always visionary  |  forever valiant
Chair’s Report

John Carethers, MD
Chair

In 2016, Michigan Medicine and the Department of Internal Medicine continued to be recognized as leaders in the field. The annual U.S. News & World Report Best Graduate Schools ranking of the U-M Medical School moved up to 9th in the nation among research-based medical schools. U-M also ranked highly among medical schools for primary care training, coming in at 5th. Four U-M specialties ranked in the top 10, including family medicine at 4th, internal medicine at 6th, geriatrics at 8th and women’s health at 9th. Our U-M Medical School graduates continue to be rated highly by the directors of residency programs across the country with the fourth highest score in the country from all residency directors and the third highest score from primary care residency directors.

Exploring the Future

I view last year’s and this year’s reports as bookends to our bicentennial celebrations. Last year’s report — “Always Healing, Forever Valiant” — was our historical perspective: how we came to be and how we developed into a top Department of Internal Medicine. Who were the people involved? What was our leadership like? What key decisions and developments were made during that time? This year’s report is on the other end, and looking forward — “Always Visionary, Forever Valiant” — moving us from how we led to how we will lead. How will the department transform care through research, innovative care models and the training of future leaders in the field?

Because one cannot think about the future without connecting how today’s research will impact tomorrow’s clinical care, we decided to break out this year’s report by the ten areas that have the greatest potential to impact the future of the field (see page 30).

There are still a few historical pieces in this report looking back at the leadership and success of our chief medical residents (page 145) and the growth of our endowed professorships (page 156). These pieces are important because they continue to help us shape where we’re going.
NEW NAME
Early in January 2017, Michigan Medicine became the new name of the University of Michigan’s academic medical center. The new name replaces the U-M Health System. The Medical School name will not change, but the school is considered part of Michigan Medicine.

This new name reflects a growing trend among world-class academic medical centers to showcase the integration and seamless collaboration of their missions: medical education, health care research and patient care.

It also reflects recent organizational changes, including the appointment of a single leader for both the Medical School and medical affairs for university. Department of Internal Medicine Faculty member Marschall S. Runge, MD, serves in that combined role.

NEW LEADERSHIP
During the reorganization of the leadership of Michigan Medicine, David Spahlinger, MD, became president of the U-M clinical enterprise and Steve Bernstein, MD, MPH, was named chief quality officer. He focuses on patient safety, performance improvement, clinical quality and quality analytics.

Internal medicine faculty member, Eric Fearon, MD, PhD, has been named director of the University of Michigan Comprehensive Cancer Center. He is the Emanuel N. Maisel Professor of Oncology and a nationally recognized investigator in cancer genetics. His research has led to a greater understanding of gene defects that cause colon and rectal cancer to develop and spread.

The department also welcomed two new division chiefs in 2016: Subramaniam Pennathur, MBBS, was named division chief of nephrology and Pavan Reddy, MD, was named division chief of Hematology & Oncology.

As Michigan Medicine continues to develop a better clinical research enterprise, Anna S.F. Lok, MD, has been named assistant dean for clinical research and our department has appointed Rodica Pop-Busui, MD, as associate chief for clinical research.

Michigan Medicine has developed close ties with affiliates at Mid Michigan Hospital in Midland and the recently acquired Metro Health Hospital in Grand Rapids. Scott Flanders, MD, was named vice chair for external relations to be a point person for internal medicine’s expanding roles at these sites.

DIVISION MILESTONES
The Division of Gastroenterology and Hepatology celebrated its 75th anniversary in 2016.

As of July 1, 2017, our department will have a newly created Division of Hospital Medicine with Vineet Chopra, MD, MSc, as its first division chief.

THE NEXT ERA
As we celebrate the university’s bicentennial this year, the University of Michigan Department of Internal Medicine continues to be a highly ranked department dedicated to providing the very best patient care. It is the dedication of our faculty and staff that has made this history possible. As you will see in this report, we are looking forward to the many possibilities that the next 200 years will bring.
Our clinical programs experienced a great leap in demand in 2016. Our volume of ambulatory care and specialty care visits both on- and off-site continues to grow. Michigan Medicine’s outpatient facilities in Ann Arbor, Livonia and Brighton continue to perform well; our new center in Northville is already being used close to capacity. There are already plans to explore building a similar facility at this site in order to meet the demand for services. We continue to seek out and implement new approaches to respond to patient care needs in all areas.

NEW FACILITIES MOVE AHEAD
Groundbreaking for both of our new West Ann Arbor and Brighton clinics occurred in 2016. There are ongoing discussions about including the East Ann Arbor clinic in future plans.

In West Ann Arbor, a new, 75,000-square-foot health center will provide expanded clinics, primary and specialty care and other health care services. This $46 million project is expected to greatly expand capacity and include specialty services in multiple areas, including allergy, cardiology, gastroenterology, neurology, ophthalmology and psychiatry, along with infusion, radiology and diagnostic imaging services. It is scheduled to open in fall 2017.

In Brighton, a $175 million ambulatory care facility is currently being built south of Challis Road on 32 acres owned by Michigan Medicine. The new building will be close to U-M’s current Brighton Health Center. It is expected to house more than 40 University of Michigan specialty services to children and adults. This facility is expected to open in fall 2018.

INPATIENT CARE
Our new 22-bed short-stay unit staffed by our Hospitalist Service has been a great success, providing more efficient use of inpatient and palliative care beds.

There are now plans for an inpatient tower expansion during 2017 that is estimated to be completed in 2022. This will allow us to convert 120 of our current beds from semi-private to private rooms.

CLINICAL SCHEDULING IMPROVEMENTS
The Department of Internal Medicine was the first department at Michigan Medicine to work with Chartis Group Consulting last year to explore ways to make our clinical scheduling process more efficient and accessible. Our goal is to enable 80 percent of our new patients to schedule an appointment within two weeks.
eCONSULTS
The University of Michigan is part of an American Association of Medical Colleges initiative to increase access to and efficiency of specialty medical services by improving collaboration and communication between primary care and specialty physicians. The initiative called Project CORE — Coordinating Optimal Referral Experiences — uses tools in the electronic medical record, or EMR, to refine the referral process.

Led by internal medicine faculty member ROBERT ERNST, MD, clinical assistant professor and senior associate chief of general medicine for ambulatory care, CORE encourages the use of eConsults and enhanced referrals, both of which are implemented and used by providers in the EMR.

An eConsult allows a primary care physician to electronically consult with a specialist regarding specific questions about a patient’s care plan. The intent is for the specialist to provide guidance on straightforward, low-complexity issues in lieu of an in-person patient visit, so that the patient’s care can remain with the PCP.

More than a quarter of primary care and family medicine physicians have utilized the system since it began. There are hopes to apply CORE in every division and department within the next two years.

METRO HEALTH AND MICHIGAN MEDICINE
The board of directors of Metro Health Corporation and the Regents of the University of Michigan approved a definitive affiliation agreement in 2016, setting the stage for Metro Health to join Michigan Medicine.

By coming together, the organizations will be able to collaborate on new and improved clinical care models across the system, enhancing patient access to physicians and other care providers at both organizations. The affiliation will enable Metro Health to further expand its primary care and specialty services, as well as enhance its use of complex medical technology.

LOOKING AHEAD
When I look toward the future of the Department of Internal Medicine and Michigan Medicine, I see both continued growth and accessibility. Whether we’re expanding, partnering, using new technologies or improving our services, we’re making top-ranked health care available to more people in more ways. That care is getting more effective and more personalized through the department’s many forward-looking efforts described in this year’s report.

RELATED SECTIONS
HEALTH TECHNOLOGIES, PAGE 78
QUALITY AND VALUE, PAGE 94
The total number of Department of Internal Medicine faculty continued to grow in 2016. Our clinical track faculty increased by more than seven percent, while our instructional and research faculty numbers increased slightly. The chart on the facing page breaks down that growth by year and by faculty type.

FACULTY PROMOTIONS
Our department handled 61 new faculty hires and 48 faculty promotions during 2016. Congratulations to these faculty members on their new status and achievements.

NATIONAL HONORS
Internal medicine faculty are regularly recognized nationally for their contributions to the field of medicine. Some examples from the past year include:

HITINDER GURM, MD, and SAMI MALEK, MD, were inducted into American Society for Clinical Investigators.

CHARLES BURANT, MD, was inducted into the Association of American Physicians.

KATHY COLLINS, MD, was elected to the National Academy of Medicine.

Internal Medicine Chair JOHN CARETHERS, MD, was named to the Masters of the American College of Physicians.

SANJAY SAINT, MD, MPH, chief of medicine at the VA Ann Arbor Healthcare System, received the Mark Wolcott
Award for Excellence in Clinical Care Delivery by the Department of Veterans Affairs. This award is the highest honor for health care providers in the Department of Veterans Affairs.

**DIVERSITY, EQUITY & INCLUSION**

During 2016, Michigan Medicine created a Diversity Network to recognize, respect, foster and maximize the strengths and differences among its key constituents — patients/families, staff, faculty, house officers, students and the community at large.

As part of this initiative, the Department of Internal Medicine has asked me and **MARISA RODGRIUEZ**, the administrator from the Division of Allergy, to act as the department’s planning co-leads. We will be working with the the Office of Health Equity and Inclusion to address these issues.

**CLINICAL EXCELLENCE**

Internal medicine inducted 10 new members into our department’s Clinical Excellence Society in 2016 (see photo at right). The society, started by our Chair **JOHN CARETHERS**, MD, recognizes faculty who, by their peers and their division, display clinical excellence toward their patients and colleagues. This initiative’s primary mission is to improve the position of clinical faculty within the department and increase job satisfaction, mentoring opportunities and academic advancement.

**ENDOWED PROFESSORSHIPS**

Departmental faculty hold more than 80 endowed professorships, up from 28 in 2009. The more endowed chairs we have, the more our department can continue to recruit and retain top faculty at Michigan, creating stability and cultivating excellence (learn more on page 154).

**CONCLUSION**

As our department continues to grow, we strive to find new ways to train and support our faculty regardless of which track they’re on. We are very proud of the number of endowed professorships that we’ve been able to generate — a number that continues to grow dramatically. Our Clinical Excellence Society is a great example of our forward-looking vision and support for our faculty. All of these elements are important for the future of internal medicine. We’re investing in leaders who will mentor and influence our trainees who will go on to create the next generation of innovation in patient care and research.

**RELATED SECTION**

PROFESSORSHIPS, PAGE 146
The VA Ann Arbor Healthcare System (VAAHS) continued to experience steady outpatient and inpatient activity in 2016. There was a 1 percent increase in outpatient visits while inpatient activity increased by 2.2 percent. Through numerous on-going initiatives and efforts, we continue to decrease our readmission rates and lengths of stay for veterans. The VAAHS continues to serve as a clinical laboratory for quality improvement and patient safety initiatives, which have now spread across the country.

A NEW WELCOME CENTER
The VAAHS is in the planning stages of creating a new Veteran Welcome Center, a one-stop shop where all patient administrative needs are located in one, easily accessible location. This project will add 10,000 square feet to the main entrance of the medical center on Fuller Road, and will offer everything from eligibility to travel to Veterans Service Officers.
FACULTY APPOINTMENTS
There are currently 170 internal medicine faculty holding VA appointments with 15 new hires in 2016. Several faculty have recently taken on new leadership roles:

• **JANE DENG**, MD, was recruited from UCLA to be chief of the pulmonary section.
• **PUNEET GARG**, MD, FASN, was named chief of the nephrology section.
• **NATE HOUCHENS**, MD, was recruited from the Cleveland Clinic to be the associate chief of inpatient medicine.
• **MIKE MENDEZ**, MD, was recruited from Henry Ford Health System to be the director of the medical intensive care unit.
• **RICHARD J. SCHILDHOUSE**, MD, became chief of hospital medicine.

NOTABLE AWARDS & RECOGNITION
During 2016, VA faculty members were making an impact on patient care, education and research in many different ways. These are just a few of the highlights:

**SUZANNE BRADLEY**, MD, was re-appointed for an additional five years as the editor-in-chief of Infection Control Hospital Epidemiology, the world’s leading journal focusing on health care epidemiology.

**VINEET CHOPRA**, MD, MSc, FHM, an assistant professor in the Division of General Medicine, was honored by the national Society of Hospital Medicine as Researcher of the Year for his work centered on improving the safety of hospitalized patients by preventing hospital-acquired complications.

**HITINDER GURM**, MD, was inducted into the American Society for Clinical Investigation and received the MHA Keystone Center Patient Safety and Quality Leadership Award.

**RODNEY HAYWARD**, MD, was honored as the inaugural recipient of the Roger J. Grekin Research Award. The award, which honors the legacy of long-time VA clinician, researcher and leader Roger Grekin, recognizes an outstanding VAAHS clinical researcher who contributes to the VA research mission through excellence in clinical care, research, mentorship and leadership.

**CAROL KAUFFMAN**, MD, received the VA Society of Practitioners of Infectious Diseases Lifetime Achievement Award.

**RESEARCH HIGHLIGHTS**
**LONA MODY**, MD, MSc, an internationally recognized translational researcher from the Division of Geriatric and Palliative Medicine, recently led the first nationwide study evaluating multi-modal interventions to reduce “superbugs” and infections in over 500 facilities across the U.S. (which was completed in 2016). The findings from this research could fundamentally change the field of infection prevention.

The VA Clinical Research Mentorship Program, led by **RODNEY HAYWARD**, MD, and **SARAH KREIN**, PhD, RN, continues to provide mentoring for VA faculty members. Started in 2015, a total of 13 faculty from seven different specialties have enrolled. The number of clinically oriented VA grants and submissions has increased substantially since the program started.

SERVING OUR COUNTRY
The entire VA system serves almost 9 million veterans a year, making it the largest integrated health care system in the country. Two out of three medical doctors in practice in the U.S. today received some part of their training at a VA hospital. VA research programs have made major breakthroughs in areas such as cardiac care, prosthetics and infection prevention. Studies comparing VA with non-VA care have found that the VA is, overall, as good as or better than the private sector.

The most remarkable aspect of VA hospitals, though, is the patient population: the men and women who have sacrificed for our country. Every single one of them should be able to receive the special kind of care they deserve. At VAAHS, we are working to ensure that their care — both locally and nationally — is superb today and well into the future.

**RELATED SECTION**
QUALITY AND VALUE, PAGE 94
During 2016, the Department of Internal Medicine produced nearly 2,600 publications and was awarded more than $170 million in federal and non-federal grants, a five percent increase from the previous year. This follows on our success of 2015, when our department had more individual grants than any other department of internal medicine in the country except for the University of California, San Francisco. The future outlook for research funding remains positive with the development of several promising new initiatives.
21ST CENTURY CURES ACT
The 21st Century Cures Act passed in late 2016. Its purpose is to put policies in place to shatter barriers and ensure that the United States keeps up the pace of its research. The act includes a wide range of processes, including the discovery of cures in basic science, streamlining the drug and device development process and unleashing the power of digital medicine and social media at the treatment delivery phase.

As part of the act, the Public Health Service Act was amended to reauthorize funding for the National Institutes of Health through fiscal year 2018. It also establishes the NIH Innovation Fund to pick up the cost for the development and implementation of a strategic plan, early stage investigators and high-risk, high-reward research.

THE PRECISION MEDICINE INITIATIVE
President Obama’s budget for fiscal year 2016 included $216 million in funding for the Precision Medicine Initiative for the NIH, the National Cancer Institute and the Food and Drug Administration.

This initiative hopes to find new, more effective treatments for various kinds of cancer based on increased knowledge of the genetics and biology of the disease. It will also focus on bringing precision medicine to all areas of health and health care on a large scale (see page 32 to view some of the exciting work being done by internal medicine faculty).

NATIONAL MICROBIOME INITIATIVE
The University of Michigan is also part of the National Microbiome Initiative which was launched by the White House’s Office of Science and Technology Policy in fall 2016. THOMAS SCHMIDT, PhD, a professor in the Division of Infectious Diseases, director of the Center for Microbial Systems and one of the leader’s of U-M’s Host Microbiome Initiative, attended the launch event at the White House.

The NMI brings together more than $520 million in new and existing federal, private and university funding to enhance microbiome research and education. This funding adds to an already strong microbiome effort across several U-M schools and colleges, fueled by nearly $45 million in competitive research grants and internal funding (see page 64 to learn more about these efforts).

BRIDGING BASIC AND CLINICAL RESEARCH
In addition to all of these developments, the potential impact of internal medicine’s basic and translational research will continue to increase as Michigan Medicine develops a more unified approach to research bridging the basic and clinical research worlds for better treatments and care (see page 54).

RELATED SECTIONS
PRECISION HEALTH, PAGE 32
RESEARCH PIPELINES, PAGE 54
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NEW ROLES

Anna S.F. Lok, MBBS, MD, was named assistant dean for clinical research at Michigan Medicine in 2016. I have just begun my role as the new associate chair for clinical research.

It’s really an exciting time to witness and be part of this large initiative at Michigan Medicine to redesign the clinical trials enterprise with a long-term goal of overhauling the entire clinical research enterprise of our institution. It is particularly exciting for the Department of Internal Medicine as a major stakeholder in this effort. We have the most faculty involved in shaping the future of this project at all stages.
UPDATES OF CLINICAL RESEARCH SUPPORT

The strengthened pre-award departmental service for our research-oriented faculty began in 2016. Seven Clinical Trial Support Units are now moving ahead full steam to optimize our ability to conduct clinical trial research.

Michigan Medicine has provided us with the infrastructure that will allow clinical investigators to become much more effective in starting new clinical trials and much more competitive. It will allow us to be serious contenders in multi-center clinical trials while reducing some of the bureaucratic patterns that can hinder and frustrate researchers.

This overhaul is an enormous opportunity that will allow our department to become a true leader in providing meaningful findings that can reshape the clinical care of our patients. Also, having highly specialized personnel help our investigators and their teams with administrative tasks will free up important time that investigators can then dedicate to performing the actual scientific and research components of a project. They will have more time to think about the data, move a project to the next step, develop new questions and design the next trial to answer those questions.

TAKING THE NEXT STEP

The Department of Internal Medicine’s goals regarding clinical research go far beyond this scale. One of our main goals is to become much more effective in linking our successful trialists with our basic researchers and to bring to the trial those molecules and pathways that are being identified by our talented colleagues working on the bench. Another important mission is to expand access of clinical research space into clinical care settings, as well as to organize and provide effective, hands-on training in clinical trials for junior faculty to develop the next generation of successful clinician investigators.

RELATED SECTION

RESEARCH PIPELINES, PAGE 54

JOINT INSTITUTE FOR TRANSLATIONAL AND CLINICAL RESEARCH

The Joint Institute for Translational and Clinical Research, a Michigan Medicine partnership with the Peking University Health Science Center in China, was renewed for another five years. It was originally established in 2010. U-M hosted the largest JI Symposium at U-M in fall 2016. In all, 75 PUHSC faculty members made the 14-hour journey from Beijing for the Oct. 12-14 meeting, the largest single delegation of visiting scholars ever hosted by the University of Michigan Medical School.

One of the main topics discussed included clinical trials. Real advancement in global health means taking discoveries from the lab into a clinical setting. One JI project is ready for the clinical trial stage, with others soon to follow in the pipeline.

RESEARCH PIPELINES, PAGE 54
The Department of Internal Medicine Quality and Innovation Program expanded our capabilities this year to support four areas of focus: improvement projects, performance dashboards, education and scholarly activity related to quality improvement (QI). While the health care landscape is rapidly changing, we believe our vision to provide high-value, appropriate and patient-centered care will continue to be relevant.

A team of four quality improvement specialists provides program and project support faculty in all divisions (photo at right). With backgrounds in engineering and business, skill sets in project management and quality improvement methodologies, and many years of health care experience, this team has been instrumental in further advancing the goals of the Q&I program this year. To further expand our capabilities and support the QI work of our faculty, we recently added a data specialist with expertise in data extraction, analytics and reporting. We are excited to utilize our team’s skill set to advance improvement projects as well as the development of quality dashboards.

The enhanced departmental infrastructure to support active quality improvement has allowed our faculty to better address a wide range of important quality problems. From improving hypertension control in chronic kidney disease patients to reducing daily lab draws for hospitalized patients, our faculty are actively engaged in identifying ways to improve care. The department’s quality improvement initiatives have touched every division in internal medicine and have opened up opportunities for collaboration with other departments including emergency medicine, pathology, pharmacy, radiology and surgery. This year we completed a total of 70 projects and have 30 active efforts underway (see chart at right). The work of our faculty has been recognized nationally, as evidenced by numerous publications and recognitions (see next page).

Education is a key part of our vision, and this year we partnered with our Graduate Medical Education program leadership to develop enhanced opportunities for residents to learn and connect with quality improvement work in the department. Key to this effort is the development of a longitudinal curriculum for quality improvement and patient safety. Our team partners with faculty facilitators to assist second-year resident groups in their project month rotation with quality improvement tools, project topic selection, data needs and opportunities for disseminating and sharing project outcomes. Additionally, we are developing an enhanced curriculum model to deliver foundational education topics in quality improvement and patient safety for first-year residents.

