.

“U-M has been a great place to work because it’s one of the few places that bring together both basic science and clinical depth. This is critical for what I do. Our lab does a fair amount of basic biology, but at the end of the day, I’m an MD, and I want to directly benefit patients. That requires translation, and translation requires good ideas, resources, terrific patient care, and terrific clinical research infrastructure — and that’s what Michigan and internal medicine offer.”
In her career as a GI researcher, Juanita L. Merchant, MD, PhD, the H. Marvin Pollard Professor of Gastrointestinal Sciences in the Division of Gastroenterology and Department of Molecular & Integrative Physiology, turned what was expected to be a lemon of a research project into lemonade and in the process shed light on the molecular underpinnings of conditions ranging from irritable bowel syndrome (IBS) to stomach cancer.

Merchant began her career with a postdoctoral project her mentor assigned but later confided he thought wouldn’t actually pan out. Not only did Merchant make it work, she parlayed it into a vigorous research program that’s been funded continuously by the National Institutes of Health (NIH) for more than two decades and now boasts an NIH Merit Award, given to researchers whose work is deemed “distinctly superior.”

The project explores gastrin, the hormone responsible for the release of stomach acid — the genes involved, how they’re regulated, and the role gastrin and related molecules play in normal GI function and disease.

**H. pylori & Stomach Cancer**

The work for which Merchant is perhaps best known is helping to clarify the mechanisms by which *Helicobacter pylori* infection causes stomach ulcers and cancer. Building on the discovery of this linkage by Nobel laureates Barry Marshall and Robin Warren, Merchant’s lab employs a combination of cell-culture and transgenic mouse models to tease out the molecular pathways responsible.

When she started her career, the prevailing belief was that *H. pylori* increased stomach acid and generated ulcers by destroying the cells that produced gastrin inhibitors. Merchant showed instead that the infection prompts the release of an inflammatory cytokine, interferon gamma. This cytokine, in turn, both stimulates gastrin production and prevents its inhibition, increasing stomach acid as a natural defense against the infection.

But this response also initiates a potentially dangerous cycle of inflammation. “It’s fine if we can treat *H. pylori* with antibiotics,”
says Merchant, “but there can be problems. Some people don’t tolerate them. There’s also antibiotic resistance. So our contribution is asking: Can we find other targets to prevent this chronic inflammation from triggering the cascade that eventually leads to cancer?”

The first step in this process is metaplasia. “This is where you have a normal cell in the wrong place, like an intestinal cell in the stomach,” says Merchant. It’s not a true cancer cell, but it’s a bad omen.

To find out what initiates this, Merchant teamed up colleagues Deborah Gumucio, PhD, the James Douglas Engel Collegiate Professor and interim chair of the Department of Cell & Developmental Biology, and Linda Samuelson, PhD, the John A. Williams Collegiate Professor of Gastrointestinal Physiology in the Division of Gastroenterology and the Department of Molecular & Integrative Physiology. Each is looking at aspects of cell-signaling pathways that appear to be important in the transition from chronic inflammation to metaplasia.

One of these is the Hedgehog pathway. Merchant showed in 2013 that blocking signaling downstream of this pathway could prevent metaplasia. She’s now looking at the molecular mechanisms at play. Gumucio has also been looking at this pathway, but with an emphasis on its role in the development and differentiation of GI tissues. And Samuelson is investigating a related pathway called Notch, including how it regulates stem cells in the stomach and how it cooperates with Hedgehog signaling in the development of stomach cancer.

Always eager to translate her findings into patients, in 2013 Merchant launched a project with a group in Spain with a large H. pylori-infected cohort. They aim to see whether a Hedgehog target her group has identified as a marker of the metaplastic transition in mice could also serve that function in humans, providing an early warning of impending stomach cancer.

SEROTONIN & IRRITABLE BOWEL
This general line of inquiry has taken Merchant in unexpected directions. One of these involves a zinc finger protein she cloned early on while investigating its role in gastrin gene expression. Looking at it more recently, her lab found that it regulates an enzyme that makes serotonin in the GI tract.

While tracing its binding site, Merchant was led to a piece of non-coding DNA called a single nucleotide polymorphism, or SNP (“snip”). SNPs often serve as biological markers of disease genes.

To determine the SNP’s relevance, Merchant partnered with colleagues from the University of California, Los Angeles and Washington University with a large cohort of IBS patients. They found that the SNP correlated with symptoms of diarrhea rather than constipation and that its prevalence varied by patients’ ethnicity.

Hoping to extend these insights into treatments, Merchant is working with two colleagues in her division, Assistant Professor Juanita L. Merchant, MD, PhD
Shanti Eswaran, MD, and Professor William Chey, MD, who are investigating a low-FODMAP (Fermentable, Oligo-, Di-, Mono-saccharides And Polyols) diet in the treatment of IBS. The diet reduces patients’ intake of gas-producing short-chain carbohydrates, and the team is eager to see if the SNP can predict which patients will respond to the diet.

**The Genetics of Gastrinoma**

The next project on Merchant’s docket focuses on gastrinoma, part of the family of neuroendocrine cancers that struck Apple co-founder Steve Jobs. “This cancer can show up in the islets of Langerhans within the pancreas or the upper part of your small intestine,” says Merchant. “It cranks out gastrin and can eventually metastasize. Through our work with gastrin, we think we’ve identified a combination of genetic changes that contribute to gastric carcinoids, one type of neuroendocrine tumor, and we hope to do the same for gastrinoma.” Given the recent attention to this class of tumor, interest in her findings is sure to be high.

Always eager to translate her findings into patients, in 2013 Merchant launched a project with a group in Spain with a large *H. pylori*-infected cohort. They aim to see whether a Hedgehog target her group has identified as a marker of the metaplastic transition in mice could also serve that function in humans, providing an early warning of impending stomach cancer.
WORKING TO BEAT PANCREATIC CANCER AT THE STARTING BLOCK
Andrew Rhim, MD

In the race against pancreatic cancer, Assistant Professor Andrew Rhim, MD, from the Division of Gastroenterology, hopes to dramatically tip the odds by changing our understanding of the rules.

Within three months of arriving at U-M in 2013, Rhim had already launched a clinical trial for the early detection of pancreatic cancer, and he hopes soon to do the same with a promising treatment.

He’s been able to make such strides against this formidable foe by questioning the fundamentals of how cancer works.

SIZING UP HIS OPPONENT
Rhim learned early how aggressive pancreatic cancer could be. As a third-year medical student, he was assigned a patient who died within three weeks of diagnosis. Rhim had spent many hours with this patient, and the experience affected him deeply. He decided then that he’d devote his career to beating this disease.

The reason pancreatic cancer is so deadly, he says, is that by the time it’s diagnosed, it’s metastasized throughout the body in 80 percent of patients. Their prognosis from here is poor; survival is on average only three to six months.

The pattern had him wondering if perhaps this cancer didn’t behave like others.

RETHINKING CANCER PROGRESSION
“For years, we’ve been taught that cancer progresses in a very organized manner,” says Rhim. “You have a cell that sustains mutations. It grows. It forms a tumor. Then this grows until it spits out cells that metastasize. In most cancers, this is true.”

But pancreatic cancer is different. Doctors find metastatic disease in patients even when their tumors are remarkably small. That left Rhim wondering: Might metastasis start earlier here?

A colony of pancreas cells grown from a single circulating pancreas cell from a genetically engineered mouse harboring an advanced precancerous lesion in the pancreas. Credit: Andrew D. Rhim M.D.
Fortunately, as he was ready to embark on this question, tools were available to help him answer it. Rhim began a postdoc in the lab of University of Pennsylvania GI researcher, Ben Stanger, MD, PhD, who allowed Rhim to develop mouse models to study the progression of pancreatic cancer. Engineered to express two of the most common genetic changes in the human disease, the mice were born normal, developed precancerous lesions within three months and had large tumors by six months.

Rhim genetically labeled all the mouse pancreas cells with a fluorescent green protein. This allowed him to identify if pancreas cells could be found in other parts of the body during various stages of the disease.