Our vision is to firmly establish the Department of Medicine as a leader in quality improvement and delivery system re-design locally, regionally and nationally. The work of our faculty, trainees and the quality and innovation program team over the past year make it clear we are achieving that goal.
Michigan Medicine was one of seven institutions recognized by the ABIM Foundation, Costs of Care and The LeapFrog Group in the 2016 Costs of Care Value Challenge. The Challenge is a competition aimed at recognizing innovative ideas and projects for teaching and implementing high-value health care among collaborative teams of clinicians, educators, quality improvement specialists, and health system administrators (www.CostsofCare.org).

A wide variety of quality improvement posters are presented by our faculty and trainees each year. Several examples of posters representing multi-disciplinary teams are listed at right:


Many of our faculty published quality improvement work this year. Selected highlights are presented here. For a full list, please visit our website https://medicine.umich.edu/dept/intmed/patient-care/quality-innovation.


I am always humbled by the dedication and commitment of our administrative teams. In 2016, this was no different. They adapted to the constant changing landscape of health care while still serving the needs of our faculty, staff, residents and students. Without their flexibility and creativity, our department would not be able to fulfill one of our most important missions — to enhance and preserve the lives of our patients by offering them the most advanced, comprehensive and compassionate care. For this, I am profoundly grateful.

OUR FOCUS ON DIVERSITY, EQUITY & INCLUSION
This past year, U-M reinvigorated their decades-long focus on diversity, equity and inclusion and introduced a five-year strategic plan. As part of this initiative, our department strengthened our commitment to make sure the recruitment of faculty and staff is fair and equitable from the onset and that everyone in our department feels respected and valued. Our divisions are using focus groups, anonymous surveys, suggestion boxes and one-on-one interviews to heighten awareness and engagement. This effort is one of the core values of our mission and requires active involvement of everyone in our department.

STRATEGIC PLANNING RETREAT
As part of our commitment to continuous improvement and to strategically position our department for the future, a multidisciplinary team of faculty leaders and administrators representing all divisions and department areas took part in a highly interactive, all-day retreat. The goal of the retreat was to provide clarity and understanding of our department’s critical priorities and to begin refining our five-year strategic plan. Once complete, leadership will share the areas of focus and continually provide updates on our progress.

PRE-AWARD ASSESSMENT RECOMMENDATIONS
In February 2016, the department formed a committee to assess our pre-award process to determine how best to meet the needs of our faculty. The pre-award process involves the preparation, review, approval and submission of research proposals to external funding agencies. After careful analysis, 19 recommendations were endorsed by departmental and divisional leadership. Several initiatives are underway. A training program has been established to support and advance the work of our junior faculty members, and research administrators can take advantage of additional opportunities for training and professional development — including the ability to become a certified research administrator through the Research Administrator Certification Council.
In addition, an on-call resource team has been established to help with work flow and the department will provide additional personnel to provide assistance during times of high volume. Over the next year, additional initiatives will be rolled out in phases.

PRE-AWARD ASSESSMENT COMMITTEE
Ben Margolis & Eric Mullen, Co-Sponsors
- Judy Carrillo, Internal Medicine Grants Manager, Committee Chair
- Elizabeth Spranger, Internal Medicine Project Manager
- Marlie Bartow, Grants Specialist Sr., General Medicine
- Marilyn Cramer, Grants Specialist Sr., Cardiovascular Medicine
- Donald May, Financial Sr. Manager, Gastroenterology
- Johannes Postma, Division Administrator, Infectious Diseases
- Susan Vandersluis, Financial Sr. Manager, Pulmonary Medicine
- June Wilson, Administrative Specialist Sr., Nephrology

2ND ANNUAL SERVICE AND EXCELLENCE CELEBRATION
The 2nd Annual Department of Internal Medicine Service & Excellence Celebration was held on Wednesday, April 27, 2016 at the North Campus Research Complex. The event recognizes the many contributions and achievements staff have made to the department. Two types of awards are celebrated: the Staff Award for Excellence and the Milestone Anniversaries of faculty and staff. Congratulations to the 2016 award winners.

AWARD FOR EXCELLENCE IN ADMINISTRATIVE ACTIVITIES
- Jeni Chapman, Lab Program Coordinator in the Division of Nephrology
- Delores Mortimer, Administrative Assistant Sr. in the Division of Gastroenterology
- Heather Refalo, Administrative Specialist Intermediate in the Division of Gastroenterology
- Debra Ventura, Administrative Specialist Sr. in the Chair’s Office

AWARD FOR EXCELLENCE IN CLINICAL SUPPORT
- Susan Olsson, Registered Nurse in the Division of Rheumatology
- Nancy Polmear-Swendris, Health Educator in the Division of Allergy and Clinical Immunology
- Lisa White, Call Center Supervisor for the Divisions of Gastroenterology and Infectious Diseases

AWARD FOR EXCELLENCE IN RESEARCH SUPPORT
- Colleen Harvey, Research Process Coordinator in the Division of Hematology/Oncology
- Carole Ramm, Clinical Research Project Manager in the Division of Metabolism, Endocrinology & Diabetes
- Kerry Ryan, Research Area Specialist Intermediate in the Division of General Medicine

NEW TEAM MEMBERS
In 2016, we were pleased to welcome two new division administrators to our department: Kim Rize, administrator for the Division of General Medicine and Dorothy Schroeder, administrator for the Divisions of Hematology/Oncology and Molecular Medicine & Genetics.
The year 2016 was a year of great transitions for undergraduate medical education at Michigan — especially for our students. As our U-M Medical School graduates entered the profession at a time of great change and promise, they received parting words from both the dean who led the school during most of their time as students and the new dean who recently took the helm.

This class was vital in shaping the development of our new undergraduate curriculum now being phased in over several years and helping the university redesign the Taubman Health Sciences Library building to make it a high-tech hub for medical and interprofessional health sciences education.

Our major curriculum transformation was spearheaded by internal medicine faculty member, James O. Woolliscroft, MD, who served as dean from 2007 to late 2015 and gave the commencement address to the graduation class.
In January 2016, Woolliscroft handed the baton to MARSCHALL RUNGE, MD, PhD, the first U-M executive vice president for medical affairs to also serve as dean of the medical school under a new leadership structure for Michigan Medicine. Runge, also a member of our faculty, hosted the ceremony.

OUR 170TH CLASS
In July 2016, we welcomed U-M’s 170th Medical School class from 28 states and 60 undergraduate colleges with educations in a wide range of fields, from biology and physics to political science, engineering and the arts. This diverse group is 56 percent female and 16.3 percent are from backgrounds traditionally underrepresented in medicine. The majority came to medical school after gaining experiences beyond college.

They are the very first class to be fully immersed in our new medical curriculum across all four years, as part of the American Medical Association’s Accelerating Change in Medical Education initiative.

Not only are they immersed in the clinical care world of Michigan Medicine from the beginning. They’ll develop an understanding of the immense importance of teamwork in the clinical setting by engaging in interprofessional education with students enrolled in U-M’s other health professions schools, including nursing, dentistry, pharmacy, public health, kinesiology and social work.

They are also the first class to be fully immersed in eight of the school’s new Paths of Excellence. Each gives students a chance to focus on an area where they can have an impact while they are in medical school, in fields such as ethics, global health & disparities, health policy, innovation & entrepreneurship, medical humanities, patient safety/quality improvement/complex systems, scholarship of learning & teaching and scientific discovery. Each path has its own faculty advisors, special experiences and a capstone project requirement for each student.

Our medical student community is brought together in the M-Home, a central part of the new curriculum. On their first day, students took part in a “sorting ceremony” to find out which of the four “houses” they’d spend their medical school careers with, as a way of creating community, support, small-group learning, wellness, service and mentoring opportunities within the school.

This new class of students could also choose from many combined-degree programs for medical students seeking to earn a master’s or doctorate degree in another field, including one of only 46 Medical Scientist Training Programs in the country offering a path to a combined MD and PhD in biomedical science.

PREPARED TO SUCCEED
For more than a century, going to medical school has meant basically the same thing across the country: four years of learning about human anatomy and physiology, and how to diagnose and treat the diseases that afflict us. Every medical student got roughly the same education, then chose a particular type of care to focus on in their residency.

This is rapidly changing and Michigan is staying ahead of the curve. Michigan was one of the original architects of the current medical school curriculum and continues to be a national leader in medical education. Michigan medical students are passionate and enthusiastic for medicine and creating a better world. We have a goal of having every graduate of the medical school be able to lead change in health, health care and health care science.

This is really an exciting time for medical education at Michigan.
This year, the Department of Internal Medicine Residency Program received more than 2,600 applications; of which, approximately 527 medicine and medicine-pediatrics candidates were interviewed with our faculty and program leadership from October 2015 through January 2016.

The Internal Medicine Residency Program welcomed its incoming intern class of 58 individuals in June 2016. They included six graduates of U-M Medical School along with other top-tier medical schools. Of this group, 58 percent are newly elected members of the Alpha Omega Alpha Honor Medical Society and 13 individuals have additional advanced degrees. The program also recruited two outstanding MD, PhD graduates for the physician-scientist track.
Seven of the incoming interns are with the program for one preliminary year of training before joining the Neurology Residency Program and are members of the combined Medicine-Pediatrics Program, directed by MICHAEL LUKELA, MD.

**CHIEF MEDICAL RESIDENTS**

Annually, the Department of Internal Medicine and Medicine-Pediatrics Residency Programs select new Chief Medical Residents (CMRs) in their respective programs. The CMRs are chosen by the leadership for each program based on their outstanding performance during residency, endorsement by their peers and their strong commitment to their respective programs.

This year, the CMRs for internal medicine are OWEN ALBIN, MD, AMIT GUPTA, MD, MEGAN SHETTY, MD and JESSICA VOIT, MD. In the Medicine-Pediatrics Program, the CMR is ADRIENNE CAREY, MD.

CMRs coordinate many of the clinical and educational opportunities for our medical residents while building their skills in education and leadership. Each is assigned to a different administrative area on a monthly rotating basis and will have the opportunity during the course of the year to direct the ambulatory and inpatient programs at the University Hospital and the VA Hospital.

**PROGRAM UPDATES**

We are in the process of developing a multidisciplinary global health and disparities track. We were able to launch a certification program in 2016.

Our primary care track, led by Kristin Collier, MD, continues to grow. There are now six students in the program. Led by Jennifer Lukela, MD, with the assistance of a group of our residents, we’ve also developed a resident-as-teacher curriculum. Pilot in 2015, it was made part of our training in 2016. Another new curriculum initiative is narrative medicine: listening to patients’ stories to help residents develop an enhanced sense of humanism.

Our vision is to continue to build flexibility into training to meet the individual needs of our learners. We have some unique areas of expertise: the physician-scientist track, the primary care track and global health and disparities. We need to keep responding to residents seeking new opportunities.

**DEPARTMENT OF INTERNAL MEDICINE RESIDENCY PROGRAM LEADERSHIP TEAM**

BACK ROW (L–R): ADAM S. TREMBLAY, MD, ASSOCIATE PROGRAM DIRECTOR; NAMITA SACHDEVA, MD, ASSOCIATE PROGRAM DIRECTOR, MEDICINE-PEDIATRICS; JOHN DEL VALLE, MD, PROGRAM DIRECTOR, SENIOR ASSOCIATE CHAIR, GRADUATE MEDICAL EDUCATION; SARA HARTLEY, MD, ASSOCIATE PROGRAM DIRECTOR; MICHAEL P. LUKELA, MD, PROGRAM DIRECTOR, MEDICINE-PEDIATRICS

FRONT ROW (L–R): JENNIFER LUKELA, MD, ASSISTANT PROGRAM DIRECTOR; THOMAS SISSON, MD, ASSOCIATE PROGRAM DIRECTOR, KRISTIN COLLiER, MD, ASSISTANT PROGRAM DIRECTOR.

NOT PICTURED: SUBRAMANIAMB PENNARTHUR, MD, ASSOCIATE PROGRAM DIRECTOR, DIRECTOR, PHYSICIAN-SCIENTIST TRAINING PROGRAM; RACHEL PERLMAN, MD, ASSOCIATE PROGRAM DIRECTOR.
SEATED (L–R): PAVAN REDDY, MD (HEMATOLOGY & ONCOLOGY); DAVID PINSKY, MD (CARDIOVASCULAR MEDICINE); POWEL KAZANJIAN, MD (INFECTIOUS DISEASES); LAURENCE MCMAHON, JR., MD, MPH (GENERAL MEDICINE); DAVID FOX, MD (RHEUMATOLOGY)

STANDING (L–R): JAMES BALDWIN, MD (ALLERGY & CLINICAL IMMUNOLOGY); CHUNG OXYANG, MD (GASTROENTEROLOGY); PETER ARVAN, MD, PhD (METABOLISM, ENDOCRINOLOGY & DIABETES); JOHN CARETHERS, MD (CHAIR OF INTERNAL MEDICINE); RAYMOND YUNG, MB, CHB (GERIATRIC & PALLIATIVE MEDICINE); SUBRAMANIAM PENNATHUR, MBBS (NEPHROLOGY); VINEET CHOPRA, MD, MSC (HOSPITAL MEDICINE)

MISSING FROM PHOTO: THEODORE STANIFORD, MD (PULMONARY & CRITICAL CARE MEDICINE); ERIC FEARON, MD, PhD (MOLECULAR MEDICINE & GENETICS)
ASSOCIATE CHAIRS

SEATED (L–R): RODICA POP-BUSUI, MD (CLINICAL RESEARCH); JOHN CARETHERS, MD (CHAIR OF INTERNAL MEDICINE); AND SCOTT FLANDERS, MD (QUALITY & INNOVATION)

STANDING (L–R): JOHN DEL VALLE, MD (GRADUATE MEDICAL EDUCATION); BENJAMIN L. MARGOLIS, MD (BASIC & TRANSLATIONAL RESEARCH); RICHARD H. SIMON, MD (FACULTY AFFAIRS); SANJAY SAINT, MD, MPH (VETERANS AFFAIRS); AND TIMOTHY J. LAING, MD (CLINICAL PROGRAMS)

MISSING FROM PHOTO: CYRIL GRUM, MD (UNDERGRADUATE MEDICAL EDUCATION)
2016 CHIEF MEDICAL RESIDENTS

FROM LEFT TO RIGHT: AMIT GUPTA, MD; MEGAN SHETTY, MD; JESSICA VOIT, MD; OWEN ALBIN, MD.
2016 Internal Medicine Awards

The Paul de Kruijf Lifetime Achievement Award
Chung Owyang, MD

Chairman's Award for Outstanding Service to the Department
Frank Brosius III, MD

Department of Internal Medicine Impact Award
Denege Ward, MD

Jerome W. Conn Award for Excellence in Research by a Junior Faculty Member
Vineet Chopra, MD
STUDENT AWARDS

William Dodd Robinson Award
APURBA CHAKRABARTI

Eli G. Rochelson Memorial Award
ANASTASIA NIEDZIELSKI

Henry Fitzbutler Award for Excellence in Hospitalist Medicine
KAORU HARADA

Department of Internal Medicine Senior Scholarships
JONATHAN BENDER
APURBA CHAKRABARTI
DANIEL CHOI
PETER FININ
ANDREW GARDNER
ANASTASIA NIEDZIELSKI
ARIANNA WILKINSON

RESIDENT AWARDS

Kenneth Stark Internal Medicine House Officer Research Award
AMY CHANG, MD
DENNIS HSU, MD
TIM KASELITZ, MD
ANDREW PUTNAM, MD

Laure Edmunds Award for the Most Outstanding House Officer I
MORGAN JONES, MD, PHD

Internal Medicine Award for the Most Outstanding House Officer
AMIT GUPTA, MD

Bruce A. Jones Award for Outstanding Housestaff Spirit
ZACH HAUP'T, MD
GARTH STROHBEHN, MD

Dr. Jacob P. Deerhake Community Service Award
STEPHANIE ROYER, MD

David S. Rosen Medicine-Pediatrics House Officer Award for Humanism
JAY FLYNN, MD

FACULTY AWARDS

H. Marvin Pollard Award for Outstanding Teaching of Residents
VINEET CHOPRA, MD

Richard D. Judge Award - Medical Student Teaching
VINEET CHOPRA, MD

Kaiser Permanente Award for Excellence in Clinical Teaching
VINEET CHOPRA, MD

Special Recognition for Contributions to the House Officer Teaching Program
HITINDER GURM, MD

Special Recognition for Contributions to the Medical Student Teaching Program
YEONG S. KWOK, MD

Steven E. Gradwohl Excellence in Continuity General Internal Medicine Teaching Award
JENNIFER LUKELA, MD

John G. Frohna Outstanding Teaching in Medicine-Pediatrics Award
REBECCA NORTHWAY, MD
2016 Dean’s Awards

Basic Science Research Award
YATRIK M. SHAH, PhD
ELIZABETH K. SPELIOTES, MD, PhD, MPH

Clinical and Health Services Research Award
JOHN Z. AYANIAN, MD, MPP

Innovation and Commercialization Award
ISRAEL HODISH, MD, PhD

Kaiser Permanente Awards for Excellence in Teaching
VINEET CHOPRA, MD, MSC

Lifetime Achievement Award in Medical Education
JAMES O. WOOLLISCROFT, MD

Medical School Community Service Award
N. CARY ENGLEBERG, MD

Outstanding Clinician Award
DANIEL F. HAYES, MD

Administrator of the Year Honorable Mention
JULIE C. BRABBS, MBA
This is in many ways a golden moment for the Department of Internal Medicine. Ranked 6th in the nation — thanks in no small part to the rich history of accomplishment highlighted in last year’s annual report — we care for more than half of Michigan Medicine’s patients, have a sizable footprint in the Medical School’s leadership and educational program, and have secured more than $170 million in research funding in 2016 alone. But we believe the best is yet to come.
Why? Because new tools and techniques, such as those highlighted on the following pages, are allowing us to ask and answer increasingly rich and probing questions from the realm of basic biology to health care outcomes — and to translate these findings into quality, evidence-based, patient-centered care.

But just as importantly the department finds itself in a period of unique institutional alignment. Internal medicine faculty and physician-scientists are at the helm, from President Mark S. Schlissel to our Dean, Executive Vice President for Medical Affairs and Michigan Medicine CEO Marschall S. Runge, to Department Chair John M. Carethers and our 12 division heads.

This year’s report focuses on how we are capitalizing on our momentum and this deep institutional support to shape the future of internal medicine. By connecting the talent in our department with the expertise across campus, we’re working to unravel the mechanisms of disease, discover new biomarkers and generate treatment approaches that will allow us to increasingly make once-lethal diseases manageable and chronic diseases curable, even preventable.

The goal is for our physicians to move from being purveyors of health care — to partners, with patients and their families, in fostering health.
Ten ways
U-M's Department of Internal Medicine
WILL SHAPE THE FUTURE
OF THE FIELD

1
PRECISION HEALTH
Why everything we do is moving Michigan Medicine toward more precise, patient-centered care.
p. 32

2
BIG DATA
Leveraging U-M’s big-data infrastructure to unmask cancer stem cells, win the microbial arms race, computer-analyze angiograms and predict the course of disease.
p. 44

3
RESEARCH PIPELINES
p. 54
Robust, integrated pipelines yield treatments now in trials for kidney disease and cancer. Vision takes researchers from bench to bedside — and beyond.

4
OMICS
Using genomics, epigenomics, metabolomics and microbiomics to identify disease risk and precision medicine opportunities.
p. 64
Developing technologies to catch cancer before it starts, grow mini organs for basic research, harness the power of e-health and more.

Internationally recognized leadership in improving quality, accessibility and value in health care.

Tinkering with the immune response holds promise in cancer therapy, autoimmunity, infection, allergy and organ transplant.

Training tomorrow’s leaders.

Research and care models that aim to increase our health span and honor our changing needs.
1. Precision Health

- WHAT WE MEAN BY "PRECISION HEALTH"  
  p. 34
- PRECISION HEALTH THROUGHOUT THIS REPORT  
  p. 34
- CLINICAL TRIALS TEST PRECISION MEDICINE IN CANCER  
  p. 35
- PRECISION MEDICINE IN ADRENAL CANCER  
  p. 37
- A NOVEL BIOMARKER FOR PRECISION HYPERTENSION TREATMENT  
  p. 38
- HOW HEALTH SERVICES RESEARCH CAN INFORM PRECISION MEDICINE  
  p. 39
- PRECISION COMMUNICATION  
  p. 42
It’s much more than an initiative. And it’s certainly not a buzzword. Precision health is, at its essence, what we’ve been working toward all along.

It’s health care tailored to the individual. When medicines can be matched to a molecular profile, we do it. And, as this report shows, we’re making enormous strides in identifying the molecular signatures of disease and making these matches possible.

But precision health is so much bigger. It’s about honoring each person’s unique symptoms, values, circumstances and goals. It’s both intensely personal and increasingly data-driven, as we develop new ways to learn from a patient’s characteristics and experiences — and mine those of similar individuals — to extract insights that will make care more informed, more comfortable and ultimately more effective.

The movement toward precision health is reflected in nearly every story in this report. And the reason for that is simple: From bench to bedside, more precise, patient-centered care is the goal of everything we do.
Because personalized, patient-centered care is the goal of everything we do, virtually every story in this report speaks to precision health. These examples reveal its many dimensions within the department’s work:

- Health services research helps individualize care p. 39
- Single cell analysis targets cancer’s heterogeneity p. 46
- Personalized readmission risk prediction p. 51
- A precision medicine research pipeline p. 58
- Omics efforts seek the molecular causes of disease and precision treatments p. 64
- A tailored behavior-change support app p. 80
- Physician decision-support tools to find the right care for each patient p. 88
- Precision insurance design p. 106
- A precision drug-delivery platform p. 119
- An app that identifies IBS patients’ personal trigger foods p. 125
- A treatment engagement tool that matches patients with programs p. 127
- Customizing care as we age p. 134

**What we mean by “Precision Health”**

Within the Department of Internal Medicine, precision health means many things. In fact, it’s less a specific approach than a philosophy. Yes, the term has its origins in efforts to match treatments to the genetic basis of disease — be it a specific cystic fibrosis mutation or a tumor’s genomic profile. But, as this report shows, it’s really about making health care more relevant and appropriate to each individual patient, along a growing number of dimensions.

Some precision health efforts focus on biology — identifying biomarkers that can tell us which patients will benefit most from a given drug. In the absence of clear biomarkers, other efforts seek to assemble a more nuanced collection of symptoms and risk factors that suggest a particular treatment. Still other efforts focus on drug delivery — finding ways to deliver drugs only to the cells that need them, for increased efficacy and reduced side effects. And, of course, there are vast efforts across the department to ensure that health care is aligned to a patient’s values, goals, preferences and life context.

Precision health is often characterized as “delivering the right care to the right person at the right time.” This can mean cancer drugs that target a tumor’s specific mutations or custom cancer vaccines derived from a patient’s own cells. It can mean data-driven methods that determine whether someone with type 2 diabetes could better manage the disease with medicine or with diet and exercise. Or it can mean a personal palliative care plan that honors the needs and wishes of a specific patient and family.

**Precision Health Rejects One-Size-Fits-All Health Care**

Traditionally, health care guidelines have been based on the “average” patient when, in truth, no one is average.

Precision health recognizes that every patient is different, every patient’s disease is different and both change over time. It aims for personalized, appropriate care that enhances patient-defined well-being and avoids overtreatment, under treatment and side effects.

**Why Precision Health throughout This Report**

Because personalized, patient-centered care is the goal of everything we do, virtually every story in this report speaks to precision health. These examples reveal its many dimensions within the department’s work:
Members of the Division of Hematology & Oncology are playing a major role in national clinical trials designed to test the value of precision cancer treatment while offering potentially game-changing therapies to patients. U-M’s participation is being led by Assistant Professor AJJAI ALVA, MD, who specializes in precision oncology and clinical research on genitourinary cancers. He’s the U-M Comprehensive Cancer Center’s principal investigator for both the NCI-MATCH study from the National Cancer Institute (see graphic) and the ASCO-TAPUR study, the American Society of Clinical Oncology’s Targeted Agent and Profiling Utilization Registry study. Both studies aim to capitalize on our recent ability to sequence tumors and identify mutations that can be targeted by existing drugs — those that are either FDA-approved or in clinical trials. This is a vital opportunity to test the effectiveness of treating cancer by its genomic profile rather than its site of origin, as well as to make precision treatments available to patients for whom standard therapies have failed.

“Right now, insurance companies will only cover and the FDA only approves drugs based on diagnoses — breast cancer, kidney cancer and so on,” says Alva. “But what if I have a patient with kidney cancer whose tumor has a gene that can be targeted by an approved breast cancer drug? Until these trials started, we couldn’t get such a drug for my kidney cancer patients — even though we know there’s a good chance the drug would work for them.”

CONTINUED ON PAGE 36
Alva believes these studies, and smaller, more specific studies like them, could be game changers for precision cancer treatment.

**CAPITALIZING ON MICHIGAN MEDICINE’S CLINICAL AND RESEARCH STRENGTHS**

Alva says oncologists throughout the department benefit from Michigan Medicine’s world-class expertise in cancer genetics and precision oncology.

One high-value resource, he says, is U-M’s Cancer Genetics Clinic under the leadership of ELENA STOFFEL, MD, MPH, assistant professor in the Division of Gastroenterology. “This cutting-edge clinic is critical for patients who may have hereditary cancer risks involving defective genes like BRCA 1 and 2,” says Alva. “The work-up for suspected familial conditions is increasingly complex, the genetic mechanisms of disease risk are not straightforward and new genetic associations are being recognized all the time. The sophisticated technology and genetic counseling offered by the Cancer Genetics Clinic is essential to helping patients understand their risk profile.”

Another important resource is the Michigan Oncology Sequencing Center (Mi-Oncoseq), an ambitious initiative in clinical sequencing designed to identify mutations within individual patients’ cancers that can be targeted with existing therapies. It’s led by Arul Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology.

**OF THE APPROXIMATELY 600 CANCER-RELATED CLINICAL TRIALS CURRENTLY IN PROGRESS AT MICHIGAN MEDICINE, NEARLY 350 HAVE PRINCIPAL INVESTIGATORS FROM THE DEPARTMENT OF INTERNAL MEDICINE.**

S.P. Hicks Endowed Professor of Pathology and Howard Hughes Medical Institute investigator.

“Dr. Chinnaiyan is one of the pioneers of tumor genome sequencing; in fact, he discovered gene fusions and DNA repair defects that lead to prostate cancer,” says Alva. “He has a world-class infrastructure for tumor sequencing in Mi-Oncoseq, and he’s sequenced more than 2,000 patients’ tumor exomes and RNA profiles. This enables us to see how we can match drugs to patients’ specific mutations. This is really groundbreaking and allows us to leverage our in-house strengths to better care for our patients.”

Another leading Michigan Medicine researcher with whom many internal medicine faculty collaborate is Weiping Zou, MD, PhD, the Charles B. de Nancrede Professor of Surgery, Immunology and Biology and co-director of U-M’s Cancer Hematopoiesis and Immunology Program.

“Dr. Zou is a leader in cancer immunology and immunotherapy,” says Alva. “He was one of the pioneers who defined immune checkpoints in the human cancer microenvironment — our bodies’ natural ‘brakes’ on the immune system.”

**HEM/ONC RESEARCHERS ARE ALSO COORDINATING NUMEROUS PRECISION MEDICINE TRIALS THAT COMPLEMENT LARGER NATIONAL EFFORTS.**

For example, PHILLIP PALMBOS, MD, is testing the approved breast-cancer drug palbociclib in patients with prostate cancer, and Alva is testing the same drug for bladder cancer patients in collaboration with researchers at the University of North Carolina. CHRISTOPHER LAO, MD, is testing the immunotherapy drug nivolumab for various cancers in which viruses have been shown to play a role in tumor development.
system, which cancer often hijacks in order to survive. We’ve been trying to get around this with immune checkpoint inhibitors, and Dr. Zou’s work suggests that combining immune checkpoint inhibitors with an epigenetic therapy called hypomethylating agents could allow them to work in a greater percentage of patients.”

Alva is leading a soon-to-open trial within the Big Ten Cancer Research Consortium designed to test next-generation combination immunotherapy for advanced kidney cancer.

Of course, testing new therapies requires methods for monitoring patients’ cancers to see if they’re responding or becoming resistant to treatment. Alva and fellow divisional colleagues such as MUNEESH TEWARI, MD, PhD, the Ray and Ruth Anderson-Laurence M. Sprague Memorial Research Professor of Internal Medicine, are advancing the use of liquid biopsies to capture DNA shed from cancer cells into the blood (page 86).

“Using circulating tumor DNA is of immense help, not only for patients in whom traditional tissue biopsies are difficult or not possible, but also for patients we need to monitor continuously,” says Alva.

A PRECISION ENDGAME

“My goal in the years ahead is to be able to take a patient’s blood or tumor, run a panel of biomarkers including sequencing that is clinically relevant for treatment at an affordable price, and have access to the drugs to act on what we find,” says Alva. “We’re getting closer. Thanks to clinical trials like MATCH and TAPUR, in five years’ time, I think we’ll be offering precision therapies first. As we increasingly target the many genomic subtypes of cancer, we’re no longer blindly throwing a dart in the dark and hoping it hits the target — we’re switching on the light.”

International research on adrenal cancer led by GARY D. HAMMER, MD, PhD, the Millie Schembechler Professor of Adrenal Cancer in the Division of Metabolism, Endocrinology & Diabetes and director of the Endocrine Oncology Program, has led to a number of promising precision medicine leads for this rare and deadly cancer which currently has limited treatment options.

One lead comes from a phase III trial of the drug linsitinib, which targets an IGF1 receptor that Hammer’s group helped implicate in adrenal cancer. The study found that a small subset of patients responded well to the drug, some with prolonged progression-free survival. A 2016 study in Cancer Cell helped shed light on why this subgroup may have responded.

Comprehensive genomic analyses within The Cancer Genome Atlas Research Network identified at least three subtypes of adrenal cancer, each with distinct molecular biomarkers. All three subtypes featured IGF2 over-expression, but in the group with a profile similar to the linsitinib responders, this was the dominant mutation, whereas other groups harbored additional mutations that likely reduced the effectiveness of the drug.

“Precision medicine is teaching us that the effectiveness of a drug is not only about which mutation it hits but which mutations it’s not hitting,” says Hammer. But because this study found additional genes that may drive adrenal cancer — including 15 frequently occurring, potentially targetable mutations — it offers the potential for precision treatment of other adrenal cancer subtypes.

The Hammer team has also developed a new precision adrenal drug, ATR-101. By targeting the enzyme ACAT1, it decreases adrenal steroid production and induces cell death specifically in the adrenal cortex. Hammer has co-founded a spinoff company to study ATR-101 in congenital adrenal hyperplasia, Cushing’s syndrome and adrenal cancer.
Precision medicine relies on biomarkers — to determine disease risk, prognosis and response to treatment. So a critical aspect of advancing precision medicine is developing and validating biomarkers for a wider range of conditions and disease subtypes.

One such effort is underway in the Division of Cardiovascular Medicine by Assistant Professor J. Brian Byrd, MD, MS. He’s using an NIH K23 grant to look for a novel biomarker of a type of hypertension that would benefit profoundly from a precision medicine approach.

This type of hypertension responds poorly to standard therapies because it is driven by a distinctive process — hormones produced in the adrenal gland called mineralocorticoids. There are FDA-approved drugs that target the mineralocorticoid receptor, but because they come with significant side effects, physicians want to ensure they prescribe them only to patients likely to benefit.

Byrd thinks he has found a specific biomarker of mineralocorticoid receptor activation and can reliably test for it in patients’ urine.

“Different factors can lead to treatment-resistant high blood pressure,” says Byrd. “We want to make it possible for clinicians to figure out in whom activation of this receptor is driving the process, so they can treat those patients appropriately. Blood-pressure control is an immensely important goal because high blood pressure is the leading risk factor for death and disability around the globe. But mineralocorticoid receptor treatments come with risks, so we want to be sure they’re used only in patients whose blood pressure will be responsive to them.”

“If this research program is successful, clinicians will have a simple way to understand when mineralocorticoid receptor blockers would be effective in patients with treatment-resistant high blood pressure — and other patients would be spared side effects from an ineffective treatment.”

— J. Brian Byrd, Cardiovascular Medicine
Health services researchers spend a lot of time thinking about issues like quality, value and access in health care. On first blush, it may not be obvious how these link to the issue of precision health — but it’s all in how you define it.

The ideal way is broadly, says Laurence McMahon, Jr., MD, MPH, division chief and professor in the Division of General Medicine and a leading health services researcher with the Institute for Healthcare Policy and Innovation (IHPI). He describes three “layers” of personal data that underpin precision health, each of which can enrich our understanding of how to care for patients in a more individualized and effective way.

The first layer is the one most classically associated with precision medicine — genomics. Tumor sequencing data, for example, is enabling precision cancer trials (page 35), and testing for other genetically driven diseases, like cystic fibrosis, can allow us to match patients with a specific mutation to the appropriate treatment.

The second layer, says McMahon, is phenomics. This involves traditional clinical data that sheds light on how genetics and environment interact to create risk factors and diseases which impact health outcomes. For example, a patient’s cholesterol level and other diseases like diabetes and hypertension can together allow us to calculate his or her risk of developing cardiovascular disease. From here, we can devise a personalized risk profile to guide tailored disease prevention or treatment strategies.

The third layer features the behavioral and social determinants of health — socioeconomic, psychological and behavioral data that can often identify individuals at higher risk of disease and how they may respond to it. This includes variables like income, education, social support, functional status, community characteristics, attitudes and beliefs that affect patients’ receptivity to various treatments and ability to access them. Thus, they are important factors to consider when developing a patient’s individualized care plan.

It is in these second and third arenas, says McMahon, that health services researchers can make a particular contribution and improve our approach to precision health.

CONTINUED ON PAGE 40
Members of the department have been pioneers in turning the principles of phenomics into precision medicine strategies. A classic example is Rodney Hayward, MD, professor in the Division of General Medicine, IHPI member and senior investigator at the VA Center for Clinical Management Research. Hayward’s seminal research on personalized cardiovascular risk prediction helped change national cholesterol guidelines.

His group challenged the appropriateness of prescribing statins based on population-level associations between LDL levels and the risk of heart attack and stroke. Their analyses showed that statins could be more appropriately prescribed based on an individual’s cardiovascular risk score — a number that takes into account a broader array of variables, such as a patient’s age, sex, blood pressure, co-morbidities, smoking history and so on. Hayward’s group helped show that these more individualized risk prediction scores better identified patients who would benefit from statin therapies, reducing over- and under-treatment.

From here, other members of the department can move such insights further toward implementation by creating tools physicians and patients can use in the clinic. The Center for Health Communications Research, directed by Laurence An (pages 42 & 80), specializes in the development of tools that can input individual patient data and output personalized treatment recommendations and tailored patient education materials.

“Where we can come in is to develop tools that help clinicians put a new formula or algorithm into practice,” says An. “For example, Dr. Hayward’s risk model might take into account a dozen or more factors, yet we know that it’s hard for people to make decisions when they have to keep in mind more than just a few factors. We develop decision-support tools that can take a patient’s data and present his or her projected risk reduction for a variety of treatment options, from medications to behavioral interventions like diet and exercise.”

McMahon says decision-support resources like this will be increasingly important to realizing the potential of precision health. Another important strategy, he says, is for researchers to reconsider how they report data from clinical trials. “In order for any type of personalized or precision approach to work, clinical investigators will need to use

IHPI Evaluates CMS Decision-Support Tool

Tools to inform physician decision making are likely to be an important pillar of precision health efforts going forward. But to ensure they’re adding their intended value, they must be rigorously evaluated.

To this end, IHPI has launched an evaluation of a new decision-support tool for the ordering of high-cost imaging tests.

“It’s a requirement of the Centers for Medicare & Medicaid Services that we implement this tool, but not a requirement that it be evaluated,” says IHPI Director John Ayanian. “As a major university and academic health system, we believe it’s our role to evaluate significant practice and policy interventions so we can understand their effectiveness and use that evidence to guide future efforts.”
multivariate risk models, rather than traditional subgroups, to determine who is most likely to benefit from a particular therapy and who might be harmed by it.”

**SOCIAL DETERMINANTS OF HEALTH**

The other realm in which health services researchers can inform precision health efforts is incorporating social determinants of health into models of care.

McMahon himself has done influential work showing the impact of social determinants on patient outcomes. “We’ve shown that adding social determinants, such as a patient’s functional impairment, economic resources and social support, into Medicare’s hospital readmission models improves their ability to predict who is likely to be readmitted,” he says. He thinks these same determinants can help guide physicians in caring for their patients within a precision health framework.

There are many ways in which these factors can impact health, says McMahon. “If you have limited resources, you may have to live in a place with terrible air or lead exposure. Perhaps you don’t have access to transportation for a screening, or you’re a single parent with a sick child and you don’t have the bandwidth to exercise and take care of yourself. All these components can modify your chances of developing disease because you’re not doing preventive things or of effectively managing a disease once you have it.”

He says health services research can help guide the integration of social determinants and community factors into disease models and treatment approaches so that they better match individual patients. Tailored care may be reflected in anything from the appropriateness of a particular medication regimen to the need for behavioral health support or social services.

IHPI Director **JOHN AYANIAN**, MD, MPP, the Alice Hamilton Professor of Medicine in the Division of General Medicine, says this integration will happen more readily as we increasingly tap data sources beyond the health system. “As big data resources move forward, we’ll have access to much more data from people’s homes, from their workplaces and from their communities to give us a much broader and deeper view of health and illness beyond the clinics and hospitals where we’ve traditionally collected our data.”

These data will include a dimension championed by the HSR community — the patient perspective. “We want to help patients achieve the best possible health in ways they personally value,” says Ayanian. “At present, we have a very clinical concept of health and illness focused on providers’ perspective on outcomes. Take, for example, survival after surgery. This is obviously important to patients, but so is how well they are functioning in their homes and communities after they leave the hospital. There has been a major effort to develop more refined patient-reported outcome measures so that we can integrate these data with patients’ preferences and values to ensure we are offering care that is right for them.”

McMahon says that incorporating more social and patient-centered variables into care will require a cultural shift in medicine. However, the technical shift isn’t as great as many might assume, because some of these data are available but unused. Of course, others will increasingly need to be collected, but he says the added value is worth it. “As we begin to integrate these factors into disease models and treatment approaches, we will become more nuanced in how we provide care than we are today.”
Precision health holds enormous potential to improve patient care, but, like most things, execution is everything. Proper communication is essential, and the Center for Health Communications Research (CHCR) is working, not only to make providers aware of this, but to give them the tools to do it.

The CHCR is directed by LAWRENCE AN, MD, associate professor in the Division of General Medicine. He characterizes the center’s mission as developing precision communication tools that “deliver the right message to the right person at the right time in the right way.” This requires careful attention to what patients need to know and how they need to be supported.

The center is working on a number of tools to help physicians better communicate with their patients in the precision health arena.

**IMPROVING COMMUNICATION IN PRECISION ONCOLOGY**

The first is a collaboration with tumor genomic sequencing expert Arul Chinnaiyan (page 36), a member of the NIH’s Clinical Sequencing Exploratory Research (CSER) Consortium. An’s center plans to develop a “precision communication” program to improve communication in the practice of precision oncology. The program will combine personally tailored education for providers, patients and families with an expert question-and-answer telephone helpline.

It’s designed to address common communication challenges that can change the precision medicine experience from a positive to a negative one for patients. It aims to ensure, first, that patients understand the nature of the genomic testing they’ll undergo and the information it can and can’t provide; second, that patients understand the implications of their own test results; and third, that they have the understanding and support they need to communicate important findings to their families.

“Some of our colleagues, such as Scott Roberts and Brian Zikmund-Fisher in the School of Public Health and MICHELE GORNICK from the Division of General Medicine have shown that patients often don’t fully understand what their tests may find and their prospects for treatment,” says An. “One example is a precision medicine trial participant who was told she had a ‘potentially actionable mutation’ but couldn’t be treated for it due to other health conditions. Because appropriate expectations for the study weren’t provided up front, the trial left this patient more stressed than if she had proceeded with standard care. Our tool aims to ensure this doesn’t happen.”

**EMOTIONAL SUPPORT FOR CANCER DECISION MAKING**

Because communication is so integral to patients’ emotional experience of disease and treatment, An’s group is also incorporating this dimension into decision-support tools the CHCR is helping to develop for breast cancer treatment. This is a collaboration with STEVEN KATZ, MD, MPH, professor in the Division of General Medicine and director of the Cancer Surveillance and Outcomes Research Team (CanSORT), and SARAH HAWLEY, PhD, MPH, CanSORT co-founder and professor in the Division of General Medicine.

The tools they’re developing aim to improve patients’ knowledge and satisfaction with decision making by providing both information and emotional support. “Medical decision making has tended to operate on this super-

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**A FOUNDATION OF PRECISION HEALTH**

Precision Health42
rational model that assumes if we give patients the pros and cons of various treatments, they will weigh them, come up with a rational decision and follow it,” says An. “People don’t work that way. Fear and anxiety can drive decisions that don’t match the evidence. So we need to improve both communication and emotional support — or all of this new information from precision tests won’t be applied well.”

After guiding patients through an interactive decision-making process in an informational and emotionally supportive manner, these online programs would then share the results with their physician to personalize and enhance treatment discussions.