What he found surprised him. “At a stage when our pathologists say there is only precancerous disease, we found evidence of fluorescent cells leaving the pancreas.” The cells were behaving like cancer — moving through the bloodstream and into distant organs — long before they would appear cancerous in a biopsy or on a CT or MRI scan. At this same stage, with the aid of his genetic label, he also found cells within the pancreas that had become cancerous, even though they too would have evaded detection in a traditional biopsy.

Rhim began to wonder if he had the makings of an early-detection test.

**MOVING TO PATIENTS**

It is not an exaggeration to say that a reliable early-detection test for pancreatic cancer could be a game-changer. Most importantly, it has the potential to overturn the grim survival statistics for this disease, now a mere 6 percent at five years according to the National Cancer Institute. But it also has the potential to spare patients with precancerous lesions an impossible choice.

“Right now, we don’t have a good way of telling whether a patient with a precancerous cystic pancreas lesion will go on to develop cancer,” says Rhim. “The vast majority won’t, but some do. And by the time we know for sure, it’s often too late. There is a way to prevent these lesions from becoming cancer — surgical resection of the pancreas. But this complicated surgery puts patients at risk for lifelong malnutrition and diabetes. So we need to be sure which patients are at the highest risk for pancreatic cancer or risk subjecting many patients to an unnecessary, morbid procedure.”

Because of this, Rhim felt a tremendous urgency to test in humans whether the presence of pancreas cells in the blood could alert doctors to lesions that were destined to become tumors.

But to do this, he needed a way to find these cells. “These cells are very rare in the bloodstream — perhaps one in a billion,” says Rhim. “It’s an engineering feat to be able to capture them.” So he sought out an engineer at Cornell University, Brian Kirby, PhD, who’d developed a technology to do this.
The next step was to see if the test they developed would work. This is one of the key reasons Rhim came to Michigan.

“I knew Michigan had a great scientific atmosphere and reputation,” he says, “but to perform a clinical trial, you need more. You need large numbers of patients, the right infrastructure, and a collaborative atmosphere — and Michigan has all these. Our division and the cancer center make it easy to run these studies. A lot of people in the administration and in the clinics came together to get this trial started quickly. That’s exactly what I was looking for.”

Launched in 2013, the study is checking for circulating pancreas cells in three groups: healthy subjects; patients with advanced pancreatic cancer; and patients with precancerous pancreatic cystic lesions.

Their preliminary findings show promise. In the first group, they found no circulating blood cells and in the second, they found large numbers of circulating tumor cells — both of which were expected. In the third group, they found approximately 30 percent of subjects with detectable pancreas cells in the blood.

“This is interesting,” says Rhim, “because these are patients who would be told to go home because they don’t have cancer.”

The study will follow subjects over five years to see whether the presence of circulating pancreas cells accurately predicts the development of cancer.

TURNING TO TREATMENT

The only thing as good as catching this cancer early is offering better treatment. Rhim’s next step is to build on work he’s done with Marina Pasca di Magliano, PhD, assistant professor in the Departments of Surgery and Cell & Developmental Biology, which shows that blocking interleukin-6 in mice with precancerous lesions can arrest the development of pancreatic cancer.

The drug they used, an interleukin-6 antibody, is already FDA-approved for the treatment of rheumatoid arthritis. Rhim is now working with Distinguished Professor of Oncology in the Division of Hematology & Oncology and Director of the U-M Cancer Center Max Wicha, MD, who is developing this drug for breast cancer, in the hopes of testing it to prevent pancreatic cancer.

In the meantime, Rhim’s lab remains busy. While pursuing their basic science projects, they are working to sequence the circulating pancreas cells’ DNA, to develop another early-detection test based on circulating nucleic acids, and to explore methods for delivering anti-cancer drugs directly to pancreas tumors.

It’s clear that Rhim won’t rest until his breakthroughs are available to those who matter most. “I think we’ve made great progress on the knowledge front,” says Rhim, “but that’s not why I got into this. Our work is most valuable when it affects patient care.”

“At a stage when our pathologists say there is only precancerous disease, we found evidence of fluorescent cells leaving the pancreas,” says Rhim. The cells were behaving like cancer — moving through the bloodstream and into distant organs — long before they would appear cancerous in a biopsy or on a CT or MRI scan.
Reimagining Cancer Biomarkers
Muneesh Tewari, MD, PhD

The new Ray and Ruth Anderson-Laurence M. Sprague Memorial Research Professor in the Division of Hematology & Oncology, Muneesh Tewari, MD, PhD, is a man with a vision. Not content with having helped birth the field of blood-based microRNA biomarkers, he wants to transform the way we conceive of and use these indicators, and in the process make them better at predicting the course of human disease.

But before exploring this vision, it helps to know where he’s brought things thus far.

BirthinG a Field
It’s surprising in some ways to find Tewari a central figure in the microRNA (miRNA) field because, he points out, when he started his MD/PhD program at U-M in 1990, these molecules hadn’t even been discovered. By the time he finished in 1997, only one had been found — in a nematode. And when he started his own lab at Fred Hutchinson Cancer Center, Seattle was far from the field’s center of action.

It was during a postdoc at Harvard that these molecules first caught Tewari’s eye. While he was investigating protein networks, one of his collaborators was looking at this new class of RNA. MiRNAs are short, non-coding sequences that put the brakes on messenger RNA and prevent it from translating genes into proteins.

“Working on these molecules made sense to me,” says Tewari, “because they were actually regulating the proteins. It seemed like one miRNA could influence hundreds of genes, so I thought they could be central actors.”

He wanted to know how they functioned and, in particular, how their failure might spawn the unchecked cell growth characteristic of cancer.

He started his research program as the field was skyrocketing. “New miRNAs were being discovered all the time,” says Tewari, “and were being shown to be important in all kinds of areas — the immune system, cell proliferation, cell division, programmed cell death, blood vessel formation. There was interest in them as biomarkers in cancer tissue — for classifying cancers and determining prognosis. And people thought it would be possible to target miRNAs as therapies. It turns out there is now a miRNA-targeted drug for hepatitis C.”

During this time, Tewari taught himself all he could about the field and became Seattle’s resident expert. His lab made numerous contributions, from discovering new miRNAs to showing how they were regulated. Among their findings was the role these molecules play in a process called epithelial-to-mesenchymal transition that’s involved in cancer metastasis.

“But the thing that really broke new ground,” says Tewari, “was that I had this idea that miRNAs might be released from cancer cells and reach the blood or other fluids. I thought, maybe if they were stable outside cells, they might tell us about what was going on in a patient in a less invasive way.”

“As it turns out, expecting to find stable RNAs in the blood was not necessarily a reasonable
idea,” he says. “There’s this enzyme in the blood called ribonuclease that just chews up RNAs. So in general they’re very unstable. But I thought, let’s just see.”

So his group started looking for miRNAs in blood samples. Not only did they find large numbers of them, they also found that these molecules were incredibly stable. “You could leave a tube of plasma out on your desk for 24 hours, and nothing happened to them,” says Tewari.

His lab would soon figure out why. They identified two mechanisms protecting miRNAs in the bloodstream. Some were walled off in membrane-bound sacs called vesicles. More often, they were engulfed within Argonaute proteins, which shielded them from degradation.

In terms of cancer, Tewari’s lab also found in both animal models and patients that tumors were indeed releasing miRNAs into the bloodstream. So he began investigating their potential as biomarkers.

**MAKING PROGRESS**

Tewari began collaborating with groups working on various types of cancer, looking for miRNAs that might help detect the disease or predict treatment response, and they’ve made great progress. They’ve identified markers for ovarian and metastatic prostate cancer, and they’re working on one for kidney cancer. Tewari’s desire to expand his lab’s disease portfolio is one of the reasons he returned to U-M. “The Department of Internal Medicine here has such broad strengths, with research and clinical programs in every area — it’s like a candy store for collaboration,” he says.

Tewari’s lab is also helping the field overcome a key technical hurdle — making miRNA testing more consistent. “One of the things that has held this field back,” he says, “is there’s been too much variability in test results. We need to be able to say that if we measure miRNAs in blood samples at U-M and someone else does it at Stanford, we can compare the numbers directly. Even with our current gold-standard method, real-time PCR, we couldn’t reliably do that. There was too much day-to-day and institution-to-institution variation.”