**VIRTUAL COMMUNICATION TRAINING FOR PROVIDERS**

Of course, even with better patient education, these conversations can be challenging for physicians. That’s why An’s group is working on yet another way to strengthen them. They’re building a digital breast cancer patient so physicians can practice these interactions and refine their communication skills.

“Mock, face-to-face encounters have traditionally been the gold standard to train providers in patient interaction,” says An. “But this approach is labor- and resource-intensive, so most doctors- and nurses-in-training have very few opportunities for practice and feedback to build these skills. The virtual training environment is at a provider’s fingertips. We think these simulations will be a valuable way to help physicians learn to communicate in the era of precision medicine.”

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**THE “I CAN DECIDE” BREAST CANCER DECISION AID HAS IMPROVED PATIENT UNDERSTANDING OF BREAST CANCER AND ITS TREATMENTS; THE NEXT VERSION WILL ADD ENHANCED EMOTIONAL SUPPORT.**

**THE “CANCER DOCTORS LIKE ME” WEBSITE PROVIDES VIRTUAL COMMUNICATION TRAINING TO CANCER SPECIALISTS.**
2. BIG DATA

- UNMASKING CANCER STEM CELLS p. 46
- COMPUTERIZED ANGIOGRAPHY ANALYSIS p. 48
- PERSONALIZED DISEASE-RISK PREDICTION p. 48
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- U-M BIG DATA SUPPORT p. 53

Please see the Omics section for more examples of our big-data work, page 64.
Thanks to the recent explosion in computing power, access to novel data sets and the development of sophisticated data analysis techniques, Department of Internal Medicine researchers are using “big data” to ask increasingly meaningful and nuanced questions.

“The biggest potential of big data,” says cardiologist Brahmajee Nallamothu, whose work is featured in this section, “is the realization that everything around us is a number — even text, images and videos are digitized. In the past, we had to content ourselves with what we could measure. Going forward, we can use this wealth of data and new analytical techniques to measure what is important to measure.”

By collaborating with colleagues in computer science and engineering, computational medicine and bioinformatics, public health and other areas, our faculty are using big data sets to answer pressing questions from the basic sciences to health services research and everything in between.
In 2016, the University of Michigan Institute for Data Science (MIDAS) awarded health sciences grants to create new structures and projects that support high-potential big-data work at U-M. One recipient was the Michigan Center for Single-Cell Genomic Data Analytics.

The new center is designed to provide the analytical tools researchers need to make sense of the complex and unique data sets coming out of single-cell sequencing platforms, such as those in place at the U-M Comprehensive Cancer Center. These platforms are capable of isolating and sequencing thousands of individual cells taken from a tumor or blood sample. However, these data require cutting-edge analytical methods to accurately characterize the cells and their function.

One internal medicine researcher joining the new center is MAX WICHA, MD, the Madeline and Sidney Forbes Professor of Oncology, founding director emeritus of the U-M Comprehensive Cancer Center and internationally recognized breast cancer expert. Wicha was the first to identify cancer stem cells in a solid tumor — the cells most resistant to existing cancer therapies and responsible for cancer recurrence and metastasis.

His basic-science goal in the new center is to use functional genomic analyses to precisely identify all the different cell types in a given sample by their unique signatures and to learn in more detail how these cells are interacting with one another.

With this information, he says, his group can develop new therapies that block the critical pathways stem cells need to survive. He also plans to use the technique to test therapies they’ve already developed, several of which are now in clinical trials. By capturing circulating tumor cells in cancer stem cells, various immune cells and so forth — to be identified by a unique genomic fingerprint.

This more detailed tumor analysis paves the way for next-generation precision medicine treatments that address cancer’s heterogeneity.

In addition, this data can reveal how cells are signaling each other, suggesting new targets for therapy.

Single-cell analysis can also be used in clinical trials to determine if specific therapies are reducing targeted cell populations and affecting targeted pathways.

The Promise of Single-Cell Analysis

Traditional examinations of tumor genomics rely on bulk samples, where all the cells’ genetic material is mixed together and sequenced en masse. While this can yield insights into highly activated pathways, the readout is an average for all the cells sampled. Since cancer stem cells are rare, their uniqueness is masked — as is the heterogeneity of the tumor cell population.

Single-cell analysis allows each cell type in a tumor — different cancer cell clonal populations, big data
a patient’s blood sample, he can assess in real time whether
the number of cancer stem cells is declining and whether the
pathways targeted by the treatments are being affected.

To accomplish this, Wicha relies on the center’s expertise in
“sparse data analysis.”

Gene expression at the single-cell level is a prime example
of sparse data, says Jun Li, PhD, the center’s co-director
and an associate professor in the Departments of Human
Genetics and Computational Medicine & Bioinformatics.

“In each cell, there will be a lot of RNA sequences for which
you detect a very low number — zero, one or two,” he says.
“Sometimes genetic information is missing from the se-
quecing readout, and we have to account for that. In
addition, small differences in abundance in a single cell are
exaggerated with low numbers. One extra copy of RNA in
a single cell can look like it represents a two-fold increase
over another cell, when the real difference between those
populations could be only 1.2-fold. So we work to develop
techniques that borrow information across genes and cells
to increase the accuracy of our conclusions.”

The center will help researchers understand the heterogene-
ity in a cell population and provide data to model cell-to-cell
interactions in any complex tissue.

Other internal medicine researchers are also tapping the
center’s expertise to probe cancer at single-cell resolution.

SAMI MALEK, MD, associate professor in the Division of
Hematology & Oncology, is using it to explore the
cellular source of relapse in Acute Myeloid Leukemia.

But Wicha and Li think the approach holds promise
well beyond cancer. They say it is particularly well-
suited to exploring the molecular changes in various
cell types as a result of environmental exposures,
with applications ranging from organ development
to gene-environment interaction. “We hope to
make single-cell analysis available to everyone at
the university,” says Wicha. “We think it will lead to
breakthroughs across the disease spectrum.”
Another recipient of a 2016 MIDAS health sciences grant is a group that aims to revolutionize precision and predictive medicine by connecting the actors necessary to translate big data into better health. Called the Michigan Integrated Center for Health Analytics and Medical Prediction, or MiCHAMP, the group is comprised of experts in methods, informatics and medicine who are developing image-analysis and disease risk-prediction tools that they hope will improve care across a range of conditions.

MiCHAMP’s director is BRAHMAJEE NALLAMOTHU, MD, MPH, professor in the Division of Cardiovascular Medicine and faculty lead for the Data and Methods Hub in the Institute for Healthcare Policy and Innovation. He was inspired to assemble a group that would seize the promise of big data during his time co-chairing a national performance measures group on coronary stenting.

“Almost all of our existing quality measures were limiting,” says Nallamothu, “because they were based on things we could easily extract from a patient’s chart. But the field of interventional cardiology is highly visual. I realized we could potentially tell more about the quality of stenting by analyzing the images and videos we use daily — our angiograms — than from whether someone checked a box in the chart about a drug being prescribed. It struck me that we were working with what we could measure, rather than what was important to measure.”

He began collaborating with a group at the Michigan Center for Integrative Research in Critical Care (M-CIRCC) on feature extraction from images. In the process, he discovered a cohort of like-minded researchers interested in thinking more creatively about both potential sources of health care data and how to turn that data into knowledge that providers could use to personalize care.

That group formed the seeds of MiCHAMP. It is a space where three types of expertise converge: health care researchers interested in out-of-the-box analytical approaches; computer scientists interested in creating algorithms for practical health care applications; and informatics experts interested in designing health information systems that can scale widely and automate the extraction of information useful to the other two groups.

Nallamothu himself is leveraging this expertise to develop a computer-assisted angiogram analysis tool. He’s also helped catalyze two MIDAS-funded pilot projects within MiCHAMP, both led on the health care side by internal medicine researchers. Each uses machine learning to find patterns in mountains of longitudinal data to flag important health risks that could dramatically improve patient care.

“What happens in MiCHAMP is truly magical — multidisciplinary researchers learning to speak each other’s languages and bringing this energy and deep collaborative spirit to address patient needs in a transformational way.”

— JOAN KELLENBERG, MiCHAMP
COMPUTER-ASSISTED ANGIOGRAM ANALYSIS TOOL

Nallamothu is hoping to enhance the quality of interventional cardiology procedures with a computer-assisted angiogram analysis tool he is co-developing with computational medicine and bioinformatics colleague and M-CIRCC Associate Director Kayvan Najarian, PhD.

The system uses advanced image processing and machine learning to add a layer of objectivity and quantitation to a physician’s interpretation of the images, reducing the potential for human error. Preliminary results show that the platform can flag a specific part of the vascular tree for further study and estimate the width and percentage of blockage in each vessel.

“We envision a tool where, as soon as you inject the contrast, the computer will read the angiogram alongside you and say, ‘Here are some areas you need to think about,’ ” says Nallamothu. “It’s still early in development, but the implications are enormous. It could be used for quality assurance to make sure we are stenting the right blood vessels and to educate trainees so we all become a bit more standardized in how we interpret these images.”

The pair are working through U-M’s Fast Forward Medical Innovation Program to develop the tool with an eye toward commercialization and implementation.
**Predicting Hepatitis C Progression**

The first MIDAS-funded risk-prediction tool MiCHAMP is piloting aims to determine which patients infected with hepatitis C virus (HCV) will be among the 20 to 30 percent who proceed to cirrhosis and the two to seven percent who progress to liver failure.

It’s an important question because, although we now have drugs that can cure HCV, they are expensive — initially as much as $100,000 per patient — so deciding how to direct treatment to those who will benefit most is essential.

Developed on the health care side by Akbar Waljee, MD, MSc, assistant professor in the Division of Gastroenterology, the tool will consider a diverse set of data points — like demographics, text in clinical notes, liver function tests, imaging findings and biopsy results — as well as how changes in these data over time affect outcomes. By changing the paradigm from using data as a “snapshot in time” to longitudinal analysis, the team hopes to pinpoint who with HCV is most likely to progress with the disease and should be a priority for treatment.

**Predicting Acute Respiratory Distress Syndrome**

The other MiCHAMP pilot project supported by MIDAS will use a similar approach to flag patients at risk for developing Acute Respiratory Distress Syndrome (ARDS), a life-threatening inflammatory lung injury that results from critical illness or trauma.

ARDS is often missed or diagnosed late because clinicians are unable to identify the essential diagnostic elements within the massive streams of data generated on these patients. As a consequence, patients with ARDS frequently fail to receive therapies that improve survival.

A team guided by Michael Sjoding, MD, MSc, assistant professor in the Division of Pulmonary & Critical Care Medicine, is developing computerized algorithms to help clinicians catch ARDS more consistently and at an earlier, more treatable stage. They’ll do this by mining the minute-by-minute, day-to-day electronic data collected on patients in critical care settings for patterns of emerging ARDS.

These researchers hope better stratification of patients will pave the way for precision care — and also for smarter clinical trials, where the right groups are enrolled based on the nature of the trial.
PREDICTING SEPSIS READMISSION

Another member of MiCHAMP, HALLIE PRESCOTT, MD, MSc, is using a recent NIH K08 grant to focus on sepsis, a body-wide overreaction to infection that can cause organ failure and death. An assistant professor in the Division of Pulmonary & Critical Care Medicine and the VA Ann Arbor Healthcare System, Prescott is taking a unique look at discharged sepsis patients’ risk for being readmitted to the hospital — trying to predict the specific complication a given patient is most likely to experience.

This is a big departure from researchers’ traditional approach to sepsis readmission. Most, says Prescott, have looked at the issue from a policy perspective, evaluating readmission penalties from the Centers for Medicare & Medicaid Services. Thus, they look broadly at a patient’s overall risk for being readmitted — and only in the 30 days following discharge. They also tend to rely on billing data, which contains relatively general information like age, gender, race and diagnoses.

But Prescott seeks to generate insights more relevant to patient care. She’s looking specifically at the five reasons she’s found that patients are most frequently readmitted: recurrent infection, heart failure, kidney failure, lung-disease exacerbation and food aspiration. To tease out which complication a patient is most likely to experience, she’s using more granular data, including labs and vital signs, from the electronic medical records of 100,000 veterans hospitalized with sepsis. In addition, she’s following them for a full 90 days, which she says is the key period during which they’re at risk for readmission.

The result, she hopes, will be a tool that primary care doctors can use to better monitor and care for their patients.

“The tool we’re developing aims to better predict an individual’s risk for these five things, all of which have pro-dromes and may be actionable in the outpatient setting,” says Prescott. “Instead of telling a primary care physician that a patient has a high risk for readmission, which they probably already know, our goal is to say, ‘Your patient’s biggest risk is in the area of heart failure or aspiration.’ If they only have 15 minutes in a follow-up appointment, they can reduce that risk most by focusing there, adjusting someone’s heart medication or ensuring they’re being assessed for swallowing difficulty.”

“HALLIE PRESCOTT’S GENIUS IS IDENTIFYING KEY AREAS OF MEDICAL CONCERN IN SEPSIS THAT A HEALTH CARE SYSTEM CAN SCREEN FOR AND FIX. I SUSPECT THAT IN THE NEXT 10 YEARS, PEOPLE WILL BE DISCHARGED FROM THE HOSPITAL WITH A PERSONALIZED PROFILE OF WHAT THEY’RE MOST AT RISK FOR IN THE COMING WEEKS, SO THEIR PHYSICIAN CAN WORK WITH THEM TO MAKE SURE THOSE RISKS DON’T COME TO FRUITION.”

—JACK IWASHYNA, PULMONARY & CRITICAL CARE MEDICINE
Assistant Professor ROBERT WOODS, MD, PhD, from the Division of Infectious Diseases, is using big data to help us stay one step ahead of the pathogens. He has received an NIH K08 grant to use evolutionary theory to understand how rotavirus, a major cause of childhood diarrheal disease worldwide, evolves and spreads in response to the use of our current, only partially effective, vaccine.

He’s probing how rotavirus uses reassortment to evolve and how new strains spread using a combination of phylogenetic analysis of viral genome sequences, lab experiments and epidemiological modeling. With this information, he hopes to shed light on where vaccine-resistant strains are most likely to emerge.

“Ideally we’d like to be able to predict whether this might happen in developed countries, where vaccination rates are higher, or in developing countries, where there is frequent interaction between human and animal populations,” says Woods. Animals provide an important source of genetic diversity to the virus.

Ultimately, he hopes his insights will allow us to more effectively monitor for the emergence of vaccine-resistant strains and to develop new vaccine strategies that make it more difficult for the virus to adapt and spread.

Woods has already had success applying a similar approach to understand how bacteria become resistant to antibiotics and spread within the hospital setting. In this case, he’s tested an intervention showing that changing antibiotic use can cause bacteria to become less resistant.

“My hope is that in the future,” says Woods, “we will look back and say we figured out how our therapies were leading to the emergence of resistance and came up with better ways to prevent that from happening.”
In 2015, U-M launched a $100 million Data Science Initiative, further enriching the support for big-data research efforts across campus, from high-throughput omics approaches to analysis of electronic medical records and other complex data sets. Some resources that are particularly useful to internal medicine researchers include:

**MICHIGAN INSTITUTE FOR DATA SCIENCE (MIDAS)**
Catalyzes big-data efforts across four strategic areas, including health and medicine. Connects an interdisciplinary core faculty of data scientists, fosters training and industry engagement, and sponsors health-related centers:

- **MICHIGAN INTEGRATED CENTER FOR HEALTH ANALYTICS AND MEDICAL PREDICTION (MiCHAMP)**
  Aims to help researchers exploit high-dimensional data to advance predictive and precision medicine, page 48.

- **MICHIGAN CENTER FOR SINGLE-CELL GENOMIC DATA ANALYTICS**
  Aims to advance single-cell analysis by developing methods to deal with sparse data, page 46.

MIDAS is complemented by a sister institute in computational science (MICDE) as well as support services in computing technology (ARC-TS) and consulting in data management, collection and statistical analysis (CSCAR).

**MEDICAL SCHOOL OFFICE OF RESEARCH**
Offers comprehensive research support from biorepositories to clinical trials to the Michigan Institute for Clinical and Health Research (MICHR). Key big-data resources include:

- **BIOMEDICAL RESEARCH CORE FACILITIES (BRCF)**
  Cores in DNA/RNA sequencing, bioinformatics, epigenomics, proteomics and metabolomics.

- **DATA OFFICE FOR CLINICAL AND TRANSLATIONAL RESEARCH (DOCTR)**
  Provides self-serve tools and custom data sets from Michigan Medicine.

**CENTER FOR COMPUTATIONAL MEDICINE & BIOINFORMATICS (CCMB)**
University-wide interdisciplinary academic center that develops methods, tools and algorithms for basic and translational research. It offers seminars and finds mentors for bioinformatics graduate students. Anchored in the Department of Computational Medicine & Bioinformatics.

**INSTITUTE FOR SOCIAL RESEARCH (ISR)**
Home to PCORnet, the national patient-centered clinical research network. Faculty expertise includes natural language processing, machine learning and knowledge management — making biomedical knowledge machine-interpretable for rapid application to clinical practice.

**DEPARTMENT OF LEARNING HEALTH SCIENCES (DLHHS)**
Home to PCORnet, the national patient-centered clinical research network. Faculty expertise includes natural language processing, machine learning and knowledge management — making biomedical knowledge machine-interpretable for rapid application to clinical practice.

**COLLEGE OF ENGINEERING**
Faculty collaborators with expertise in machine learning, systems modeling, optimization methods, multi-scale modeling and systems biology.

**SCHOOL OF INFORMATION**
Faculty collaborators across the IT spectrum, including health informatics, large-scale data analytics and data visualization.

**VA CENTER FOR CLINICAL MANAGEMENT RESEARCH/CCMR**
A research center funded by the Department of Veterans Affairs that has access to data for over 8 million enrolled veterans. Data can be accessed by faculty with VA appointments.

**INSTITUTE FOR HEALTHCARE POLICY AND INNOVATION (IHPI)**
A magnet for more than 500 U-M faculty engaged in health services research. Provides access to and expertise with large national and regional databases including public and proprietary claims data, clinical registry data and clinical data from Michigan Medicine.

**DEPARTMENT OF BIOSTATISTICS, SCHOOL OF PUBLIC HEALTH**
Faculty with expertise in cutting-edge analysis of biomedical data, including data for billing, organ transplantation and allocation, cancer, genetics/genomics, imaging and survey research. Collaborating on world-class data sets such as those for the Michigan Genomics Initiative and Kidney Epidemiology Cost Center.

**OTHER SOURCES OF DATA, COLLABORATION AND/OR ANALYTICAL SUPPORT INCLUDE:**

- Institute for Social Research (home to the Health and Retirement Study), page 133.
- U-M Comprehensive Cancer Center Biostatistics and Bioinformatics Core
- Michigan Center on Lifestage Environmental Exposures and Disease/M-LEEaD
3. Research Pipelines

- A Cancer Drug-Development Pipeline p. 56
- A Kidney Disease Translational Pipeline p. 58
- Building Pipeline-Enabling Infrastructure p. 61
- Special Feature: Clinical Trials in the Decades Ahead p. 62
The days of the lone scientist toiling away in a lab are over. Breakthroughs in medicine are increasingly born at the intersection of disciplines — and for many researchers in internal medicine, team science is just the beginning.

Some have achieved remarkable productivity and impact by assembling robust pipelines that move research seamlessly, and at remarkable speed, along the translational continuum.

Shaomeng Wang has assembled a cancer drug-development pipeline that he says can turn drug targets into promising drug candidates in as little as two to three years. Matthias Kretzler has ignited the nephrology world by helping to catalyze an international network of cohort studies and biobanks, which forms the starting point for a pipeline that links systems biology, animal models and human studies to yield much-needed biomarkers and mechanism-based drugs.

The department’s new head of clinical research, Rodica Pop-Busui, sees these examples as a vision for the future. And she’s hoping to transform research in the department and the Medical School by helping her colleagues build similar well-supported, interconnected structures to take their work from bench to bedside — and beyond.
An ideal example of the type of pipeline researchers have built to accelerate bench-to-bedside discoveries is the one crafted by Shaomeng Wang, PhD, a prolific professor from the Division of Hematology & Oncology who works to convert biological targets into the drugs of the future.

A member of the National Academy of Inventors, Wang has more than 46 patents on novel compounds, six anti-cancer drugs in clinical development and four start-up companies that aim to shepherd them to the marketplace. He hopes soon to usher in a new type of medicine that induces the degradation of cancer-causing proteins. He calls the discovery "one of the most innovative small-molecule drug technologies in the last 30 years."

ASSEMBLING THE PIPELINE

One clue as to how Wang has been able to marshal the expertise necessary to propel drug targets into compounds ripe for clinical application is his campus affiliations. He is the Warner-Lambert/Parke-Davis Professor of Medicine, with appointments that span internal medicine and pharmacology in the Medical School to medicinal chemistry in the College of Pharmacy. He directs the Cancer Drug Discovery Program and the Michigan Center for Therapeutic Innovation and also co-leads the Experimental Therapeutics Program at the U-M Comprehensive Cancer Center.