So Tewari, who is deeply interested in technology and holds a joint appointment in the Department of Biomedical Engineering, set out to remedy this. In 2013, his group published a paper in *Nature Methods* showing that a new technology called droplet digital PCR could reduce the day-to-day variability in test results seven-fold. “We also showed in our prostate cancer and control specimens that if you use this approach, you could better classify patients and have fewer false positives and negatives,” he says.

While advances like these may help bring miRNA screening a step closer to the clinic, Tewari has his sights set even higher.

**A BROAD VISION**

The reason he chose to focus on miRNAs as biomarkers, says Tewari, is because having a minimally invasive way to detect cancer at its earliest stages could change the face of the disease.

“For a lot of cancers, if you detect them early enough, you can cure them surgically,” he says. “But you could also make an impact by better..."
“Disease is like a movie; it’s constantly unfolding. But with biomarkers, we generally take a snapshot. We use a value from a person at one point in time then compare that to a population. But in reality, we all have our own normal. So I thought: What would happen if you had more dynamic measurements where you wouldn’t use a population to define a normal range, but instead use a patient’s own history of biomarker measurements?”

Yet for all this promise and all the research advances, relatively few blood-based biomarkers ever reach the clinic. Tewari began to reflect on the reasons for this.

“One reason,” he says, “is that there are a lot of confounding factors when you move into real people. So many things can affect a disease and its associated biomarkers — things you’re exposed to, your lifestyle, medications, your metabolism, exercise, even your thoughts. We may think we have a blood test that can tell if someone has early cancer, but if we don’t realize that certain medications can increase this marker in the blood, we’ll have a lot of false positives. We need holistic data to tease out things that could be confounding the results.”

“The other thing we’re missing,” he says, “is dynamics. Disease is like a movie; it’s constantly unfolding. But with biomarkers, we generally take a snapshot. We use a value from a person at one point in time then compare that to a population. But in reality, we all have our own normal. So I thought: What would happen if you had more dynamic measurements where you wouldn’t use a population to define a normal range, but instead use a patient’s own history of biomarker measurements?”

His quest is for a more holistic, dynamic approach to biomarkers. He envisions things like at-home, finger-stick blood tests for circulating miRNAs that could not only be read by a cell phone but interpreted alongside data like how well a person is sleeping, their activity levels and their medications — much of this captured through wearable health technologies. This is what it will take, he says, to make these measures more personalized and meaningful.

It is this vision that ultimately brought Tewari back to Michigan. “I realized that doing this would require bringing together not just molecular biology and clinical oncology, but areas like bioengineering, tech transfer, bioinformatics, computer science, and health economics and policy,” he says. “Michigan has excellence across all these areas under one roof with people who are just itching to collaborate. This place is a powerhouse.”
Frank Wilson, MD, spent almost his entire career at the University of Michigan, where he became a pioneer in use of the electrocardiogram machine. In the 1920s and 1930s he showed how the instrument could be used not only for diagnosing abnormal rhythms but also for detecting structural abnormalities of the heart, and in so doing correctly identified the differences between left and right bundle branch block. When Wilson started his career most people used only three ECG leads; he played a key role in developing our current system of leads. Wilson made fundamental contributions to the theory of electrocardiography, using sophisticated mathematical analysis to design a new type of ECG lead, one now used for aVR, aVL, and aVF. He also helped create six more leads (the precordial leads), which together with the three original leads make up our current 12-lead ECG. Wilson helped establish cardiology in the United States and trained many of the next generation of cardiologists in the United States and around the world.
For someone who jokes that he got into intestinal work “a little by accident,” Jason Spence, PhD, assistant professor in the Division of Gastroenterology and the Department of Cell & Developmental Biology, has become a sought-after collaborator among some of the field’s leading players.

That’s because he’s had remarkable success creating what some have called “intestines in a dish.” Termed “organoids,” these tiny hollow spheres are cultured from stem cells and contain functional versions of the major cell types found in the human intestine. They provide researchers with a tantalizing new model for studying both intestinal development and disease.

“Organoids are a middle ground between traditional cell cultures and animal models,” says Spence. “With two major tissue layers and multiple cell types, they’re more complex than cell cultures, where you’ve got just one cell type in a dish. And unlike traditional cultures, they originate from stem cells, not cancer cells, so they’re as close to the native intestinal tissue as you can get. But they’re simpler than animal models; they don’t have things like immune cells, blood vessels or lymphatic vessels. That makes them a really nice reductionist system. We can ask a question about how something injures the intestinal epithelium, for example, without worrying about starting an inflammatory cascade. All that complex signaling between different tissues can sometimes confound the answers to very specific questions.”

A SERENDIPITOUS DISCOVERY THAT LAUNCHED A CAREER

Spence created the organoids during his postdoc at Cincinnati Children’s Hospital while working to turn human pluripotent stem cells into insulin-producing beta cells as a treatment for diabetes. As a developmental biologist, he also began tinkering with creating other tissues from stem cells. “The intestinal project just took off,” he says.
In building the organoids, he and his colleagues largely mimicked the steps embryos use to create intestine: turning stem cells into endoderm — the cell lineage that gives rise to the lining of the GI tract — then adding growth factors to drive the tissue toward becoming intestine.

What surprised Spence and his colleagues was not only that the culture yielded multiple functioning intestinal cell types, but that it underwent an unusual 3D shape change, becoming a sphere with an internal epithelial layer surrounded by a mesenchymal layer.

It’s this highly organized, functional structure that attracted the attention of fellow researchers and piqued the department’s interest in Spence’s work back in 2011. For his part, Spence was equally drawn by what he calls “one of the strongest GI research programs in the country” with a rich environment of collaborators with whom he could answer key questions in intestinal disease. He was also excited to be part of U-M’s Center for Organogenesis.

INAUGURAL PROJECTS & NEXT STEPS

Since arriving at U-M, Spence has formed multiple collaborations. Among these is one with Vincent Young, MD, PhD, associate professor in the Division of Infectious Diseases and the Department of Microbiology & Immunology. The pair have used the organoids to examine the cellular and molecular effects of toxins produced by the bacterium Clostridium difficile. “One of the beautiful things about the organoids,” says Spence, “is that we can characterize the epithelial response to these toxins in a very controlled manner in terms of the time after exposure and not have to worry about confounding factors like a massive immune response.”

Spence has also recently published some work with University of Pennsylvania GI researcher, Ben Stanger, MD, PhD. The team have used the organoids to confirm that human intestinal cells can be reprogrammed into insulin-producing beta-like cells, as Stanger had shown in mice. They’re now exploring whether these insulin-producing cells are functional and can respond to glucose. If not, they plan to use the organoids to try to identify missing elements that might impart this functionality.

Recognized for his work with a Basil O’Connor Starter Scholar Award from the March of Dimes in 2013, Spence is eager to build on his momentum and push the organoids further. He wants to make them more complex, introducing internal fluid flow and adding immune components so that he and his collaborators can explore more aspects of bacterial-host interactions. He’s also trying to understand how their 3D structures arise so he can use these insights to make organoids from related lineages like thyroid and lung.

He’s working hard on these projects because he believes deeply in the organoids’ potential as a research tool. They provide, he says, a new human model to screen drugs, understand gene function, generate transplantable tissue, and study complex human diseases from inflammatory bowel disease to asthma. Spence is eager to continue building relationships on campus to fully exploit this potential.

E. coli bacteria (green) next to the organoid epithelium (orange).
PATIENT CARE
It is estimated that 1.9 million adult outpatient visits took place at the U-M Health System’s 40 ambulatory care locations last year, and that demand for that is rising around 3 percent a year. Major renovations to internal medicine clinics at the Taubman Center, a new health center in Northville, Mich. and a new Acute Care for Elders unit at St. Joseph Mercy Hospital have all been developed to meet this growing demand and provide excellence in patient care.

**Taubman Center Renovations:**
**Built on Teamwork**
In December 2013, the Department of Internal Medicine celebrated the opening of new clinic spaces on the third floor of the Taubman Center. This $7.5 million renovation marked the first full-scale renovation of clinic space since the building opened in 1986.

“This was a major undertaking and a remarkable project. Our staff made a lot of sacrifices to make this renovation work. We did not miss one day of clinic throughout all of the transitions and moves that were needed. These areas had not been touched in 25 years. It is so much better now and puts us in a great position to meet the future needs of our patients.”
— Timothy Laing, MD
Department of Internal Medicine Senior Associate Chair for Clinical Programs

One of the new clinic spaces on the third floor of Taubman Center.
$7.5 MILLION PROJECT

67 EXAM ROOMS AND CLINICAL SUPPORT SPACE
U-M’S NEW NORTHVILLE HEALTH CENTER

With a planned 100,000 square feet of clinical and diagnostic space, the U-M Northville Health Center opening in July 2014 will be bringing U-M’s patient care to a whole new community. “The Northville Health Center will provide a broad range of services to our current patients living in the I-275 area and expands the University of Michigan presence in the I-275 market,” explains Connie Standiford, MD, the executive medical director of ambulatory care services at the U-M Health System (UMHS) and an associate professor of internal medicine in the Division of General Medicine.

The two-story building will be located on the corner of Seven Mile and Haggerty Roads. This expansion in space and services offered will support the U-M facilities in Livonia. The Livonia Health Center will be moving its services to the new Northville Health Center. This location will then be renovated and reopened as to offer U-M Family Medicine services. The Livonia Center for Specialty Care will expand its otolaryngology and urology services, while the allergy, ophthalmology and majority of gastroenterology services will be moving to the new Northville Health Center.

“The comprehensive services offered at Northville Health Center will include adult and pediatric primary care and specialty services, cancer and some surgical disciplines including ophthalmology, a musculoskeletal center, procedure and infusion units, labs and radiology services. These offerings will complement services already offered at the UMHS Livonia Center for Specialty Care and Surgical Center. We are very excited to provide patients and our referring physicians with a new state-of-the-art facility and improved access to University of Michigan physicians.”

— Connie Standiford, MD
Executive Medical Director of Ambulatory Care Services
In a joint effort to improve health outcomes for the region’s older adult patient population, in 2013 the University of Michigan Health System and St. Joseph Mercy Ann Arbor opened a medical care unit specializing in geriatric care.

The new UM-SJMAA Acute Care for Elders (ACE) unit brings together the area’s foremost geriatric experts in a brand new, state-of-the-art facility designed especially for senior patients. Housed on the tenth floor of St. Joe’s East Tower, the ACE unit provides elder care by a skilled team of health care providers led by Karen Hall, MD, PhD, a professor from the Division of Geriatric and Palliative Medicine.

“Our ACE unit follows a national model of care shown to increase the likelihood of a shorter average length of stay, preservation of physical and mental functions, and reduced rates of hospital readmission compared to care in traditional hospital units,” explains Hall.

Patients receive specialized acute medical care that also addresses the changes that result from the aging process, including health concerns tied to independent functioning, comfort level, skin health, nutrition and response to treatment. The medical problems treated span the gamut of disease, with serious infections such as pneumonia, urinary infections and cellulitis, acute confusion, falls, acute kidney impairment and heart failure as primary diagnoses in approximately 2/3 of admissions.

The ACE unit’s team includes board-certified geriatrician physicians, nurse practitioners, geriatric medicine-trained nurses, physical occupational therapists, a social worker, chaplain, pharmacist, and dietitian who work closely with patients and family members to customize care for each patient. This approach to healing is designed to aid in quicker, more complete recoveries and improve patients’ mobility, mental health and successful

Karen Hall, MD, PhD, medical director of the ACE unit
transitions back to home. The team also
places particular emphasis on discharge
planning and communication with patients’
primary care providers.

The new ACE unit provides care for patients
age 65 and older who are admitted from
UMHS and SJMAA emergency departments,
geriatric clinics, physician offices and sub-
acute rehab facilities. The ACE unit currently
has 16 beds and is capable of growing up
to 32 beds. The physical space is
designed to be geriatric-friendly,
with spacious private rooms, and
interventions to decrease falls and
injuries.

“Together, the highly trained and
dedicated medical professionals of
UMHS and St. Joseph Mercy Ann
Arbor are providing top-notch care
leading to quicker, more complete
recoveries for our older patients with
complex health care needs,” says
Raymond Yung, MD, chief of the
Division of Geriatric and Palliative
Medicine. “Our shared goal is to
help these patients return to a productive,
meaningful life as quickly as possible.”

To date, more than 400 patients have been admitted from a variety of different
sites, including the Emergency Departments of the U-M Hospital, and St.
Joe’s, and direct admissions from geriatric clinics, physician offices and sub-
acute rehabilitation facilities.
In contrast to research grants and papers, teaching evaluations, and national talks—all of which factor heavily into the academic promotion process—clinical excellence is harder to measure but nonetheless is an essential aspect of academic medicine. Until last year, recognition of the many internal medicine faculty who provide outstanding clinical care has been limited. With the strong support of Chair John Carethers, MD and Senior Associate Chair for Clinical Programs, Timothy Laing, MD, the department initiated a clinical excellence society named Academiae Laureati Medici to recognize faculty who, by acclaim of their peers and their patients, provide exemplary clinical care. The inaugural group in 2013 consisted of 23 members. There were 14 new members elected in 2014 (see photo at right).

Membership is for a lifetime while in the Department of Internal Medicine at the University of Michigan. Members are elected and inaugurated at an annual dinner. Benefits include website recognition, an enhancement of annual CME discretionary funds, selection of subsequent members, selection of the speaker for annual induction dinner and participation in other functions that the society initiates.

The Department of Internal Medicine expects members and the society as a whole will also serve as a thought group providing advice on clinical excellence to the department and help promote clinical excellence through example and mentoring.

“It is my hope that the initiation of this society will highlight the importance of clinical excellence, recognize those who live it on a daily basis and ensure an enduring presence that spotlights this aspect of our tripartite mission of clinical excellence, education and research.”

— John Carethers, MD
Chair, Department of Internal Medicine
2014 CLINICAL EXCELLENCE SOCIETY INDUCTEES

Standing (left to right):
Hakan Oral, MD; Stan Chetcuti, MD; David Wesorick, MD; David Bach, MD; James Riddell, MD; David Smith, MD; Mark Mcquillan, MD; Elisa Ostafin, MD; Mark Zalupski, MD and Richard Simon, MD

Seated (left to right):
Linda Terrell, MD; William Chey, MD; Erik-Jan Wamsteker, MD and James Baldwin, MD
As the gap between the number of patients and primary care physicians in the U.S. continues to grow, many health systems are finding it crucial to reevaluate how they provide care. While aging and population growth are projected to account for 81 percent of the change in demand between 2010 and 2020, the remainder of the change is associated with the expansion of health insurance coverage under the Affordable Care Act, which is expected to bring 32 million new patients into the U.S. health care system.

There is already a national shortage of doctors, according to the Association of American Medical Colleges — estimated at about 20,000 now, and the number is expected to get worse as nearly half the nation’s physicians are over age 50 and nearing retirement age.

A recent study in the Annals of Family Medicine projected the country will need 52,000 more primary care physicians by 2025. Most of those extra doctors are needed because of projected population growth. But the problem also begins in training; only one in five graduating medical residents currently plan to go into primary care, according to the Journal of the American Medical Association.

As the first stop for many patients who will be newly insured under health reform, primary care physicians expect to see an uptick in volume and demand. With more financial barriers removed, providers will now have the opportunity to provide patients who choose him or her as their regular physician with more comprehensive care. This will create more patients to be seen and the need for more time with each patient. With a national shortage of primary care providers and those that are practicing are already stretched thin, how can the best health care be provided?

To truly provide the comprehensive, preventative, whole-person care many believe that a team approach to care will take on even greater importance.
“Clearly, the old way of providing care, the old traditions about who did what kind of work and how patients interact practices and who they spend time with about which problem — that’s all going to need to change,” says John Carethers, chair of the Department of Internal Medicine. “We are entering a completely new era of primary care. This is a major focus for our department given that general medicine is our largest division.”

THE UMHS PRIMARY CARE TASK FORCE
The Department of Internal Medicine has been focusing on the increased need for primary care by recently creating the Clinical Excellence Society to help reward and retain excellent clinicians and developing a new primary care track in its residency program to train the next generation of providers. Now the department is playing a prominent role in a new Primary Care Task Force that is exploring how to restructure primary care at the U-M Health System.