"We have developed a pipeline that allows us to discover high-quality drug candidates for exciting targets and take them all the way into clinical trials. That is possible because of the resources, collaborations and support available here."

— Shaomeng Wang, Hematology & Oncology

This gives him the reach to assemble expertise across three complementary laboratories, which form the backbone of his pipeline. The first is a computational lab that uses structure-based methods and informatics tools to identify and optimize drug leads. Then his medicinal chemistry lab synthesizes complex small-molecule compounds with desirable pharmaceutical properties. Finally his biochemistry, cell biology and pharmacology lab examines these compounds for their mechanisms of action, biological activity, efficacy, pharmacokinetics and pharmacodynamics, often in assays and models they’ve developed themselves.

Wang begins by taking the most promising drug targets identified by his collaborators at U-M and across the globe — such as abnormal proteins vital to cancer cells — and channeling them through his labs. Working with clinical
investigators, his team factors in FDA requirements and clinical trial considerations from the very start. For the most promising compounds, Wang engages U-M Tech Transfer to launch start-ups able to fund continued development, license the drugs and work with pharmaceutical partners to bring them to market.

“With this process, we can move a promising target into clinical development in just two to three years,” says Wang. “This is possible because of the strong support from the Department of Internal Medicine, Medical School and Cancer Center for our early-phase work, which allows us to develop new ideas to the point that they’re ready for external funding. We also have excellent basic and clinical science collaborators, strong cores and a progressive Tech Transfer office. No other place I know is this supportive of taking discoveries from the lab to the marketplace.”

**THE RESULTS**

Wang has advanced six small-molecule therapeutics into clinical development, but two examples highlight the range and novelty of his work. The first, SM-406, targets the proteins in cancer cells that keep them from undergoing apoptosis, or programmed cell death. The target of SM-406 was originally discovered at U-M in the 1990s. Currently in multiple phase II trials, SM-406 shows promise in patients with several tumor types, including ovarian, head and neck, breast and small-cell lung cancer. In addition, it was shown to enhance the effectiveness of various cancer immunotherapies. Now licensed to a pharmaceutical company, the drug could reach the market in the next few years, says Wang.

Another new type of medicine Wang’s lab has brought to the brink of clinical development uses small molecules to induce the degradation of cancer-causing proteins. The drug is designed so that one side bonds to the target protein and the other bonds to the cell’s protein degradation machinery, bringing the protein to that machinery to be destroyed. “Typically small-molecule drugs work by changing the activity or function of their target,” says Wang, “but this type of drug completely eliminates the protein that’s causing disease. This new approach has the potential to revolutionize the treatment of cancer and other human diseases.”

Wang is starting another company to accelerate the clinical development of this new class of cancer medicines and bring them to market for patients.

“**WE ARE DEVELOPING A NEW CLASS OF CANCER DRUG THAT COMPLETELY DEGRADES THE PROTEIN THAT CAUSES DISEASE. THIS NEW APPROACH HAS THE POTENTIAL TO REVOLUTIONIZE THE TREATMENT OF CANCER AND OTHER HUMAN DISEASES.**”

—SHAOMENG WANG, HEMATOLOGY & ONCOLOGY

SEVERAL OF WANG’S ANTICANCER DRUGS HAVE BEEN PART OF CLINICAL TRIALS CONDUCTED AT THE U-M COMPREHENSIVE CANCER CENTER BY HIS CLINICAL COLLEAGUES AND COLLABORATORS.

![Illustration represents one of Shaomeng Wang’s drugs bound to its target.](image-url)
“Michigan is implementing the future of nephrology now,” says Matthias Kretzler, MD, the Warner-Lambert/Parke-Davis Professor of Internal Medicine and Computational Medicine & Bioinformatics.

For more than a decade at Michigan, Kretzler has been piecing together the elements of a visionary pipeline for translational kidney disease research. Not only has it generated both the first-ever biomarker of chronic kidney disease progression and the first new treatment for diabetic kidney disease in 20 years, it has been cited as a model of precision medicine by NIH Director Francis Collins (see facing page).

The pipeline covers the full spectrum of translational medicine. Though the key elements are in place at U-M, the process is made more robust with international and industry collaborations.

“MICHIGAN IS IMPLEMENTING THE FUTURE OF NEPHROLOGY NOW. OUR TRANSLATIONAL PIPELINE MEANS THAT PRECISION MEDICINE IS NOT A VISION — IT’S REALITY IN OUR DIVISION.”

—MATTHIAS KRETZLER, NEPHROLOGY

It begins with rich data from kidney-disease patients, such as biosamples, medical histories, lab results and sequencing data. Under Kretzler, the Division of Nephrology has catalyzed biobanks for both chronic kidney disease (C-PROBE) and rare kidney diseases (NEPTUNE). However, the team also partners with similar facilities around the world for access to diverse patient populations.

Kretzler and his collaborators use bioinformatics and systems biology to probe these samples for molecular pathways that are altered in kidney disease. Their goals are to molecularly characterize specific subtypes of disease, identify biomarkers and discover potential drug targets. They can further explore their findings in custom mouse models of kidney disease — and ultimately test them in human studies.

CONTINUED ON PAGE 60
CITED AS A MODEL BY THE NIH

Francis Collins, in his NIH Director’s Blog, praised the Michigan Nephrology Pipeline, writing, “The results demonstrate the power of identifying new biologically important indicators directly from patients and then testing them in large, diverse cohorts of people. I look forward to the day when these sorts of studies will become possible on an even larger scale through our U.S. Precision Medicine Initiative cohort.”

INTERNATIONAL & INDUSTRY PARTNERSHIPS

Nephrology’s translational research pipeline is made more robust with international and industry partnerships. Partners in Europe, Asia and Africa share biobank data and participate as human study sites. U-M provides biobank, systems biology and bioinformatics resources to researchers worldwide through the George M. O’Brien Kidney Translational Core Center. Michigan Nephrology has also launched the first-ever pre-competitive academic-industry partnership to accelerate the identification of molecular kidney disease targets and speed drug-development efforts.
This is the very pipeline Kretzler and his team, including nephrology colleague and Associate Research Scientist WENJUN JU, PhD, MS, used to identify the first-ever biomarker of chronic kidney disease progression. They determined that reduced levels of epidermal growth factor in urine can identify which patients are likely to progress to end-stage kidney disease, requiring dialysis or transplant.

Not only does this finding open the door to precision treatment opportunities, it may also both speed up and reduce the cost of clinical trials by more efficiently identifying potential end-stage kidney disease patients as study participants.

The pipeline has also generated the first new treatment for diabetic kidney disease in two decades. Kretzler and his collaborators, including Professor Emeritus FRANK BROSIUS, MD, discovered that increased activation of the JAK/STAT signaling pathway in diabetes is a primary cause of kidney scarring and dysfunction.

The pair approached Eli Lilly & Co., which already had the JAK II inhibitor baricitinib in clinical trials for rheumatoid arthritis. Within just 14 months, they launched an international clinical trial for diabetic nephropathy. Results from the phase II study showed that the drug substantially reduced key measures of kidney dysfunction (urinary albumin-to-creatinine ratio) and inflammation (IP-10 and TNFR2), with few side effects and with signs of sustained impact even after patients stopped taking it.

The team will continue to support efforts to bring JAK inhibitors to market for diabetic kidney disease, as the current treatments focus on controlling high blood pressure rather than targeting the mechanisms responsible for kidney damage.

They also hope to streamline the development of new treatments for kidney disease through a first-of-its-kind industry partnership. Called the Renal Pre-Competitive Consortium (RPC2), it brings together Michigan’s strengths in large-scale clinical and molecular data analysis in kidney disease with four pharmaceutical companies’ expertise in drug development. The group hopes that by openly sharing data and analyses, they can bridge the gap between target discovery in academia and drug development in industry to achieve further precision medicine breakthroughs.
When RODICA POP-BUSUI, MD, PhD, professor in the Division of Metabolism, Endocrinology & Diabetes, assumed her role as associate chair for clinical research, she knew she was committing to an ambitious overhaul of the Medical School’s clinical trial enterprise (page 12). But it turns out her vision is even grander.

“We are uniquely poised as an institution that is at the cutting edge of disciplines ranging from medicine and public health to engineering and information technology to use the molecular targets and medical devices we are working on to truly reshape patient care,” says Busui. “What we want to do is create mechanisms that foster communication along the entire pathway, from our talented bench colleagues who are identifying critical disease pathways to our clinical researchers who can design trials for proposed interventions to our outcomes researchers who can study the intervention in clinical practice.”

The resources are already largely in place, she says; the trick is getting the right people connected to those resources — and to each other.

Her vision includes mechanisms for encouraging dialogue across the basic, translational, clinical and outcomes research continuum early and often, and then ensuring that as research teams form and begin to build their own pipelines, they are aware of how existing resources can support each step in the process.

“We already have vast infrastructure to support research,” says Busui. “such as the Michigan Institute for Clinical & Health Research/MICHR, the Center for Discovery of New Medicines, the Fast Forward Medical Innovation Program and the Institute for Healthcare Policy and Innovation, as well as facilities for high-throughput sequencing, big-data analysis, biorepositories, animal models and so on. All we need is to be sure interested investigators know how to best utilize these resources.”

The pipelines assembled by SHAOMENG WANG and MATTHIAS KRETZLER are precisely the type of structures she believes will increasingly self-assemble as researchers see the impact of these models, connect with colleagues across the continuum, learn how to tap into existing infrastructure and see the benefits of the clinical trial transformation.

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BUSUI BRINGS TO HER POSITION DEEP EXPERIENCE WITH BENCH-TO-BEDSIDE RESEARCH IN DIABETIC COMPLICATIONS. SHE AND NEUROLOGY COLLEAGUE EVA FELDMAN, MD, PhD, HAVE AN NIH R01 GRANT THAT AIMS TO REPURPOSE AN FDA-APPROVED ARTHRITIS DRUG FOR THE TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY (DN) AND CARDIOVASCULAR AUTONOMIC NEUROPATHY. THIS WORK HAS BEEN BUILT ON A FOUNDATION OF MECHANISTIC RESEARCH IN ANIMALS AND PATIENT NERVE SAMPLES, AS WELL AS PILOT HUMAN TRIALS. THEY HOPE IT WILL YIELD THE FIRST SPECIFIC TREATMENT FOR DN.
While the clinical trial transformation may have served as an early impetus for this vision, it will be realized, says Busui, because of the alignment and teamwork among herself, Assistant Dean for Clinical Research ANNA S.F. LOK, MD, and Associate Chair for Basic and Translational Research BEN MARGOLIS, MD, with support and leadership from Department Chair JOHN CARETHERS, MD.

“We have the talent and infrastructure to support pipelines in a number of priority areas of medical discovery, from cancer to cardiovascular disease to diabetes and obesity,” says Busui. “Our job in the years ahead is to ensure we translate our work into meaningful interventions to help our current patients and prevent the younger generation from acquiring the chronic diseases that are so rampant today. This will not only improve their lives, it will have an immense benefit on the cost of health care delivery as well.”

As the Medical School commits to a “Clinical Trials Transformation” that aims to improve, streamline and support the clinical trials process at U-M, it’s useful to consider what innovative clinical research will look like in the foreseeable future.

According to the past and present associate chairs for clinical research in the Department of Internal Medicine, the future of clinical trials will embrace a number of emerging trends.

INTERNATIONAL COLLABORATION
One trend that will certainly continue is the movement toward international collaboration. This is essential to meet enrollment targets quickly, to ensure that trial results are applicable to a range of racial and ethnic groups, and to provide actionable data to various countries’ regulatory agencies. U-M has already positioned itself for cooperative clinical research efforts in China through the Joint Institute for Translational and Clinical Research, a partnership between U-M and the Peking University Health Science Center. With institutional partnerships and collaboration platforms in over a dozen countries around the globe, future efforts could span both the geographic and translational research continuum.

PATHWAY STUDIES
With the movement toward precision medicine, treatments are increasingly designed to target an identified molecular pathway driving disease. This is beginning to shape how clinical trials are designed. “Trialists, particularly in oncology, are beginning to say, ‘The reason this drug came about is because it blocks pathway A, which drives cancer,’ ” says ANNA S.F. LOK, MD, past associate chair for clinical research and the Alice Lohrman Andrews Research Professor of Hepa-

“It’s why we focus on training to keep us at the cutting-edge — whether we’ve been in the field for 30 years or are a brand new trainee.”

—ANNA S.F. LOK, GASTROENTEROLOGY
**ADAPTIVE STUDY DESIGN**

Another trend that will take on increasing importance is adaptive study design, where a study can be modified in a predetermined way as results come in. Thus, if a study comparing two treatments begins to show that one is superior, particularly in patients with certain characteristics, researchers can shift patients to that treatment to achieve optimal results.

**COMMUNITY-BASED TRIALS**

Lok also sees a need to move trials beyond large academic centers to community-based health care sites. She says it would make trials more convenient, increasing the pool of potential participants. And by casting a broader net, it would make the trials more representative of the larger patient population. That’s why she and the current associate chair, **Rodica Pop-Busui**, MD, PhD, are exploring ways to facilitate clinical research in off-campus sites.

**BEHAVIORAL STUDIES**

Though the classic image of a clinical trial is “pill versus placebo,” increasingly researchers will be testing behavioral health interventions, from nutrition classes to exercise programs to smartphone apps. As they do, they will be poised to help such interventions become increasingly tailored, evidence-based and effective in fostering the self-management of chronic conditions.

**NEW PHARMA PARTNERSHIPS**

As part of her vision for evolving clinical research, Busui would like to see a shift in the relationship between universities and pharmaceutical companies in clinical trials. Traditionally, she says, universities have largely been implementers of trials on behalf of pharmaceutical companies once a drug has been developed. She’d like to see a deeper partnership, where universities more readily feed the drug-development pipeline with target leads and then serve in a leading role in study design and large-scale implementation. She envisions faculty researchers devising innovative, patient-centered trials, which would later be linked to outcomes research once a drug or device has been introduced into clinical practice.
4. OMICS

- GENOMICS OF FATTY LIVER & CARDIOVASCULAR DISEASE p. 66
- METABOLOMICS OF KIDNEY DISEASE & ADRENAL INSUFFICIENCY p. 69
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- MICROBIOMICS: HOW OUR PERSONAL ECOSYSTEMS FOSTER HEALTH & DISEASE p. 75
The early, prototypical example of using big data for precision medicine is, of course, genomics. With the sequencing of the human genome, futurists envisioned subsequent generations receiving a lifetime of personalized risk prediction from a newborn heel stick, allowing us to tailor our lifestyles and medical treatment for maximum health.

While we’re not there yet, that’s still the destination, say internal medicine researchers working in the various “omics” disciplines — though the path is more complex than initial predictions implied.

It will take the integration of many areas — genomics, transcriptomics, proteomics, metabolomics, epigenomics and microbiomics — analyzed within a systems biology framework to truly understand how our genes and environment interact to increase our personal risk of disease.

Fortunately, internal medicine researchers are assembling various pieces of this puzzle, building a clearer picture of how all these elements work together. In the process, they are uncovering crucial disease mechanisms, subtypes, biomarkers and treatments. Each discovery moves us closer to precision strategies to reduce our risk and, when needed, to treat us early — and well.
Two internal medicine researchers have emerged as leaders in the genomics arena, identifying numerous genetic regions that contribute to an individual’s risk for obesity, fatty liver and cardiovascular disease — and gaining insight into their sometimes-surprising effects and interactions.

NON-ALCOHOLIC FATTY LIVER DISEASE

The first is Elizabeth Speliotes, MD, PhD, MPH, associate professor in the Division of Gastroenterology and the Department of Computational Medicine & Bioinformatics.

She is using the largest human genome-wide association studies (GWAS) to find the genetic variations that explain our susceptibility to obesity and non-alcoholic fatty liver disease (NAFLD). “These are diseases that have escalated to epidemic proportions and for which there aren’t good cures,” says Speliotes. “Part of the reason is that we don’t know what’s causing them. But by using genomics to understand the root cause of these problems, we can be more directed in how we diagnose, manage and treat them.”

This is important because it wasn’t long ago that NAFLD was considered a relatively benign effect of being overweight. Now it is clear that a percentage of those with NAFLD will progress to Nonalcoholic Steatohepatitis (NASH), experiencing inflammation and cell damage in the liver. A further subgroup will go on to cirrhosis, and some will progress to liver failure or cancer.

Speliotes wants to learn which patients’ genes predispose them to each outcome and why.

She starts with imaging and GWAS, then follows up interesting hits in engineered mouse models and cell lines. Her findings provide insight into the varying mechanisms by which genes confer risk and clues as to the types of treatments most likely to be effective given the causes at play.

Thus far, Speliotes has identified more than 150 genetic regions associated with obesity or NAFLD. She’s shown that overall obesity, abdominal obesity and NAFLD are influenced by genes expressed in the nervous system, fat cells and liver, respectively.

In terms of obesity, Speliotes has found that many of the genes that influence overall obesity are expressed in the brain. These genes may play a role in learning and memory, motivation, smell and emotion, and function alongside those that regulate satiety, energy expenditure and insulin biology.

In contrast, the genes most associated with NAFLD primarily affect lipid and glucose metabolism. “We’ve identified genetic variants that put some individuals at much higher risk for developing fat in the liver, even without being overweight,” says Speliotes. “For example, we’ve identified one variant that confers a sixfold higher risk for developing scarring and cirrhosis, and another variant that is associated with a twofold higher risk for developing liver cancer.”

Another finding that may lead to more refined risk prediction is that some variants associated with obesity and NAFLD raise the risk of dyslipidemia, diabetes and cardio-

IDENTIFYING NAFLD GENES

WORKING WITH THE GENETICS OF OBESITY-RELATED LIVER DISEASE CONSORTIUM, SPELIOTES AND HER FELLOW INVESTIGATORS CALCULATED LIVER FAT BASED ON CT SCANS OF APPROXIMATELY 7,000 PEOPLE AND CARRIED OUT GWAS TO RECOGNIZE GENETIC PATTERNS RELATED TO FATTY LIVER. THEY THEN PERFORMED DEEPER GENETIC ANALYSES OF PEOPLE WITH NAFLD. AS A RESULT, SPELIOTES’ TEAM HAS IDENTIFIED FIVE GENETIC LOCI ASSOCIATED WITH NAFLD.
vascular disease, whereas others are protective for one or more of these conditions. This begins to get us closer to the molecular reasons some but not all obese individuals develop related metabolic diseases and why those who do, develop different combinations of these diseases. This in part is due to the constellation of genetic variants these people carry, which can now be assayed.

Since genes interact with the environment to cause disease, Speliotes has recently begun probing the relationship between NAFLD-related genes and environmental factors. Her results show that individuals with certain variants are at highest risk for NAFLD in the context of a specific environmental trigger. For example, one genetic variant seems to have a large effect on developing fatty liver if patients develop diabetes, but not as large an effect if they simply gain weight or have elevated serum lipids. “This kind of knowledge can help us make more directed recommendations about what to avoid in the environment to lower a patient’s risk of developing particular outcomes,” she says.

Speliotes’ work suggests that genomics is moving us closer to being able to identify which patients are most at risk for developing obesity, NAFLD and related metabolic disorders — and defining what we can do to mitigate these effects.

CARDIOVASCULAR DISEASE
Also making rapid headway with GWAS is **Cristen Willer**, PhD, associate professor in the Division of Cardiovascular Medicine and the Departments of Human Genetics and Computational Medicine & Bioinformatics.

Her goal is to be able to identify those at risk for developing specific cardiovascular conditions years before the disease process starts. She envisions doing this by combining our known risk factors — such as blood pressure, cholesterol and lifestyle — with the genetic variants she’s identifying.

Willer is using GWAS to probe conditions as diverse as diabetes, heart attack, high cholesterol, atrial fibrillation and bicuspid aortic valve.

Among her findings is that, much like obesity and fatty liver disease, there are numerous genetic regions that affect our cholesterol levels — as many as 200 at her most recent count. What’s surprised her is that most of these occur in the so-called non-coding DNA — the parts of the genome that don’t encode for a protein.
“These places appear to be very important in an individual’s future risk of disease,” says Willer. “We think it’s related to how genetic material is unwound and turned on. Understanding how this affects cholesterol may have huge implications for the development of new therapies.”

Willer also thinks her work has strong potential to guide the development of therapies in other areas, such as atrial fibrillation. In a recent GWAS, her group identified two new regions of the genome associated with this condition. She’s now working with JOSÉ JALIFE, MD, the Cyrus and Jane Farrehi Professor of Cardiovascular Research, professor of Molecular & Integrative Physiology and co-director of the U-M Center for Arrhythmia Research, and TODD HERRON, PhD, associate research scientist in the Division of Cardiovascular Medicine and Department of Molecular & Integrative Physiology, to discover the role these variants play in the development of arrhythmia using engineered heart muscle cells created from induced pluripotent stem cells (iPSCs).