The University of Michigan's Primary Care Network is made up of a system of community-based U-M Health Centers in Washtenaw, Livingston, Oakland, and Wayne Counties. More than 170 providers, both physicians and nurses, specializing in internal medicine, pediatrics, obstetrics and gynecology and family practice see patients for a wide range of services, from routine office care and minor outpatient procedures, to immunizations and specialist referrals.

The group will be examining how to handle the rapidly growing volume of patients, the financial impact, the current care process and flow, as well as how to prevent physician burnout and increase provider satisfaction to maintain competitive in the recruitment of the best clinicians. The task force is made up of the chairs from the departments of internal medicine, family medicine, pediatrics and obstetrics and gynecology, as well as three to four faculty representatives from each department.

“The task force will have a strong focus on population health management, quality and provider satisfaction. These are areas we’ve been examining for some time. Faculty from internal medicine have led patient-centered medical home projects at both UMHS and the VA Ann Arbor Health System. We’ve also been instrumental in demonstration projects and the Pioneer Accountable Care Organization model that are improving the quality and efficiency of care we provide our patients. We have a great foundation to build on for the future of U-M’s Primary Care Network,” adds Carethers.
Cancer is a common disease, and in most cases it occurs by chance. But about 5 percent to 10 percent of cancers develop because a person has inherited a change in a gene, called a mutation, which puts him or her at a higher risk of developing cancer. Knowing if family members are at risk for hereditary cancer can allow patients to plan strategies to prevent cancer, catch it earlier or treat it more aggressively.

Although most cancers are not “inherited,” a variety of cancers can have a genetic component. Clues to identifying patients who may be at higher than average cancer risk lie in review of the personal and family cancer history. Patients who have had a diagnosis of cancer at an earlier than average age (such as young breast cancer or colon cancer before age 50), have had more than one primary cancer, have a rare or unusual cancer or have more than one relative with the same or related cancers, may benefit from a genetics risk assessment.

The Cancer Genetics Clinic works with patients to determine if their family is at higher than average risk of developing cancer. And if they are, specialized physicians and genetic counselors work with them to develop a plan for additional screening or lifestyle changes to help reduce their cancer risk. As part of the cancer genetics evaluation, team members evaluate a patient’s family and personal medical history to determine if there is concern for an inherited cancer syndrome, and if genetic testing is indicated. Recommendations for cancer screening and surveillance are communicated to patients’ physicians and health care team.

“We take care of families as a whole,” says Elena Stoffel, MD, director of the Cancer Genetics Clinic and an assistant professor in the Division of Gastroenterology. “To identify familial
cancer syndromes you have to look beyond a single diagnosis. If there are other cancers in the family, and those diagnoses fit a particular pattern, there may be more going on.”

**TO KNOW OR NOT TO KNOW**

While genetic testing is considered the gold standard for identifying inherited mutations related to cancer risk, it is considered most beneficial when targeted for patients and families with suggestive personal or family history. Before any decisions are made about testing, a genetic counselor reviews the patient’s family history to try to determine the potential risk for either having the condition or passing it on to future generations. They then explain how genes work, specifically, how gene mutations can lead to cancer development and the differences between mutations that are passed down in families (inherited) and those that are acquired during an individual’s life. The counselor will talk about the risks, benefits and limitations of genetic testing, and, along with a physician, discuss options that may help reduce the risk of developing cancer. This counseling often helps patients address their concerns as well as prepare for future scenarios or any surgical decisions they may face.

Pursuing genetic testing can be extremely helpful for some families. A negative genetic test result can help relieve anxiety or uncertainty. In the same way, a positive result can help patients make important decisions about their future, including proven interventions to reduce their cancer risk. A positive result could also identify individuals who would benefit from specialized screening, providing an opportunity to detect cancers early or even prevent these from developing. For others, the comprehensive risk assessment and genetic counseling provide enough information to develop a plan for lowering the risk of cancer. “It’s a very personal choice. We see patients on both ends of this spectrum. Some want to know as much as possible while others would rather not know if they have an inherited susceptibility. As long as they understand their risks and what they can do to manage them, we’ve hopefully helped them get on a path to a longer, healthier life,” explains Victoria Raymond, MS, a genetic counselor at the Cancer Genetics Clinic and clinical instructor of internal medicine.

**A GROWING ROLE**

With the growth of personalized medicine and increasing knowledge of the role of genetics in health, specifically cancer risk, genetic testing will play an even larger role in cancer risk assessment, detection and treatment in the future. “There are genetic tests — some available and some being developed — that are helping doctors personalize treatment for patients,” adds Stoffel. “Many new cancer medicines are being developed based on gene changes found in cancer cells. Doctors can test cancer cells for these changes to see if a treatment will be effective for a specific patient.”
Each and every day patients are given the opportunity for a new life at the U-M Transplant Center.

Since the very first transplant in Michigan took place there in 1964, more than 9,500 patients have benefited from its services. It is the largest and most experienced transplant center in Michigan — and one of the largest in the nation. Over this time, transplantation has evolved from an experimental, risky procedure to a successful medical therapy.

The Transplant Center currently performs more than 400 solid organ transplants per year that include heart, kidney, pancreas, liver, lung and cornea. In addition, over 200 adult and pediatric stem cell transplants (bone marrow transplants) are performed annually.

While patient outcomes are generally excellent, many need to take medications to prevent their body from rejecting their transplanted organ. This suppression of the immune system makes an organ vulnerable to a variety of infections. While bone marrow transplant recipients don’t typically take anti-rejection medicines, because of their fragile immune systems they are also at high risk of infection. This is where internal medicine faculty from the Division of Infectious Diseases are making a difference in the care of transplant patients. “Our Transplant Infectious Disease Service at U-M works closely with the transplant surgeons and many other medical specialists to both treat and prevent infections in these complex patients,” explains Associate Professor Daniel Kaul, MD, director of the service. “We are fortunate to have three faculty members from our division, Marisa Miceli, MD; Kevin Gregg, MD and James Riddell, MD, who all have expertise and are committed to the care of transplant patients, he says.

Each member of the Transplant Infectious Disease Service team helps ensure the best possible care for transplant patients by
developing clinical protocols to manage and prevent infections in this population. Dr. Kaul is currently the chair of a national committee, the United Network for Organ Sharing Disease Transmission Advisory Committee, that works to make transplantation safer by reducing the risk of unexpected transmission of infection from donor to recipient. While these transmission events are uncommon, they can be devastating for recipients. For example, a recent high profile case involved the transmission of rabies from an undiagnosed donor to a kidney recipient. In an editorial in the Journal of the American Medical Association that accompanied a description of the case, Dr. Kaul suggested some strategies to reduce the frequency of these events.

The service’s integrated, multidisciplinary approach involves all aspects of clinical care, basic, clinical and translational research, and education devoted to patients with an increased risk for infections.

**CLINICAL RESEARCH**

Research is an important component of the care of transplant patients at U-M. The Transplant Center is currently conducting more than 30 clinical research studies designed to improve the understanding of transplantation and enhance the outcomes for all patients. U-M researchers are currently studying the diseases that are treated by transplantation, developing alternative options and surgical procedures and examining therapies to prevent rejection, post-transplant infection and other post-transplant complications.

Current research includes clinical trials testing new antiviral drugs that treat Cytomegalovirus (CMV) infection, the most common and often serious viral infection that can occur after transplantation. While there are drugs that often prevent this infection, drug resistant infection does occur and currently approved alternative drugs are very toxic particularly to the kidneys and can often result in the loss of the kidney graft or native kidneys. “We are testing new antiviral drugs to both treat prevent the development of CMV disease and treat established disease. For a number of patients in our center, it is quite clear that without these newer drugs CMV disease would have caused considerable morbidity and likely even loss of function of their kidneys. We hope in the future that this research will lead to more effective prevention and treatment of viral infections after renal transplantation,” explains Kaul. “In addition, Dr. Gregg is leading a trial of a strategy to prevent a very common cause of infectious diarrhea (*Clostridium difficile*) after bone marrow transplantation. As one episode of c-dif early after transplant can lead to significant complications later, we hope this research will improve the overall outcome after bone marrow transplantation” he adds.
THE PERILS OF HYPERGLYCEMIA

Several studies have found high blood glucose, otherwise known as hyperglycemia, to be associated with worse recovery and a higher risk of infection and death for hospital patients. When some patients are admitted to the hospital they may already have hyperglycemia from previously diagnosed or new onset diabetes or from stress. Major surgical procedures, critical illnesses, medications, nutrition and procedures can further contribute to this. For example, a heart operation on the bypass machine (with hypothermia to protect the heart muscle), glucocorticoids for asthma and parenteral nutrition for abdominal procedures have all been found to be common causes of hyperglycemia.

Interventional studies have found that outcomes can be improved through glucose control especially in postsurgical, post-myocardial and post-burn patients. The level to which glucose should be controlled still remains controversial, but the consensus currently is a moderate target which avoids hypoglycemia. Hospital patients with diabetes and those with critical illnesses currently have their blood sugars monitored and receive insulin for the management of hyperglycemia.

More than 30 percent of cardiac surgery patients may experience blood sugar level elevations that require temporary insulin treatment after their operation, even though they have never had diabetes. A few of them may need to take medicines for days or even weeks after they leave the hospital to help their blood sugar levels reach normal again.

Based on this data, the American Diabetes Association, the Critical Care Society, cardiac surgery programs have adopted hospital glucose management as a standard of care to improve clinical outcomes.

THE HOSPITAL INTENSIVE INSULIN PROGRAM

The U-M Health System has a team of dedicated physicians and mid-level providers,
known as the Hospital Intensive Insulin Program (HIIP) that was established in 2004 by U-M endocrinologist Roma Gianchandani, MD, an assistant professor in the Division of Metabolism, Endocrinology & Diabetes. This team is charged with managing patients with elevated blood glucose levels from cardiac surgery, thoracic surgery, vascular surgery, heart failure and now also cystic fibrosis related diabetes. This management includes treatment of the blood glucose elevation until a patient is stabilized or discharged home and also diabetes related education necessary for a safe discharge. The patients can also be seen back in a stop-gap clinic before follow up with their established physician or endocrinologist to close the loop. The most important group HIIP manages are the Type 1 diabetes patients who have complicated regimens and insulin pumps and can develop major complications if not managed appropriately.

In addition to caring for patients, the HIIP team has worked with the rest of the U-M Hospitals to establish glucose management programs, helped standardize several inpatient diabetes protocols and led efforts to institute the use of basal-bolus insulin therapy hospital-wide. The HIIP program actively trains health care professionals, at all levels, including house officers and nurses who provide frontline diabetes care.

The HIIP program has also published on several aspects of hospital diabetes management and created a shift in awareness about the importance of blood glucose management since it began 10 years ago.

“For most patients the inpatient hospitalization is an opportune time to address their blood glucose issue so it is no longer lurking in the background and is addressed carefully. Glucose control has now become part of the U-M Health System culture and has led to improved understanding and implementation of hospital glucose management in other areas of the hospital. It has also contributed to improving the outcomes for morbidity and length of stay for diabetes UMHS patients,” explains Dr. Gianchandani.

In addition to the work of the HIIP Program, Dr. Gianchandani is currently investigating other diabetes treatments in the hospital. In a multicenter trial with Emory University, OSU and Temple University, the safety and efficacy of the medication sitagliptin as a blood glucose management agent in hospitalized and surgical patients with type 2 diabetes is being evaluated.

A recent pilot study completed at U-M found that treatment with sitagliptin alone, or in combination with basal insulin, resulted in similar glycemic control compared to the basal-bolus regimen, but patients treated with sitagliptin alone required a lower total daily insulin dose and fewer number of insulin injections than patients treated with the basal-bolus insulin regimen.

Since few studies have addressed the efficacy and safety of insulin or oral anti-diabetic agents after hospital discharge, an outpatient phase of this study is also being conducted.

“The protocols developed for hospitalized patient care and the studies evaluating outcomes and processes of standards of care are directly helping patient management and outcomes and contributing to the Michigan difference,” adds Gianchandani.

HIIP Program Team
Christina DeGeorge
Nicole Desbrough
Elizabeth Dubois
Nimita Mehta
Yunyan Qu

FACULTY
Palak Choksi, MD
Dimaraki, MD, MS
Nazanene Esfandiari, MD
Jennifer Franzese, MD
Roma Gianchandani, MD
Israel Hodish, MD, PhD
Andrew Kraftson, MD
Arno Kumagai, MD
Elif Oral, MD
Rodica Pop-Busui, MD, PhD
Imagine living in fear each day that something you eat, touch or breathe in could cause a severe or life-threatening allergic reaction. This is what life is like for up to 15 million Americans who currently have food allergies where their immune system mistakes certain foods for something harmful and overreacts by releasing histamine and other chemicals in the body. Currently, there is no cure. The only way to prevent an allergic reaction is to completely avoid the problem food.

This potentially deadly disease is estimated to affect 1 in every 13 children (under 18 years of age) in the U.S. — According to a study released in 2013 by the Centers for Disease Control and Prevention, food allergies among children have increased approximately 50 percent between 1997 and 2011. This number continues to grow and there is no clear answer as to why.

The U-M Division of Allergy & Clinical Immunology has long been at the forefront of helping patients recognize and cope with food allergies and studying ways to improve food allergy diagnosis, treatment and awareness.

In 2007, the division opened a new Allergy Specialty & Food Allergy Clinic at Domino’s Farms, which includes space devoted specifically to the Food Allergy Service that sees thousands of patients each year. Two rooms are devoted to performing “food challenges” that evaluate a patient’s response to a specific food, with the help of a nearby kitchen. Most patients have reactions to one
of the “big eight” which account for about 90 percent of all food allergies nationwide: milk, tree nuts, peanuts, shellfish, eggs, soy, wheat, and fish.

In the clinic, allergy faculty and fellows evaluate patients from all over the region and country to identify their specific allergies and assist families in understanding the severity and provide education to help them adjust to the diagnosis. Resources available to families include an educator, registered dietician, social workers, and nursing support. Each family is provided with a specific food allergy action plan and educational materials. The team also works with parents on how to educate schools, daycare centers, family and friends to the dangers of an allergic reaction and steps that can be taken to protect the child.

The clinic’s comprehensive family-centered approach so inspired prominent supporters Marc and Mary Weiser whose daughter, Cate, was diagnosed with multiple, life-threatening allergies that they are helping the division develop the U-M Food Allergy Center (FAC). Mary believes so strongly in the potential of the FAC that she has become one of its biggest advocates and is also its fundraising chair.

The mission of the FAC is to provide comprehensive food allergy related patient care and expand food allergy research, education and community services. To date, more than $6.2 million has been raised for the center, including a $1 million matching grant from the Food Allergy Research and Education, which is the largest private source of funding for food allergy research in the United States.

“U-M is a world-class facility for medical care and research, and the Food Allergy Center will be among the national and world leaders in expanding our knowledge and understanding of food allergy. The center will provide clinical care, family support services and cutting-edge research to help find a cure for food allergy,” explains James Baldwin, MD, interim director of the FAC and interim chief of the Division of Allergy & Clinical Immunology.

PATH TO A CURE
With donor support, the FAC is building on a solid foundation to become a national center of excellence and a model for comprehensive food allergy care and services. Its expansion over the next 5 to 10 years will also offer a critical opportunity to accelerate the discovery of food allergy treatments and advance research on a path to a cure.

The FAC is researching the causes, epidemiology and therapies of food allergy and eosinophilic esophagitis, a form of allergic response characterized by an overwhelming number of eosinophils, a type of white blood cell, which leads to swelling of the esophagus.

The first research projects conducted by the Food Allergy Center examined the safety of the H1N1 Influenza vaccine and the seasonal Trivalent Influenza vaccine in egg allergic recipients. Its findings...
revealed that both vaccines were well tolerated even among those with a history of anaphylaxis to egg. "I'm hoping that findings like this and others will help protect the health of these populations for years to come," explains Matthew Greenhawt, MD, MBA, MSc, research director of the FAC. Findings from this and two follow up studies have already influenced the CDC to change the vaccine recommendations for egg allergic recipients. Dr. Greenhawt is currently working with both the American Academy of Allergy, Asthma and Immunology as well as the American Academy of Pediatrics to study the dissemination and implementation of these guidelines.