“My colleagues are able to use iPSCs to create a layer of myocytes that actually beat in unison in a Petri dish,” says Willer. “They start by applying state-of-the-art genome-editing techniques to perturb the areas we’ve identified through GWAS. Then they induce the cells to differentiate. and we measure the impact of our genetic changes on the electrophysiology of the cells. The beauty and complexity is that we don’t know what mechanism we’ll discover. But I think there’s great therapeutic potential as we better understand why atrial fibrillation arises.”

Looking ahead, Willer thinks another way we’ll unravel disease development is by increasingly studying the genomes of those without disease. For example, we can learn a great deal about risk factors for, say, type 2 diabetes by comparing individuals with the condition to those with a family history who have not developed it. This latter group still carries about half the predisposing variants. Willer is doing just this kind of work in a data set containing participants’ genomic information, biosamples and detailed personal and family histories. She thinks it may help tease out the relative contributions of different variants, or combinations of variants, to disease development.

“There is also a lot to be gained by studying the super-healthy,” says Willer. “For example, we’ve started to turn our focus to people with really low cholesterol. Working with cardiologists ROBERT BROOK and MELVYN RUBENFIRE, we’ve identified families with LDL levels below 10 — well below the average of 140. Understanding the genes responsible can help us home in on potential therapeutic targets.”

Willer says a similar approach helped identify PCSK9, the basis for new blockbuster cholesterol-lowering drugs. She thinks studying groups across the health continuum is how we’ll ultimately advance our understanding of the genetic basis of cardiovascular and metabolic disease.
If genomics excels in highlighting our risk for disease, the other end of the “omics cascade” — metabolomics — reveals how this risk combines with our environment to move us toward either fulfilling, or evading, that risk.

While Department of Internal Medicine researchers are generating insights along the continuum of this cascade, those who focus on metabolomics do so because it provides accessible, meaningful signals of health or disease.

“Currently, many chronic diseases are diagnosed by measuring metabolites,” says SUBRAMANIAM PENNATHUR, MD, chief of the Division of Nephrology, Norman Radin Professor of Medicine and Molecular & Integrative Physiology, and director of the O’Brien Kidney Translational Research Center. “For example, in my own lab, I work with diabetic kidney disease, and both diseases are diagnosed this way — diabetes, with high glucose, and kidney failure, with high creatinine.”

Metabolites are particularly useful in clinical medicine because they can be measured noninvasively in biofluids, such as blood or urine, whereas gene expression requires a biopsy of the target tissue type.

What’s held the field back is that, though they’re easy to capture, metabolites are challenging to analyze. This is because they’re so chemically diverse — including lipids, amino acids, carbohydrates, nucleic acids and organic acids. Such a wide range requires large, expensive analytical platforms based on mass spectrometry and nuclear magnetic resonance. Even with these platforms, one or two samples can take days to analyze for a couple thousand metabolites.

But this is changing, says Pennathur, as developers work to both speed up and miniaturize the analysis systems, incorporating nanotechnology to reduce the required sample size.

As this happens, he says, the platform holds tremendous potential to not only diagnose, but predict and monitor the course of disease — and develop treatments that target factors either upstream or downstream of the harbinger metabolites. In addition to new equipment, this will require systems biology approaches that put metabolomics data into context with the other omics.
"Right now the typical clinical blood test measures only 20 to 30 metabolites," says Pennathur. "But I envision a day in the decades ahead where patients would have a sensor under their skin that could continuously measure some 20,000 metabolites. Then, just like the insulin pumps of today, we could manage even multiple diseases in real time by dispensing therapies very precisely to correct the metabolic disturbances while minimizing side effects."

Pennathur expects that by then the range of diseases with useful metabolite-based biomarkers will have exploded. In his own lab, he’s been working to make this happen with diabetic kidney disease.

METABOLITE PREDICTORS OF DIABETIC NEPHROPATHY

Like many of the other diseases discussed in this report, there is a step-wise progression from diabetes to end-stage kidney disease and a real need to ascertain which patients are likely to take each subsequent step along this path.

"Not everyone who is obese gets diabetes," says Pennathur. "Not everyone who has diabetes gets kidney disease. And not everyone who gets kidney disease progresses to end-stage disease needing dialysis or transplantation. The issue for us is identifying those at risk for progression so that we can aggressively treat those individuals and avoid treating the other group, where treatment may actually cause harm rather than good."

Members of the Pennathur lab, including Assistant Professor FARSAD AFSHINNIA, MD, and postdoctoral fellow KELLI SAS, PhD, from the Division of Nephrology, have already identified a number of changes in glucose and fatty acid metabolism that appear to predict several years in advance who will and will not progress with diabetic kidney disease.

"I ENVISION A DAY IN THE DECADES AHEAD WHERE PATIENTS WOULD HAVE A SENSOR UNDER THEIR SKIN THAT COULD CONTINUOUSLY MEASURE SOME 20,000 METABOLITES. THEN, JUST LIKE THE INSULIN PUMPS OF TODAY, WE COULD MANAGE EVEN MULTIPLE DISEASES IN REAL TIME BY DISPENSING THERAPIES VERY PRECISELY TO CORRECT THE METABOLIC DISTURBANCES WHILE MINIMIZING SIDE EFFECTS."

—SUBRAMANIAM PENNATHUR, NEPHROLOGY
in additional patient cohorts, Pennathur hopes they have the makings of a panel of signature metabolites for patient screening, as well as important starting points for new treatments targeting the pathways that generate or use these pivotal molecules.

In fact, his lab collaborates extensively with that of nephrology colleague and systems biology expert, MATTHIAS KRETZLER, MD, (page 58), who models these pathways to identify potential drug targets and assess the potential of various inhibitory compounds.

However, Pennathur stresses that the metabolomics platform is applicable to every type of disease. In his role as the associate director of the metabolomics core, he works to help researchers from the Department of Internal Medicine and across campus use it to advance precision medicine opportunities from diabetes to kidney disease to cancer. “One of the major advantages we have in Michigan is our collaborative big-science endeavors,” he says. “The work we’re doing involves people from analytical chemistry, biomedical engineering, mathematics, systems biology, various Medical School disciplines, even industry. That’s one of Michigan’s great strengths, and it’s what will help us make our future vision a reality.”
WHY DOES KIDNEY DISEASE ACCELERATE CARDIOVASCULAR DISEASE?

A member of Pennathur’s lab is using her recent NIH K08 grant to combine metabolomics and proteomics to answer a pressing question in her field: Why does chronic kidney disease dramatically increase a patient’s risk of cardiovascular disease?

ANNA MATHEW, MD, assistant professor in the Division of Nephrology, uses the omics toolkit to explore this question in both mouse models and patient cohorts to determine why patients with kidney disease have as much as 15 to 30 times higher risk of cardiovascular disease than patients of the same age with normal kidney function.

It’s a critical question because cardiovascular disease is the primary cause of death among end-stage kidney disease patients (see box).

Mathew suspects that an enzyme called myeloperoxidase is to blame. In the context of kidney disease, she believes the enzyme becomes overactive, causing oxidative protein modification — actually changing high-density lipoproteins, the so-called “good cholesterol,” into a dysfunctional version that increases atherosclerosis in a subset of kidney patients.

Her grant proposes to use proteomics and metabolomics to probe this process, resulting ultimately in biomarkers that can predict which chronic kidney disease patients are most at risk for cardiovascular disease.

“Once we figure out the mechanism behind the increased risk of cardiovascular disease in these patients,” says Mathew, “it may open up avenues to create drugs and identify lifestyle changes to help end-stage kidney patients have a longer, more disease-free life. Dialysis will no longer just be a supportive measure, but may bring patients back to a normal life expectancy, which is our goal.”

BIOMARKERS FOR CONGENITAL ADRENAL HYPERPLASIA

Another disease that is ripe for metabolite-based biomarker development is congenital adrenal hyperplasia (CAH). This is the focus of ADINA TURCU, MD, assistant professor in the Division of Metabolism, Endocrinology & Diabetes (MEND), who is using her NIH K08 grant to identify much-needed markers for its diagnosis and precision treatment.

She’s focusing on the most common form of the disease, which involves a deficiency of the 21-hydroxylase enzyme needed for cortisol synthesis. With the normal cortisol pathway blocked, cortisol precursors are diverted into excess androgens, or male sex hormones.

“ONCE WE FIGURE OUT THE MECHANISM BEHIND THE INCREASED RISK OF CARDIOVASCULAR DISEASE IN THESE PATIENTS, RENAL REPLACEMENT THERAPIES LIKE DIALYSIS MAY NO LONGER BE JUST A SUPPORTIVE MEASURE, BUT A MEANS TO SUSTAIN A NORMAL LIFE EXPECTANCY.”

— ANNA MATHEW, NEPHROLOGY
In the condition’s most severe form, newborns can die of cortisol deficiency if not identified at birth, and girls are born with ambiguous genitalia from androgen exposure. In the milder form, patients make sufficient cortisol but still suffer androgen excess symptoms, ranging from early signs of puberty in boys and girls to unwanted body hair, acne and infertility in women.

The mild form of the disease is easy to manage but difficult to diagnose. The severe form of the disease is easy to diagnose but difficult to manage. Standard cortisol replacement regimens are not enough to normalize adrenal androgen production in severe CAH. Clinicians must walk a tightrope between undertreatment, which causes tumor formation and fertility problems, and overtreatment, which causes weight gain, bone loss and glucose intolerance.

Turcu hopes to meet both of these needs using the infrastructure developed at U-M by her mentor and MEND colleague, Professor Richard Auchus, MD, PhD. Auchus has built a rich platform for “steroidomics” — sensitive metabolomics-based tests for active steroid hormones and their intermediates.

Turcu is using the platform first to identify a panel of steroids that would form the basis of a reliable diagnostic blood draw. Then she hopes to identify biomarkers that will guide clinicians toward precision treatment regimens for individual patients, avoiding long-term complications.

“The biomarkers we currently use for treatment have been in place since the 1950s,” says Turcu. “They are very crude tools because they don’t tell us the source of the excess androgens — whether they originate in the adrenal glands or the gonads — and they don’t correlate well with the clinical manifestations of disease.”

This information is important because it helps differentiate between, say, polycystic ovary syndrome, where excess androgens arise primarily from the ovaries, and CAH, where the source is adrenal. Treatment for each is very different — contraceptive pills for the former and steroids for the latter.

Turcu believes she can tease this out by targeting under-examined intermediates that are specific to the androgens’ source. Her work has recently demonstrated that an androgen thought to be important only in fish is actually the dominant androgen in CAH.

But this project is just a small slice of Turcu’s vision for the future. “I think soon we’re going to witness an explosion of biomarkers for adrenal disorders — from Cushing’s syndrome to primary aldosteronism to cancer. Some may replace current invasive studies; others may allow us to monitor cancer treatment and detect recurrence early. I think this will be possible through a combination of advanced technology and an adrenal group that is arguably the most talented in the nation.”

“[W]e’re going to witness an explosion of biomarkers for adrenal disorders. I think this will be possible through a combination of advanced technology and an adrenal group that is arguably the most talented in the nation.”

—Adina Turcu, Metabolism, Endocrinology & Diabetes
Since the early days of epigenetics, the Department of Internal Medicine has contributed to our growing understanding of how mechanisms such as DNA methylation, histone modification and microRNAs can turn genes on or off — helping to unveil a dazzling means by which the environment impacts gene expression.

Though much of the early work focused on cancer, research in the department now covers topics as diverse as how epigenetic changes accumulate during aging to increase autoimmunity risk (Raymond Yung, MB, ChB, chief of the Division of Geriatric & Palliative Medicine) and how these changes can occur in a setting of chronic stress to enhance pain perception in irritable bowel syndrome (John Wiley, MD, professor in the Division of Gastroenterology).

An especially intensive study of epigenetics resides in the Division of Rheumatology, which now has an NIH Basic Autoimmunity Center of Excellence devoted to the topic. The center’s director, Bruce Richardson, MD, PhD, the Fredrick G.L. Huetwell Research Professor of Rheumatology, helped pioneer the epigenetics of lupus, showing how lupus-causing drugs change lymphocytes’ gene expression and trigger autoimmunity. He’s now teamed up with Amr Sawalha, MD, the Marvin and Betty Danto Research Professor of Connective Tissue Research; they’re using the center to apply state-of-the-art genomic and epigenomic approaches to unravel the mechanisms causing lupus, identify new therapeutic targets and test a novel biomarker of disease progression.

“Richardson and Sawalha are at the leading edge of this,” says Division Chief David Fox, MD. “They’ve identified a unique subset of CD4-positive T lymphocytes that are epigenetically abnormal and driving lupus — and they’re now extending this to other autoimmune diseases. This subset of cells gives us a very specific treatment target, so we can develop precision therapies to replace the broad-brush immunosuppressive treatments we use now.”

“U-M’s Division of Rheumatology really created the field of epigenetics in autoimmune disease, and we continue to lead it. It won’t be long before genetics will be able to tell us which diseases a person is prone to and epigenetics, whether the person is actually developing them, so we can initiate protocols for prevention or cure.”

— David Fox, Rheumatology
One of the youngest but decidedly high-potential members of the omics family is microbiomics — the high-throughput-enabled study of all the microorganisms on and in us. Supported since 2012 by the sophisticated infrastructure of the Host Microbiome Initiative, microbiome-related work has been a grassroots strength of the Department of Internal Medicine for much longer.

**DYSREGULATED MICROBIOME A KEY COMPONENT OF LUNG DISEASE**
In fact, pioneering work in the department upended the notion that the lungs were sterile, unearthing a completely new mechanism to explain lung disease. **ROBERT DICKSON**, MD, assistant professor in the Division of Pulmonary & Critical Care Medicine, and divisional colleagues Professor **JEFFREY CURTIS**, MD, and **GARY HUFFNAGLE**, PhD, the Nina and Jerry D. Luptak Research Professor, have shown that inflammatory lung diseases like COPD, pneumonia and ARDS each appear to exhibit a unique and characteristic dysregulation of the lung’s normal ecosystem.

**U-M MICROBIOME RESOURCES**
THE ARDS FINDINGS FEATURED IN THIS ARTICLE WERE MADE POSSIBLE BY RESOURCES IN THE MEDICAL SCHOOL’S HOST MICROBIOME INITIATIVE. THESE INCLUDE OXYGEN-FREE GROWTH CHAMBERS, GERM-FREE ANIMAL FACILITIES AND ADVANCED GENETIC SEQUENCING AND CULTIVATION TOOLS. TOGETHER THEY HELPED SHOW THAT THE GUT BACTERIA WERE ALIVE IN THE LUNGS, NOT DETECTABLE DNA FROM DEAD BACTERIA.
“The idea now is that many chronic lung diseases are not a true ‘infection,’ but represent a persistent, low-grade change in the lungs’ ecosystem with signature bacteria,” says Huffnagle. “So we’re asking: Is this actually a contributor to the chronicity of these diseases?”

A dysregulated microbiome indeed appears to be a key component of Acute Respiratory Distress Syndrome. ARDS is a life-threatening condition that causes fluid to leak into the lungs, preventing oxygen transfer.
Dickson and Huffnagle were lead authors on a 2016 Nature Microbiology paper showing that the lungs of patients with ARDS contained bacteria from the gut not found in healthy lungs. They were able to show in animal models that these bacteria didn’t arrive via the usual route of the nose or throat, suggesting that critical illness either makes the guts “leaky,” allowing bacteria to leach into the lungs, or provides the conditions for a small number of already-resident gut bacteria to “bloom.” Either way, it suggests that a disordered microbiome is a key initiator of the vicious cycle of inflammation and tissue injury that occurs in ARDS.

“Our results suggest that past attempts to find treatments for ARDS may have been overlooking a major part of the story,” says Dickson. “Virtually all of our attempts to treat this critical illness have been aimed at fixing the inflammation and tissue injury we see in our patients. But our study raises the possibility that this inflammation and injury may actually be downstream consequences of an upstream source: disordered bacterial communities in the gut and lung.”

The group is now knee-deep in the molecular biology of this question because answering it holds real promise for treatment. “If changes in microbial ecology are important for these diseases, perhaps we can devise things like inhaled probiotics and antibiotics,” says Huffnagle. “Or maybe we can make a big impact with simple supportive therapies like changing the position of patients or their temperature — creating conditions for the preferred microbes to survive.”

**METABOLITES: THE KEY TO THE MICROBIOME’S IMPACT?**

Huffnagle says the mechanism by which the microbiome impacts health and disease may very well be confirmed with help from an omics sibling — metabolomics.

“The trillion dollar question right now is how does the microbiome mediate immunity,” he says. “Many of us think it’s through the metabolites from all of these microbes, which have effects throughout our systems. In fact, we’re pretty confident that the drugs of the future are already being made inside our bodies.”

“WE’RE PRETTY CONFIDENT THAT THE DRUGS OF THE FUTURE ARE ALREADY BEING MADE INSIDE OUR BODIES.”

—GARY HUFFNAGLE, PULMONARY & CRITICAL CARE MEDICINE

One investigator using metabolomics to probe the microbiome is **VINCENT YOUNG**, MD, PhD, professor in the Division of Infectious Diseases and co-director of the Host Microbiome Initiative. His focus is *Clostridium difficile*, a major cause of life-threatening diarrheal disease following broad-spectrum antibiotic use. Young has already helped demonstrate the therapeutic mechanisms of fecal transplant for this condition. He’s now working with the metabolomics core to measure gut metabolites, which are products of the combined activities of the microorganisms and their host, hoping to learn precisely how they increase susceptibility to this widespread and dangerous infection.

**RESEARCHERS THROUGHOUT THE DEPARTMENT ARE USING MICROBIOICS TO STUDY THE PATHOGENESIS OF COLON CANCER, INFLAMMATORY BOWEL DISEASE, LUPUS, MULTIPLE SCLEROSIS, OBESITY, FOOD ALLERGY (PAGE 116) AND GRAFT-VERSUS-HOST DISEASE (PAGE 117).**
5. Health Technologies

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- Health Tech in the “Routine” Care of Tomorrow  p. 92
When one envisions the future of medicine, technology is generally front and center — mission control for a critical care unit where computers flag a patient’s downturn hours before it happens, custom-grown biological replacement parts designed to avoid rejection, and virtual house calls featuring video chat and sensors that track vital signs and biomarkers from the comfort of a living room.

They’re all coming, say internal medicine faculty, many of whom are leading the charge. Other futuristic visions are already here. Infectious Diseases Professor Keith Kaye, for example, is testing germ-zapping robots in the battle against hospital-acquired infections (see image at left).

There are a few keys to getting the best from health technology going forward, say those involved. The first is ensuring that any data, whether generated by sensors or captured by smartphone apps, is secure. Second, technology must help connect patients and providers, not distance them. And third, it must support and empower patients to better understand and manage their own health.

With these principles in mind, internal medicine faculty are working to develop and apply technologies that they hope will shape the future — from patient-support apps and cutting-edge diagnostics to decision-support tools and new biological models for studying disease.
The Future of Health Communication Technology

We all know Siri can help us find the nearest Starbucks in all 50 states, but can an artificial intelligence agent also help our doctor see a pattern in our family’s past that calls for an early colonoscopy or BRCA test? Lawrence An thinks so. An, MD, is an associate professor in the Division of General Medicine and directs the Center for Health Communications Research, a unique and valuable resource at U-M that has developed hundreds of high-tech tools for both patients and providers which use tailored communications to improve patients’ health.

An shared some examples of projects he’s working on with collaborators across campus. They provide a glimpse of the future of health communication technology — a future that offers personalized information and support when and where they’re needed.

“If we can prove that an artificial intelligence agent can take an accurate family history, the world is wide open. How about a history of chest pain or sore throat? There are a huge number of conversations these agents could help with.” — Lawrence An, General Medicine

An’s first project shows how technology can set the stage for a more productive health care visit. The project aims to use an artificial intelligence (AI) agent to take patients’ family histories. “A family medical history is an ideal AI project,” says An. “It’s very structured, it’s foundational to good care and yet many people in health care do not have the training or time to collect a high-quality family history. As people become more comfortable talking to their devices, we want to see if these agents can improve the information available to their providers.”

Among An’s collaborators are AI and natural language processing expert Rada Mihalcea, PhD, professor in the Department of Electrical Engineering & Computer Science, and Elena Stoffel, MD, MPH, assistant professor in the Division of Gastroenterology and director of U-M’s Cancer Genetics Clinic. Their goal is to determine whether an AI agent can collect a family history that is as detailed and accurate as a genetic counselor’s.

An’s next project shows how technology can extend the reach of health care — providing support at times and places providers can’t. It’s an app that helps patients with hypertension and heart disease follow a low-sodium diet.

Using geo-sensing, it can recognize where they’re shopping or dining and make recommendations of lower-sodium options tailored to users’ health conditions, food preferences and motivations for change. “We can help users make — and stick to — a change in their sodium intake.