As an example of how the FAC is achieving this goal, recent and ongoing work from the center has focused on the key patient-oriented outcome of quality of life. Building off a divisional patient registry, funded by a generous anonymous donation to the center, Greenhawt and his team have noted several key findings related to food allergy quality of life. These have included the discovery that parents of milk or egg allergic children have worse quality of life than peanut or tree nut allergic children; and that socioeconomic disparity, past severe reaction, and incorrect parental perception of reaction influence poor quality of life.

Moreover, the team also showed that food challenge is associated with better quality of life — caregivers of patients with children who had undergone food challenge had better quality of life than those who had not undergone challenge, and quality of life was no different in caregivers of children who passed versus who failed challenge. This shows the potential of the food challenge, a service for which that the FAC is nationally recognized as a leader in providing, as a potential positive intervention to improve patient lives. This work follows closely on the tail of a previous FAC study that showed a self-regulation intervention improved quality of life in the caregivers of newly diagnosed food allergic children. Collectively, these works demonstrate the FAC’s mission and commitment to actively improve the lives of families living with food allergy.

“Our ongoing work regarding patient-centered outcomes is focusing on the principle of self-efficacy in food allergy, the role of nutrition support in improving quality of life, and using the patient care registry to understand how food allergy patients utilize health services. The FAC is a national pioneer in understanding food allergy health service utilization and leverages strong ties to the Child Health Evaluation and Research Unit in the Division of General Pediatrics, and the School of Public Health,” adds Greenhawt.

“Our patient-centered research is focused on providing concrete solutions for food allergy sufferers and helping to find a cure for this condition. We want our results to be able to shape health care policy that improves the day-to-day lives of families,” he adds.
Conn Syndrome

Jerome W. Conn, MD, devoted his entire professional career to U-M and served as the Department of Internal Medicine’s first chief of the Division of Endocrinology & Metabolism from 1943-1973 (now known as the Division of Metabolism, Endocrinology & Diabetes [MEND]). Dr. Conn’s greatest contribution to medicine was the description in the mid-1950s of the new entity called primary aldosteronism — later named Conn Syndrome — a curable form of high blood pressure. Caused by an adrenal tumor secreting excessive amounts of the adrenal hormone aldosterone, this disorder is one of the few serious hypertensive diseases that can be cured completely by the surgical removal of the adrenal tumor if it is recognized early. Dr. Conn subsequently devised new diagnostic techniques for the early detection of this adrenal tumor. Due to this work, the U-M Hospital became a worldwide center for study and treatment of patients with primary aldosteronism and related conditions between 1955 and 1975.
NEW HOPE FOR HIGH-RISK HEART PATIENTS
THE TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) PROGRAM

A PROMISING NEW TREATMENT
Approximately 300,000 people worldwide suffer from severe narrowing of their aortic valves, which prohibits blood from efficiently pumping from their heart to the body. One-third of these patients are deemed too ill or frail to undergo open-heart surgery. Without aortic valve replacement, half of these patients will not survive more than an average of two years after symptoms begin.

Open surgical repair of the aortic valve is the preferred treatment for patients with severe aortic stenosis and low to intermediate risk for surgery. For high- to extreme-risk patients the emergence of transcatheter aortic valve replacement (TAVR) procedures in the U.S. is providing a viable option. The procedures allow access to the diseased aortic valve percutaneously, meaning through the skin, usually through an artery in the leg, rather than through open surgery.

Once in place, TAVRs are designed to take over the native valve’s function and ensure that oxygen-rich blood flows into the aorta and circulates throughout the body. Patients currently have two TAVR options with the FDA approved Medtronic CoreValve device and the Edwards SAPIEN Heart Valve.

THE STRUCTURAL HEART PROGRAM
The University of Michigan Samuel and Jean Frankel Cardiovascular Center’s Structural Heart Program, led by Stanley Chetcuti, MD, the Eric J. Topol Collegiate Professor of Cardiovascular Medicine and an associate professor in the Division of Cardiovascular Medicine and G. Michael Deeb, MD, the Herbert Sloan Collegiate Professor of Cardiac Surgery and a professor of Cardiac Surgery, offers both TAVR options and has performed more than 300 procedures — more than any other Michigan hospital. It is considered one the top programs in the nation.

POSITIVE RESULTS
This team of U-M experts is on the leading edge for aortic stenosis treatment and has access to all the newest devices available through clinical trials as well as FDA approved devices. They recently participated in two landmark heart valve trials that included patients from the U-M Frankel CVC that showed positive results for those whose lives were impaired by aortic stenosis.

The first clinical trial evaluated the new Medtronic CoreValve System and revealed some of the lowest stroke rates ever reported.
U-M was one of 45 sites in the U.S. to enroll patients in the extreme-risk study of the trial — patients with severe aortic stenosis who were too ill to have their aortic valves replaced through traditional open-heart surgery. One year after receiving a CoreValve implant, nearly three-quarters of patients were alive without a major stroke, which is highly significant given their complex medical conditions.

The rate of stroke — one of the complications physicians and patients fear most because it increases mortality and affects quality of life — was 2.4 percent, and it remained low over time with a one-year rate of 4.1 percent.

The second trial, recently published in the New England Journal of Medicine, was the first to ever show that the TAVR procedure was superior to open heart surgery at one year from the time of enrollment.

In addition to Dr. Deeb and Dr. Chetcuti, the TAVR team includes Paul Michael Grossman, MD, director of the cardiac catheterization laboratory at the Veterans Administration Ann Arbor Healthcare System, Himanshu J. Patel, MD, associate professor of surgery, Daniel Menees, MD, assistant professor of internal medicine and Matthew Romano, MD, assistant professor of surgery.

**ONLY THE BEGINNING**

The Frankel Cardiovascular Center was the first hospital in the state of Michigan to offer both the Edwards Heart Valve and the Medtronic CoreValve for patients who have limited surgical alternatives. It is now one of the few heart centers in the United States participating in the Medtronic CoreValve Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial and the Edwards Sapien 3 registry, for aortic stenosis patients who are at an intermediate risk to undergo open-heart surgery. This is only the beginning. As the center continues to look to the future to find new technologies, they expect to offer more options to heart patients when they become available.
We often take our kidneys for granted while they’re healthy. They work quietly behind the scenes releasing needed hormones and regulating chemicals in the blood such as sodium, potassium, phosphorus and calcium but their most important job is removing wastes and fluid from the body.

It’s estimated that 940,000 adults living in Michigan have chronic kidney disease. Many do not know it because there are little or no symptoms during the early stages. That means 1 in 8 Michigan adults are gradually losing function in their kidneys over time. Damage to the kidneys can result in high blood pressure, heart disease, anemia, weak bones, poor nutritional health and nerve damage.

"Unless they are screened appropriately, most individuals do not realize they have kidney problems since symptoms only develop when they are approaching complete kidney failure," says Frank Brosius, MD, chief of the Division of Nephology. "At that point, patients may have to resort to advanced treatment options like dialysis. That’s why annual screening for kidney disease is so important for individuals at risk. One simple blood test and a urine dipstick test are all it takes to screen for kidney disease."

"Renal or kidney failure occurs when a person’s kidney loses its ability to filter wastes, allowing toxins to build up," explains Dr. Brosius. "Dialysis is a life-saving procedure for patients whose kidneys have failed due to disease or injury. Dialysis treatment removes waste and extra fluids from patients and can be used temporarily until the kidneys resume function or the patient receives a transplant. However, most patients require dialysis for the rest of their lives since not enough kidneys are available for transplantation."

More than 115,000 new patients start dialysis in the U.S. each year. The rate of kidney failure in Michigan is higher than the average rate for the rest of the United States. This has resulted in a growing need for dialysis services in the region.
Dialysis is a serious commitment and is extremely demanding on people’s schedules. Treatment at home offers a lot of flexibility in the dialysis schedule, and helps people be more engaged in their care. That can really make a positive difference in someone’s quality of life.”
A PAINFUL MYSTERY

Scleroderma is a crippling autoimmune disorder that affects more than 300,000 people in the U.S. alone and 2.5 million worldwide. It is characterized by a thickening and hardening of the skin that is so severe, it steals away the use of patients’ fingers, hands and limbs. As it advances across their bodies, the uncontrolled growth of fibrous tissue can also damage patients’ hearts, lungs and other organs, often leading to a prolonged and painful death.

“Currently there are no good treatments for scleroderma and no cure,” says Dinesh Khanna, MD, MS, the Frederick G. Huetwell Professor of Rheumatology of Internal Medicine and director of the U-M Scleroderma Program. Its cause is not currently understood and there are no proven effective therapies for the underlying disease process. There have been many breakthroughs over the years in the ability to treat specific internal organ complications and survival from scleroderma is constantly improving — especially through developments being made at U-M.

The Department of Internal Medicine’s Division of Rheumatology created the U-M Scleroderma Program 2004 to develop effective therapies for scleroderma and its complications and to research the causes and mechanisms of disease.

Since scleroderma is an inherently complex disease, the program addresses it through a multidisciplinary team approach to treatment and research. In addition to the Division of Rheumatology, faculty from many disciplines, including the Interstitial Lung Disease Program in the Division of Pulmonary and Critical Care Medicine, the Pulmonary Hypertension Program of the Division of Cardiology, pediatric rheumatology, the Department of Dermatology, the Division of Hand Surgery, the Department of Occupational Therapy; and the U-M Cancer Center, currently participate in the program’s activities. Clinical care is provided primarily on a consultative basis to patients from Michigan and the Midwest, but the program also serves as an international referral center.
Innovative research being done by the program is coming closer to a cure each day. New compounds recently developed in a lab hold promise for shutting down the progression of scleroderma by targeting the molecular mechanisms driving it.

Teams from U-M and Michigan State University have developed a new approach to stopping the reaction that leads to the scleroderma. Most treatments have focused on blocking the initial inflammation but have not been able to stop the progression of the associated fibrosis. These new compounds target the genetic switch that controls the formation of myofibroblasts — the cells that produce too much collagen leading to the thickening of the skin and damage to other organs.

The next steps for the Scleroderma Program is to expand testing in patient cells, continue to improve and refine the compounds and demonstrate success in rodent models. If proven successful, other conditions, like idiopathic pulmonary fibrosis and Crohn’s disease, may also have the potential to be slowed or stopped by this approach.

Given the difficult environment for federal research funding at this time, the Division of Rheumatology is hoping that philanthropic support will help accelerate the translation of this laboratory research into a new treatment for scleroderma sufferers.

“As a clinician, the promise of this research makes me very hopeful. If successful, it could mean a huge improvement in the quality of life and function for patients in Michigan and around the world,” adds Khanna.
**AMERICAN SOCIETY FOR CLINICAL INVESTIGATION MEMBERS**

Peter Arvan, MD, PhD  
David Aronoff, MD  
John Z. Ayanian, MD, MPP  
Ariel Barkan, MD  
Ernesto Bernal-Mizrachi, MD  
George Brewer, MD  
Ronald Buckanovich, MD, PhD  
John Carethers, MD  
C. William Castor, Jr., MD  
Eugene Chen, MD, PhD*  
Kathleen Cho, MD  
Kathleen Collins, MD, PhD  
Daniel Eitzman, MD  
Stefan Fajans, MD  
Eric Fearon, MD, PhD  
David Fox, MD  
Thomas Gelehrter, MD  
David Ginsburg, MD  
Thomas Glaser, MD, PhD  
Stephen Gruber, MD  
Jeffrey Halter, MD  
Gary Hammer, MD, PhD  
Joel Howell, MD, PhD  
Patrick Hu, MD, PhD  
H. David Humes, MD  
Ken Inoki, MD, PhD*  
Mariana Kaplan, MD  
Eve Kerr, MD, MPH  
John Kao, MD*  
Alisa Koch, MD  
Ronald Koenig, MD, PhD  
Matthias Kretzler, MD  
Vibha Lama, MD, MS  
Kenneth Langa, MD, PhD*  
Ivan Maillard, MD, PhD  
Benjamin Margolis, MD  
David Markovitz, MD  
Laurence McMahon, Jr., MD, MPH  
Juanita Merchant, MD, PhD  
David Miller, MD, PhD  
Fred Morady, MD  
Martin Myers, MD, PhD  
Akinlolu Ojo, MD, PhD  
M. Bishr Omary, MD, PhD  
Chung Owyang, MD  
Marc Peters-Golden, MD  
Kenneth Pienta, MD  
David Pinsky, MD  
Bertram Pitt, MD  
Pavan Reddy, MD  
Bruce Richardson, MD, PhD  
Theodora Ross, MD, PhD  
Sanjay Saint, MD, MPH  
Alan Saltiel, PhD  
Amr Sawalha, MD*  
Jim Shayman, MD  
Elizabeth Speliotes, MD, PhD, MPH  
Robert Sitrin, MD  
Theodore Standiford, MD  
Andrea Todisco, MD  
Thomas Wang, MD, PhD  
Stephen Weiss, MD  
Max Wicha, MD  
Roger Wiggins, MB, BChir  
John Williams, MD, PhD  
Xiaochun Yu, MD, PhD

*New member in 2013-2014

**ASSOCIATION OF AMERICAN PHYSICIANS MEMBERS**

Peter Arvan, MD, PhD  
John Z. Ayanian, MD, MPP  
John Carethers, MD  
C. William Castor, Jr., MD  
Kathleen Cho, MD  
Kathleen Collins, MD, PhD  
Stefan Fajans, MD  
Eric Fearon, MD, PhD  
David Fox, MD  
Thomas Gelehrter, MD  
David Ginsburg, MD  
Gary Hammer, MD, PhD  
Daniel Hayes, MD  
Rodney Hayward, MD*  
H. David Humes, MD  
Jose Jalife, MD  
Stevo Julius, MD  
Alisa Koch, MD  
Ronald Koenig, MD, PhD  
Anna Lok, MBBS, MD  
Malcolm Low, MD  
Benjamin Margolis, MD  
David Markovitz, MD  
Juanita Merchant, MD, PhD  
Fred Morady, MD  
Martin Myers, MD, PhD  
Akinlolu Ojo, MD, PhD  
M. Bishr Omary, MD, PhD  
Gilbert Omenn, MD, PhD  
Chung Owyang, MD  
Marc Peters-Golden, MD  
David Pinsky, MD  
Bertram Pitt, MD  
Jim Shayman, MD  
Theodore Standiford, MD  
Galen Toews, MD  
Joel Weinberg, MD  
Stephen Weiss, MD  
Max Wicha, MD  
Roger Wiggins, MB, BChir  
John Williams, MD, PhD
INSTITUTE OF MEDICINE MEMBERS

John Z. Ayanian, MD, MPP
John Carethers, MD
Stefan Fajans, MD
Eric Fearon, MD, PhD*
David Ginsburg, MD
Juanita Merchant, MD, PhD
Gilbert Omenn, MD, PhD
Alan Saltiel, PhD
Stephen Weiss, MD
James O. Woolliscroft, MD*

*New member in 2013-2014

FOR MORE INFORMATION ABOUT THE UNIVERSITY OF MICHIGAN DEPARTMENT OF INTERNAL MEDICINE, GO TO: MED.UMICH.EDU/INTMED

FOR DETAILED INFORMATION ABOUT INDIVIDUAL DIVISIONS, PLEASE VISIT THEIR WEBSITE:

- Allergy and Clinical Immunology: med.umich.edu/intmed/allergy
- Cardiovascular Medicine: med.umich.edu/cvc
- Gastroenterology: med.umich.edu/gi
- General Medicine: med.umich.edu/intmed/genmed
- Geriatric and Palliative Medicine: med.umich.edu/geriatrics
- Hematology/Oncology: med.umich.edu/intmed/hemonc
- Infectious Diseases: med.umich.edu/intmed/infectious
- Metabolism, Endocrinology & Diabetes: med.umich.edu/intmed/endocrinology
- Molecular Medicine & Genetics: med.umich.edu/intmed/mmmg
- Nephrology: med.umich.edu/intmed/nephrology
- Pulmonary & Critical Care Medicine: med.umich.edu/intmed/pulmonary
- Rheumatology: med.umich.edu/intmed/rheumatology

University of Michigan
Department of Internal Medicine
3110 Taubman Center, SPC 5368
1500 East Medical Center Drive
Ann Arbor, MI 48109
(734) 936-4340