GEO-SENSING APP TO REDUCE SODIUM INTAKE BY PATIENTS WITH HYPERTENSION.
by delivering the right message to people in time and space,” he says.

This project is a joint effort among Michael Dorsch, PharmD, MS, clinical associate professor in the College of Pharmacy, and Assistant Professor Scott Hummel, MD, MS, and Professor Todd Koelling, MD, both from the Division of Cardiovascular Medicine.

An’s third project showcases the potential of technology to bridge the gap between research and clinical care. In fact, this is precisely his charge in his new role as Michigan Medicine’s medical director for eHealth Programs.

It’s an often-cited statistic that research findings can take as many as seven years to make their way into clinical practice. An thinks he can help speed things up with well-designed tools. For example, when research — and U-M surgeons from several departments — identified that patients are often not optimally prepared for surgery, he began to work with them on apps to guide patients and their families through this process.

“Usually when patients are scheduled for surgery, we give them a big stack of papers telling them what to do,” says An. “But we don’t know if they’re actually doing those things, if they have questions and so forth. Our apps can count them down to surgery, telling them each day what to do. We can tell whether they’ve seen each message, completed each task and/or have any questions. Based on their needs and progress, an alert can go back to them, to a designated family member and/or to the health care team so there can be prompt follow-up. And we can do the same with recovery.”
Biomedical engineering (BME) has a message for the clinicians and basic scientists in internal medicine: We’re ready to collaborate.

So says Lonnie Shea, PhD, the William and Valerie Hall Chair and Professor of the Department of Biomedical Engineering. That’s because he’s seen firsthand the kind of breakthroughs that can happen when the tools and perspectives of engineers are melded with the approaches, technologies and questions of clinicians and medical scientists.

**BIOMATERIAL SCAFFOLDS HELP LUNGS-IN-A-DISH MATURE**

A perfect example of the kind of advances that can happen when internal medicine researchers and biomedical engineers team up comes from Shea’s recent collaboration with JASON SPENCE, PhD, associate professor in the Division of Gastroenterology and the Department of Cell & Developmental Biology.

Spence is well-known for creating organoids, sometimes called “organs in a dish.” These tiny hollow spheres are cultured from human-induced pluripotent stem cells and contain functional versions of the major cell types found in an organ of interest. They’re a valuable model system for probing organ development and disease.

Spence became interested in pushing his lung model further. In a project led by PhD candidate Briana Dye, his lab set out to create 3-D mini-lungs, which they aimed to transplant into immunosuppressed mice as a more developed model for screening drugs, probing gene function and exploring complex diseases like asthma.

They’d made substantial progress on the lungs, generating structures with both bronchi and alveoli. Yet, the tissue remained immature. But by employing a biomaterial scaffold developed in Shea’s lab, the collaborators were able to grow a more mature version that was successfully transplanted in mice, became vascularized and featured more developed airway structures and specialized cell types.

Even the remaining hurdle — that the alveolar cell type didn’t grow in the transplants — is something Shea’s lab can help

“Faculty across the medical school have made enormous progress using highly sophisticated methods in their research. But the value of working with engineers is that we can bring different tools that allow you to ask different kinds of questions.”

—LONNIE SHEA, BIOMEDICAL ENGINEERING
address. The biomaterial scaffolds can be refined, guided by a combination of computational modeling and a technology Shea co-developed, termed TRACER (Transcriptional Activity Cell aRray). TRACER can identify the signals required to stimulate alveolar development, which can then be incorporated into the scaffold.

RIPE FOR COLLABORATION

The technologies offered by BME are just as applicable to internal medicine’s clinical questions as its basic science work, says Shea — as evidenced by Thomas Wang’s molecular imaging technology for early cancer diagnosis (page 84). Shea believes passionately that the sky’s the limit when medicine and engineering team up.

He says the trick to unleashing the power of these complementary approaches is for each side to become better acquainted with the other, “Biomedical engineering has evolved so dramatically in recent years that many people don’t realize the role we can play in areas like immunomodulation, drug delivery, cellular therapy and the modeling of big data,” says Shea. “Likewise, we as engineers need to be tapped into the challenges faced by physicians who are involved in clinical practice and bench research because we often have tools and a perspective that can make a contribution to these important areas.”

Shea says his department is particularly suited to supporting its Medical School colleagues in areas such as regenerative medicine, precision health and big data (see graphic at right).

In fact, BME has developed a resource called “Collaboratories” to help other departments explore the tools and technologies BME has available and how they can be applied to various clinical and basic science problems. It is available at bme.umich.edu/collaboratories.

BIOMEDICAL ENGINEERING’S COLLABORATIVE EXPERTISE

ORGANOIDS PROBE THE MICROBIOME

Spence is also collaborating with microbiome expert Vincent Young, MD, PhD, professor in the Division of Infectious Diseases, using Spence’s “guts in a dish” to probe how disease-causing bacteria and viruses affect the gut’s ecosystem. A five-year, $6.4 million federal grant will allow their team to expand development of these human intestinal organoids, or HIOs.

Because HIOs develop in a sterile environment, investigators have a blank slate and can inject them with the microbes of their choosing. The team plans to study the interaction between HIOs and the normal gut microbiome as well as disease-causing pathogens.

“It is incredibly powerful to be able to study host-microbe interactions when you have total control over which microbes you introduce into a pristine environment,” says Young. “One area in which we’re using HIOs is to investigate the gut of the newborn, which for all intents and purposes is sterile, and how it reacts after birth when it initially gets colonized with microbes.”

TOP: HUMAN INTESTINAL ORGANOID (HIO) INJECTED WITH TOXIGENIC STRAIN OF C. DIFF, RESULTING IN SEVERE DAMAGE TO THE INTESTINAL EPITHELIUM. INSET SHOWS A ZOOMED IMAGE OF THE BACTERIA.

BOTTOM: HIO INJECTED WITH NON-TOXIGENIC STRAIN OF C. DIFF, RESULTING IN AN UNAFFECTED EPITHELIUM.

CREDIT: JASON SPENCE
Another researcher who is combining engineering and medicine for the benefit of patients is **Thomas D. Wang**, MD, PhD, the H. Marvin Pollard Collegiate Professor of Endoscopy Research in the Division of Gastroenterology and the Departments of Biomedical and Mechanical Engineering.

Wang’s lab has developed a new molecular imaging approach that allows physicians to detect precancerous lesions in the digestive tract by “lighting up” these cells hiding within the mucosa.

This has been accomplished by developing fluorescently labeled peptides designed to bind to specific proteins that are expressed on the surface of cancer cells — proteins which play a role in adhesion, migration and invasion. The peptides are applied directly to the mucosal surface, attach to cancerous cells and can be imaged by a special endoscope that detects fluorescence.

One of Wang’s signature applications is esophageal cancer. It’s long been appreciated that a percentage of patients with acid reflux will go on to develop Barrett’s esophagus — where the esophageal lining begins to resemble intestinal lining. A small percentage of these patients will go on to develop potentially fatal esophageal cancer.

Early detection is critical, but it’s been a challenge because early cancerous lesions in the esophagus are flat, patchy and can be widely dispersed. Therefore traditional imaging can often miss them.
However, Wang’s new platform identifies cancer cells — and those in the process of becoming cancerous — by their molecular signature rather than their appearance. This innovative approach may be a game-changer in esophageal cancer, as well as cancers of other hollow organs, such as the colon, pancreatic duct, biliary tract and stomach.

“We can see certain cells that have a high likelihood of becoming cancer and just take them out,” says Wang. “so they’ll never form cancer in the first place.”

He’s now working to commercialize and translate this methodology into clinical practice through the Barrett’s Esophagus Translational Research Network (BETRNet). This NIH-funded multi-center network aims to advance new methods to visualize the spatial distribution of genetic mutations, evaluate tumor heterogeneity and assess impact on disease progression.

Wang was recently part of a team that used a similar imaging approach to identify unstable arterial plaques by the presence of specific enzymes that release fluorescence. He hopes techniques like this could help physicians find plaques at risk of rupture before they lead to heart attack or stroke.

A sophisticated development process

To develop this imaging approach, Wang collaborates with David Beer, PhD, in thoracic surgery. They use genomic data on esophageal cancer to identify promising imaging targets and create specific peptides capable of binding to these targets, and have developed a special endoscope to detect the lesions.

This work is made possible by a sophisticated research infrastructure that includes Wang’s biology and optics lab, the Center for Molecular Imaging (for small animal studies) and the Medical Procedures Unit (U-M’s endoscopy facility for supporting “first-in-human” clinical studies).
Hem/onc develops liquid biopsy techniques

Supports Cancer Breakthroughs 2020

“Our team members at U-M are already seeing how circulating tumor DNA and circulating tumor cells can show how a tumor is evolving throughout treatment. This has the potential to alter the treatment plan in real time based on the markers we see in the blood, which could produce a much more individualized and adaptive treatment approach for each patient.”
—MUNEESH TEWARI, HEMATOLOGY & ONCOLOGY

A Michigan Medicine team anchored by MUNEESH TEWARI, MD, PhD, the Ray and Ruth Anderson-Laurence M. Sprague Memorial Research Professor of Internal Medicine and professor of Biomedical Engineering, is offering its expertise in blood-based cancer testing — or “liquid biopsies” — to Cancer Breakthroughs 2020 (formerly called the Cancer Moonshot).

Fast, accurate, minimally invasive testing techniques are key to helping the effort achieve its goal of delivering effective immunotherapies for multiple cancer types by 2020. Tewari is well-known for his breakthroughs in liquid biopsy. He first discovered that microRNAs are shed from cancer cells and circulate in the blood — turning these silencers of gene expression into potential cancer biomarkers.

Tewari has been collaborating closely with Chemistry Professor Nils Walter, PhD, and Research Assistant Professor ALEX JOHNSON-BUCK, PhD, from the Division of Hematology & Oncology, to develop an efficient, highly specific technique for detecting these microRNAs in the blood. It uses bits of fluorescent-tagged DNA, which alternately bind to and release their complementary microRNAs, revealing each RNA’s identity through a distinctive pattern of blinking fluorescence. Tewari hopes this technique will lead to simple blood tests that can scan for multiple types of cancer.

Also bringing their expertise to Cancer Breakthroughs are DANIEL HAYES, MD, the Stuart B. Padnos Professor of Breast Cancer Research; Scott Tomlins, MD, PhD, assistant professor of pathology; and Todd Morgan, MD, associate professor of urology. Hayes is known for advancing the use of circulating tumor cells as biomarkers. Tomlins has been collaborating with Morgan and Tewari to develop a
new approach for studying tumor-derived, cell-free DNA in patients with multiple kinds of advanced cancer.

The U-M team is sharing best practices for collecting and processing blood specimens for liquid biopsy analysis. They’re also providing data for the initiative’s Blood Profiling Atlas, including sequencing data on DNA and RNA in patient blood samples.

The team is pleased to be part of this national effort, but equally excited about the possibilities for liquid biopsy to enable more precise cancer treatment.

“Our team members at U-M are already seeing how circulating tumor DNA and circulating tumor cells can show how a tumor is evolving throughout treatment,” says Tewari. “This has the potential to alter the treatment plan in real time based on the markers we see in the blood, which could produce a much more individualized and adaptive treatment approach for each patient.”
When one thinks of how technology can transform a subspecialty, cardiovascular medicine almost certainly comes to mind. In many ways, it’s an ideal case study for how technology can make care simultaneously less invasive, more personalized and more effective.

The Frankel Cardiovascular Center regularly makes headlines for advancing and adopting new technologies, from left ventricle assist devices and transcatheter aortic valve replacements to miniature leadless pacemakers and MRI-safe implantable cardioverter defibrillators.

But this is just the tip of the iceberg, say representatives of the Division of Cardiovascular Medicine, who share their vision for the future and how their work is moving us toward it.

CUSTOM DEVICES AND COMPUTER-GUIDED CARE
One of the bolder predictions comes from Division Chief DAVID PINSKY, MD, the J. Griswold Ruth and Margery Hopkins Ruth Professor of Internal Medicine. “I think at U-M in the decades ahead, we’re going to have biological replacement parts for the heart,” says Pinsky. “We already have experience with mechanical hearts, and with our expertise in cardiac cells, blood vessels, organoids and induced pluripotent stem cells, we’ve got what it takes to do it.”

He envisions a day when we could customize valves, vessels, muscle patches and biological pacemakers to give patients a new lease on life.

Another physician who sees great potential in custom devices is Professor HITINDER GURM, MD. An interventional cardiologist, Gurm envisions patient-customized stents that could be 3-D printed or manufactured on demand to provide an ideal fit for challenging vessel architecture.

However, Gurm is also an award-winning leader in patient safety and quality improvement. So while he believes personalized devices are important, he thinks technology can make the greatest impact on health at a population level by offering scalable precision medicine platforms.

“Imagine if I could predict the best drug for you on your first visit,” says Gurm, “so you wouldn’t have to try a first drug, then a second, then a third to see what is best for your biological makeup. Then imagine if your therapy could be increasingly personalized based on your experiences in the health care system.”

This is precisely Gurm’s vision; he’s working on computational algorithms for the precision treatment of hypertension. In collaboration with Professor Emeritus BERTRAM PITT.

SEE PAGE 48 TO LEARN HOW BRAHMJEET NALLAMOTHU IS USING ARTIFICIAL INTELLIGENCE FOR COMPUTER-GUIDED ANGIOGRAM ANALYSIS.
MD, he’s launching a project called Controlling Hypertension using Artificial Intelligence (CHAI). Their goal is to use big data and artificial intelligence to guide physicians in selecting the right treatment for patients, given their biology, geography, response to previous drugs and other factors, and to tailor that treatment over time.

They’ve chosen to focus on hypertension because of its potential population-level impacts. It’s pervasive, growing globally, often under-recognized and poorly treated — and is perhaps second only to smoking as a cause of cardiovascular morbidity and mortality worldwide.

“I think we’ll see more and more computer-human interaction to ensure that patients are getting the right treatment and are not over- or under-treated,” says Gurm. CHAI is an important start.

“**A GOOD DOCTOR IS OFTEN SOMEBODY WHO SAY**S, ‘OH, I’VE TREATED THIS PATIENT AND I KNOW HOW HE OR SHE WILL RESPOND.’ WE’RE TRYING TO CREATE A COMPUTERIZED PROGRAM THAT COMBINES THE WISDOM OF ALL THESE GOOD DOCTORS AND CONTINUOUSLY LEARNS SO WE CAN IMPROVE THE TREATMENT OF SOMETHING THAT IS VERY COMMON AND YET IS NOT VERY WELL DONE.”

— HITINDER GURM, CARDIOVASCULAR MEDICINE

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**ADVANCED CARDIOVASCULAR IMAGING**

The Division of Cardiovascular Medicine is also taking a leadership role in moving advanced imaging techniques into the clinic. Two areas now being employed in clinical care are quantitative cardiac PET imaging and ultrasound speckle tracking. The faculty leading these efforts believe these quantitative, precision imaging techniques will allow researchers to dig deeper into underlying disease processes and enable clinicians to diagnose disease earlier, identify appropriate treatments and improve patient outcomes.

**PET IMAGING QUANTIFIES CARDIAC BLOOD FLOW, INFLAMMATION**

One team has been leading the charge to translate positron emission tomography, or PET imaging, into clinical use for measuring myocardial blood flow and cardiac inflammation.

“This method has been around for a long time in the research arena, but has been very technically challenging to scale up to the thousands of patients we’d see clinically or in large-scale research,” says team member **VENKATESH MURTHY**, MD, associate professor in the Division of Cardiovascular Medicine and the Department of Radiology. “But we’ve pushed it to the point that we can evaluate close to 2,000 patients a year, and that’s growing.”

Murthy’s team includes **JAMES CORBETT**, MD, professor in the Division of Cardiovascular Medicine and the Department of Radiology, and Edward Ficaro, PhD, research assistant professor in the Department of Radiology.

Murthy has worked hard to develop clinical protocols, such as careful manipulation of patients’ diet and medication, which are needed to image large numbers of patients quickly, consistently and accurately. Corbett and Ficaro have led the development of software to take these complex scans and deliver quantitative measurements in real time. The team has also worked with collaborators at MIT and in industry to bring to market a mini-cyclotron, which can make the radiotracers needed for this imaging widely available at a fraction of the traditional investment.

The precision measures of blood flow that cardiac PET imaging makes possible — down to how many milliliters of blood are getting to each gram of heart muscle per minute

CONTINUED ON PAGE 90
— can allow physicians to identify arterial blockages at a much earlier stage. It also allows them to better separate patients appropriate for medical management from those requiring bypass surgery or stents.

The team sees huge potential for the technique in heart failure, particularly a type driven by reduced blood flow in the small arteries that penetrate the heart muscle. “Angiograms allow us to find blockages in the large arteries on the surface of the heart, but the small arteries that penetrate it seem to contribute to a form of heart failure where the overall pumping function of the heart is close to normal, yet the patients accumulate fluid in their legs and lungs,” says Murthy. “It probably accounts for as much as half of all heart failure and appears to be common among women with chest pain. Using PET, we can now evaluate for it.”

The team is also using PET to image inflammation in the heart muscle and valves due to autoimmunity or infection. For example, they’re using it in the autoimmune disease sarcoidosis, in which granulomas can form in the heart. They’re hoping that serial imaging with this sensitive, quantitative technique will allow them to tailor the precise regimens of immunosuppressants needed to interrupt the underlying disease process without over-suppressing patients’ immune systems.

They’re doing similar work with infections of implanted cardiac devices, like pacemakers, valves and cardioverter defibrillators. They hope that by being able to quantify the amount of infection, they can treat patients earlier — and determine which patients can be treated more conservatively with antibiotics and which need their devices removed.
BRINGING SPECKLE TRACKING TO THE CLINIC

The Echo Lab at the Frankel Cardiovascular Center is advancing the clinical use of ultrasound speckle tracking, a technique that measures the contraction and relaxation of the heart muscle, known as strain. Because of its sensitivity, speckle tracking can detect abnormalities earlier than traditional techniques and provide insight into prognosis and appropriate treatment.

Led by Echo Lab Director and Associate Professor THEODORE KOLIAS, MD, the effort to apply this technique is most developed in determining damage to the heart caused by chemotherapies. The Echo Lab now routinely evaluates chemo patients for the earliest signs of cardiotoxicity so that treatment can be adapted.

Kolias and colleagues are exploring whether speckle tracking can provide new insights into the evaluation of patients with heart failure with preserved ejection fraction, which accounts for nearly half of all cases of heart failure. They are also applying it to the challenging task of assessing right ventricle function in pulmonary hypertension, and exploring its clinical utility in assessing left atrial function.
As demands on physicians in the Department of Internal Medicine change in the years ahead, so too will the organization of routine care and the role of technology in streamlining it.

One of the bigger changes ahead is Michigan Medicine’s expanded scope. “U-M will soon become the source of primary care for 400,000 people, mainly in southeastern Michigan, and there will be another 3.5 million in the referral pattern for tertiary and quaternary care,” says RICHARD SIMON, MD, professor in the Division of Pulmonary & Critical Care Medicine and associate chair for faculty affairs.

Another issue, which has been building for some time, is that in many parts of this catchment area, the demand for physicians vastly outstrips supply — from general internists to subspecialists in areas like geriatrics, rheumatology and endocrinology.

Among the many ways Michigan Medicine is working to address these issues is with the use of technology. “We are working to set up robust telemedicine platforms so that physicians here in Ann Arbor can get the information they need to provide high-quality consultations to patients across the state,” says Simon. “The maldistribution is going to be solved not by convincing physicians to set up practice in various underserved communities, but instead by coordinating care between advanced practice providers there and physicians at academic centers like ours capable of delivering high-quality care at a distance.”

KIM EAGLE, MD, the Albion Walter Hewlett Professor of Internal Medicine and director of the Samuel and Jean Frankel Cardiovascular Center, believes high-quality distance care is at our fingertips. He sees great potential in the synergistic use of technologies like wearable sensors, video chat services and smartphones.

Care will become increasingly “rapid-fire, virtual and patient-focused,” says Eagle. He envisions patients being monitored, sometimes continuously, with sensors that record their vital signs and a growing number of key biomarkers, all of which would feed into smartphone apps able to alert patients, family members and providers at the first sign of trouble.

“Part of this future will be allowing patients and families to take more ownership of their health, and part will be ensuring we have a network in place where clinicians can provide answers and make care adjustments to keep people out of the hospital,” says Eagle. “Our goal will be to identify poorly controlled blood pressure or arrhythmia, for example, before it hurts a person. With sensors and smartphones, we can find this out in real time and take action.”

He also sees video chat technologies playing a major role not only in caring for long-distance patients, but in linking primary and subspecialty care. “Instead of a patient needing two separate appointments, I could be patched in to her primary care visit,” he says. “I could see her on my screen, we could listen to her heart together with an electronic stethoscope, I could look at her EKG online and we could, right then and there, collaborate on a plan to improve the patient’s cardiovascular health.”

Michigan Medicine is already using technology to better coordinate primary and subspecialty care. “We’ve started an eConsult program to leverage our electronic health records, so that primary care physicians can get questions answered without requiring patients to seek a subspecialty visit,” says ROBERT ERNST, MD, assistant professor in the Division of General Medicine and assistant chair for primary care. “This is a great example of how a shared electronic health resource is getting the system interconnected.”
The benefits, he says, are ensuring that low-risk patients get their questions answered efficiently and seamlessly, while preserving subspecialty appointments for patients with greater needs. The eConsult initiative is designed to achieve expeditious, high-quality care while also reducing costs.

But Ernst sees the role of technology going beyond connectivity to one that may subtly but significantly shape the role of physicians in the years ahead. “I think artificial intelligence will increasingly be used in decision-support resources,” he says. “While this will never replace us, it may mean that we’re less likely to need to recall vast amounts of information and literature as we’ve done historically because the knowledge will be brought to us. Instead, our role may focus more on our clinical judgment, advocacy for our patients and understanding the nuances of their situation.”

All of which brings him to a refrain voiced consistently in discussions of health care technology. “The future is favorable as we work to create systems that optimize the health and wellness of our patients,” he says. “But we need to be thoughtful to ensure that technology is used to enhance our relationships — with patients, with colleagues and with other subspecialties. I believe strongly that the quality of the care we’re able to provide depends on the quality of those relationships, and I hope technology will help deepen them.”

GI: Testing the Value of Telemedicine

The Division of Gastroenterology is implementing a telemedicine platform to help more patients access its multidisciplinary care teams. “Telemedicine is a perfect model for providers like dieticians and behavioral therapists who don’t need to examine or touch their patients; they just need to see and interact with them in real time,” says gastroenterologist William Chey, MD.

Chey and colleagues have just launched a preliminary study comparing factors such as patient outcomes, satisfaction, costs, follow-ups and appointment attendance for telemedicine and face-to-face visits. Their goal is to inform the design of a randomized trial to more fully investigate the value of these care-delivery methods.
6. QUALITY & VALUE

- REDEFINING ACCESS  
  p. 96
- MAKING CARE A FAMILY AFFAIR  
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The federal Agency for Healthcare Research and Quality defines quality health care as “doing the right thing, at the right time, for the right person and having the best possible result.”

There are many dimensions of “quality” as a concept — that it incorporates access (bringing care to where patients are), it is patient- and family-centered (focuses on their communication patterns, cultural mores, economic/social context, etc.), it is safe. It also is administered in a way that provides the best value for both the patient and the health system.

Quality is one of the key areas where the Department of Internal Medicine has current clinical care and research efforts that are serving as models for other institutions. While Michigan Medicine is slated to become the primary care provider for 400,000 Michigan residents with another 3.5 million in the referral pattern for tertiary and quaternary care, our mission is to bring quality and value to an even larger segment of the state while developing standards that will impact the future of health care delivery across the country and the world.
The Department of Internal Medicine’s primary care providers are out on the frontlines as the first point of contact for health issues and as patient advocates. As the demand for primary care continues to outpace the supply of providers, how will it be possible to maintain the same quality of care?

ROBERT ERNST, MD, assistant chair for primary care and associate chief for the Division of General Medicine, has a few ideas. “As Michigan Medicine’s network continues to grow, we’ll need to be creative and expand our vision of how we provide access to care. It can be addressed in several different ways: through emerging health technologies like telemedicine and eConsults (page 93) and also by continuing to build our interprofessional teams and developing community partnerships.”

INTERPROFESSIONAL TEAMS

“The days of the single provider doing comprehensive care by themselves with individual patients are already gone. I think that we’ll have to continue to enhance this notion that provision of care in the primary care world is highly dependent on our interprofessional relationships with other physicians, physician extenders, nursing support, clerical support and medical assistants,” Ernst explains.

Increasingly at U-M, pharmacists are also becoming part of the team. “I think it has really been a very important innovation to embed pharmacists into the team, so that they can work off of a plan of care and see patients more frequently and optimize management of disorders like diabetes or hypertension.”

Looking toward the future, Ernst would like to build the teams even further. “Another important goal would be to embed a behavioral health specialist into interprofessional teams, so we would have dedicated experts to help patients identify and address important issues that can adversely affect one’s health like depression, anxiety, adjustment disorders and stress,” he explains.

COMMUNITY PARTNERSHIPS

He also believes that a real innovation in access to patient care is going to come through the growth of community partnerships. “I base this on the general notion that constructive care, if it’s really patient-centric, would be flipping upside down the model where we’re setting the schedule and they’re coming to us. Instead, it would make care available when and where it’s convenient for patients. For instance, just this past year Michigan Medicine entered into a partnership with CVS and its MinuteClinics, so that patients can more easily walk in, get quick care for straightforward issues and then still have that ability to upload information into the integrated medical record,” he explains.

Through the affiliation, CVS Health will share prescription and MinuteClinic visit information with Michigan Medicine providers by enabling communication between their secured electronic medical record systems. For example, with the patient’s consent, a MinuteClinic provider can view the patient’s U-M medical record and will electronically share patient visit summaries with the patient’s U-M provider.

In addition, U-M providers will receive data on interventions conducted by CVS pharmacists to improve medication adherence. This enhanced information sharing between the two organizations will improve the coordination of care for U-M patients who use CVS pharmacy and MinuteClinic locations nationwide.

The two organizations recently worked together on a pilot project. The project allowed for collaboration between selected CVS pharmacists and Michigan Medicine providers in Ann Arbor to improve chronic disease management of U-M patients in the local community. Building on the
lessons learned from the pilot, the two organizations are exploring other opportunities to engage community pharmacists in direct patient care.

“We can now have physicians establish a plan of care and then the patients can go see a community-based pharmacist who has access to our record and can then work with the patient in the pharmacy setting to help optimize their treatment,” he explains.

“Another great example of a community partnership would be the relationship that our Blue Cross Blue Shield of Michigan and Premier Care partner has with the YMCA. Patients who are identified as either pre-diabetic or at-risk for pre-diabetes can qualify for a diabetes program focused on lifestyle management, nutrition counseling and physical activity coordinated by the YMCA.”

While these examples are not traditional medical office interactions, they are built around the needs and schedules of the patient and helping them manage their health.

Ernst adds, “With these options, a primary care provider can have both an internal team and a community partner working with their patient. The more we can broaden the scope of our team, the greater flexibility we will have in providing timely access to care — which is one thing that most patients value more so than anything else. Patients would love this and it would be better for their health. It’s also good for us. As we become more distributed at various sites within the community, we will be able to innovate and identify best practices that can be shared and supported broadly across the organization.”

**WHAT IS A MINUTECLINIC?**

CVS HEALTH HAS 17 MINUTECLINIC WALK-IN MEDICAL CLINICS IN MICHIGAN, LOCATED IN RETAIL PHARMACY LOCATIONS. MINUTECLINICS ARE OPEN SEVEN DAYS A WEEK, OFFERING EVENING HOURS WITH NO APPOINTMENT NECESSARY, AND MOST HEALTH INSURANCE IS ACCEPTED. THE CLINICS ARE STAFFED BY NURSE PRACTITIONERS AND/OR PHYSICIAN ASSISTANTS WHO PROVIDE TREATMENT FOR COMMON ILLNESSES AND ADMINISTER WELLNESS AND PREVENTION SERVICES, INCLUDING HEALTH-CONDITION MONITORING FOR PATIENTS WITH CHRONIC DISEASES.
There has been a shift over the past ten years. We now understand why providing patient- and family-centered care is critical to addressing challenges in our current health care system — challenges including continuity of care and care transitions; patients and families understanding their illness and treatment plans; and engaging patients and families in shared decision-making.

Many studies have shown that patients with the skills, ability, and willingness to manage their own health and health care experience better health outcomes at lower cost. Yet there are many times when focusing on the patient alone is not enough. Sometimes, especially during a critical illness, including partners and families can make a world of difference in the quality of patient outcomes. Department of Internal Medicine faculty have been inventing and integrating new approaches to help clinicians better communicate, engage and partner with patients and families to provide higher-quality, safer care.

**KEEPING FAMILIES IN MIND AT EVERY STAGE**

**THEODORE “JACK” IWASHYNA.** PhD, MD, is an associate professor from the Division of Pulmonary & Critical Care Medicine; he practices at both University Hospital’s Critical Care Medicine Unit and the VA Ann Arbor Health System’s Medical Intensive Care Unit. He has come to believe that one of the keys to quality care is to view critical illness as a family condition, not an individual condition.

“The experience of having a loved one be critically ill is so disruptive and devastating to families. As we think about recovery, we need to think about both the patient and their loved ones as the survivors of critical illness. We know there are profound rates of depression among family caregivers of critically ill patients for months to years afterwards. We know that people give up enormous amounts of time and provide enormous amounts of unpaid, informal care as part of recovery,” he explains.
trying to provide structured ways to help family members figure out what role they want in the decision-making process. Are they micro-managers who want to be involved in every decision? Or do they want the doctor to make all of the decisions? What kind of partnership are they comfortable with? We also need to provide ways to help patients and families effectively communicate their values to us to make sure we fully understand their perspective."

This involvement shouldn’t end after the patient is discharged from the hospital. “Increasingly we prepare families for life after discharge right from the get-go, as opposed to just focusing on hospitalization. In the ICU, we say: ‘survivorship begins at the moment of rapid sequence intubation.’ I think the future involves us working more with families and their primary care providers to provide a better continuum of care,” he explains. “A quarterback needs to know where the receiver is going to be in order to coordinate how he’ll pass the ball. Quarterbacks don’t just get into position and then look to see if there’s a receiver at the last second. We can not assume everything is going to magically fall into place at our convenience.”

PARTNERING WITH PARTNERS

Christine Veenstra, MD, MSHP, is an assistant professor in the Division of Hematology & Oncology who treats patients with colorectal cancer. She currently holds a K07 Award from the National Cancer Institute to investigate new ways to include loved ones in a cancer survivor’s surveillance care.

“Most research on cancer outcomes has focused primarily on patient factors,” she explains. “We know that minority patients, patients of low socioeconomic status, patients who have poor geographic access to medical centers and patients without insurance are less likely to receive surveillance care. Unfortunately, there’s little that clinicians can do to change those factors other than being aware that those patients are vulnerable to missing care and trying to keep them from falling through the cracks,” she explains.

“In my clinical practice I have been struck by the ways in which cancer patients require support from spouses and partners, family members and other caregivers to help them navigate their diagnosis and, beyond that, to help them get through treatment and into the survivorship period.”

After curative treatment for colorectal cancer, ongoing surveillance is necessary to detect cancer recurrence. Limited recurrences in the liver, lung and at the site of the primary cancer can be surgically resected with a cure rate as high as 50 percent. However, currently, nearly half of the 1.2 million yearly survivors of colorectal cancer in the U.S. fail to receive potentially life-saving surveillance.

Veenstra is hoping that engaging the spouses or partners of patients may represent an opportunity to improve cancer surveillance. The majority of colorectal cancer patients are married or partnered. Partners may serve as a potential resource that providers can engage to increase patients’ receipt of surveillance.

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“My hypothesis is that when partners are engaged in this surveillance care process — meaning that they’re aware of the surveillance care, they’re involved in tests and appointments, and they know about the patient’s preferences for care — the patients are more likely to receive surveillance. When partners are less engaged in the surveillance care process — perhaps due to cultural or gender differences in engagement, or other factors — those patients may be particularly vulnerable to missing recommended surveillance care and therefore experience poor clinical outcomes. The findings of this study will lay the foundation for patient- and family-centered interventions to improve care among cancer survivors.”

She is hoping this research will help define where the barriers are to receipt of surveillance care from the perspective of the couple and develop a decision tool that clinicians could use with couples. It could help inform partners of the need for surveillance and provide strategies partners could use to help patients get the surveillance care they need. And ultimately improve receipt of surveillance care and overall survival.

“Once we know the mechanisms by which partners help patients get surveillance care, perhaps we can also replicate that in some way or provide that source of support for patients who don’t have partners. That would be ideal,” she adds.
Hospitals should be considered places of healing not hazards. While Michigan Medicine regularly receives high marks for hospital safety, internal medicine faculty are leading the charge to provide better patient care. Through numerous initiatives, many of which are garnering state and national attention, they are designing ways to anticipate and counteract human error and infections, ensure improved communication and better prepare both doctors and patients to succeed.

A UNIQUE PERSPECTIVE
VINEET CHOPRA, MD, MSc, FHM, chief of the newly-formed Division of Hospital Medicine (effective 7/1/17) and research scientist in the Patient Safety Enhancement Program and Center for Clinical Management Research at the VA Ann Arbor Healthcare System, brings a unique and valuable perspective to his work.

His medical career started out on a different path than most researchers and sparked his interest in improving the safety of hospitalized patients by preventing hospital-acquired complications. “I was recruited to help develop and lead a hospital medicine group for several years before coming to Michigan. I loved the clinical work, but I grew frustrated with the fact that some of my partners would come in after me and undo some of the things I worked hard to achieve — such as withholding antibiotics or invasive devices that I thought were inappropriate. Why? Because the evidence you need at the point of care often isn’t granular enough to apply it to that one patient at that one moment in time. So what may seem best to me at the time may not seem wise to someone else. Rather than changing one patient at a time and trying to fix things on a case-by-case basis, I thought ‘Wouldn’t it be great if we could change physician behavior?’” he explains.

CREATING MAGIC
By looking at data from 10 Michigan hospitals participating in the Michigan Hospital Medicine Safety Consortium (a collaborative quality-improvement effort funded by Blue Cross Blue Shield of Michigan), Chopra and his team found that substantial variation exists when it comes to the use of intravenous devices called peripherally inserted central catheters, or PICCs. PICCs have become extremely common in American health care in the last decade as the delivery mechanism for everything from chemotherapy for cancer patients to antibiotics and fluids in intensive care unit settings.

In addition to seeing wide variation in how and when PICCs are used, his group also found variation in how often patients experienced complications known to be associated with PICCs. Although most complications were minor, some were more dangerous. Since PICCs are inserted in the arm and include a tube that extends deep into the body’s circulation system, they can act like a highway for infectious organisms to get access to the bloodstream, or can promote blood to clot around them. If a clot breaks off and travels into the body, it can block blood flow to the lungs.

“One of the things that I’ve taken away from Creating Magic is the fact that the questions that we have to answer need to be asked not from the perspective of disease or outcomes, but rather from the perspective of what matters to patients.”

—VINEET CHOPRA, HOSPITAL MEDICINE

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“One way of preventing complications and ensuring the appropriate use of PICCs is to follow evidence-based recommendations for use,” says Chopra. But until recently, those didn’t exist.

In 2012, he received an investigator award from the Society of Hospital Medicine and a career development grant to develop appropriateness criteria for PICCs. These guidelines provide insights on topics such as whether you should or should not use a PICC, estimating the risk of complications and defining innovative ways to improve decision-making for these devices. His team launched the website Improve PICC (www.improvepicc.com) as a central point of information for clinicians and offers free access to the Michigan Appropriateness Guide for Intravenous Catheters, also known as MAGIC.

Chopra believes that including the patient’s perspective has been critical to MAGIC’s success. “One of the things that I’ve taken away from creating MAGIC is the fact that the questions that we have to answer need to be asked not from the perspective of disease or outcomes, but rather from the perspective of what matters to patients.

MAGIC was developed by an international, highly multidisciplinary panel of professionals, members of HMS hospitals — and with a patient.

Chopra believes that including the patient’s perspective has been critical to MAGIC’s success. “One of the things that I’ve taken away from creating MAGIC is the fact that the questions that we have to answer need to be asked not from the perspective of disease or outcomes, but rather from the perspective of what matters to patients.

MAGIC APP

CHOPRA HEARD FROM VASCULAR NURSES WHO WANTED TO USE MAGIC AS A TOOL THAT THEY WOULD LOVE TO HAVE AN APP VERSION THAT THEY COULD FOLLOW. HE’S CURRENTLY BUILDING AN APP THAT WALKS THROUGH MAGIC AND THEN PROVIDES RECOMMENDATIONS. “THIS COULD REALLY BE USEFUL FOR A NUMBER OF STAKEHOLDERS — FOR A DOCTOR ORDERING THE LINE OR FOR A SURGEON OR A NURSE OR AN INTERVENTIONAL RADIOLOGIST WHO ACTUALLY WANTS TO INSERT THE LINE THEMSELVES TO MAKE SURE THEY’RE DOING THE RIGHT THING. IT COULD ALSO BE A WONDERFUL EDUCATIONAL TOOL FOR PATIENTS,” HE EXPLAINS.
These are invasive devices that we place in patients, so we must have some sense of what patients prefer. Having a patient engaged at the very beginning was so helpful in that respect, because this person challenged some of the assertions that we had. ‘Well you know, surely a patient won’t mind getting a needle stick in the arm for a few blood draws,’ and the patient said, ‘Of course I would mind. I don’t want to be stuck by a needle ten times a day. Would you want that?’

**Implementation is Key**

It can take, on average, 17 years from the time a study is published to when it actually gets implemented into practice. Chopra hopes to change that statistic dramatically by thinking about implementation from the start. “As we designed and deployed MAGIC, it became clear that we needed to create a way to make it easier to use. We thought of several options. For instance, we should build electronic order entry sets that make choices for IV devices easy. If you have an external resource like a paper, and you expect someone to find it, read it, understand it and then use that knowledge to order a PICC, it may never happen. Rather, you need to build it into the workflow.”

Much of the content in MAGIC was created with that in mind. At the point of ordering an IV, walk-through questions are provided to give guidance on whether a PICC should or should not be used. This approach has already been implemented at Michigan in the PICC order entry set. It is also being done at Beaumont Hospital in Dearborn. “Beaumont leadership figured that getting their physicians in private practice or in the community to read evidence and follow it may not be easy. So they built decision-making about PICCs into their workflow. They developed a checklist for the nurses and a tool for physicians to determine whether they should use a PICC, and implemented it in their electronic health record. Since launch, use of PICCs has dropped by almost 40 percent and decreased complications substantially,” adds Chopra.

All 51 hospitals in the Michigan HMS Consortium are now assessing how to incorporate MAGIC to guide use of IV devices. And all are now collecting data and reviewing PICC practices to improve care for their patients. Because five of the 15 contributors came from HMS hospitals, they are uniquely able to apply MAGIC to their sites. HMS is led by fellow internal medicine faculty member **Scott Flanders**, MD, a professor from the Division of General Medicine. Flanders, who is also the department’s vice chair for external relations and quality, was a senior author of the new paper.

Chopra is pleasantly surprised by how quickly and largely MAGIC has been adopted and used. “It’s heavily cited in several guidelines for intravascular device use and is being actively tested and deployed in adult and pediatric settings. It’s also being used in countries across the world – investigators in Brazil, Australia, China and India, for example, have even developed their own set of MAGIC criteria to implement recommendations.”

This success may have a little bit to do with the unique perspective he brought to Michigan. “Going from what works in a lab, a study, a paper or a model, to what works in the real world — you need to be thinking about that from the very beginning. I’ve been fortunate to work with a number of people at Michigan who actually get that. It’s one of the many things that makes Michigan such a special place — and allows us to be leaders and best in transforming care delivery in the future.”

**Collaborative Quality Initiatives**

Through engagements like the Michigan Hospital Medicine Safety Consortium (HMS), a collaborative of 52 Michigan hospitals and Blue Cross Blue Shield of Michigan (BCBSM) focused on IV catheter and PICC (peripherally inserted central catheter) line use, Chopra and his colleagues are focused on bringing research into daily practice.

Listed below are statewide quality collaboratives sponsored by BCBSM and run out of the Department of Internal Medicine.

- BCBSM Cardiovascular Consortium – Percutaneous Coronary Intervention
- BCBSM Cardiovascular Consortium – Vascular Interventions Collaborative
- Genetic Testing Resource and Quality Consortium
- Integrated Michigan Patient-Centered Alliance on Care Transitions Collaborative
- Michigan Anti-Coagulation Quality Improvement Initiative
- Michigan Breast Oncology Quality Initiative
- Michigan Hospital Medicine Safety Consortium
- Michigan Oncology Quality Consortium
Implementing Delirium Prevention and Safety with the ABCs

Between 60 to 80 percent of ICU patients experience delirium, characterized by inattention and confusion and the inability to think clearly and make sense of what is happening. Delirium is typically caused by diseases like sepsis combined with the sedatives patients are given.

When critically ill patients experience delirium, which can occur over a short period of time, it is a predictor of longer stays in the hospital, higher cost of care, threefold higher likelihood of death by six months and long-term cognitive impairment that looks a lot like dementia.

Michigan Medicine’s Critical Care Medicine Unit and the State of Michigan were among the first in the country to adopt the ABCDE(F) bundle, an evidence-based guide for clinicians to prevent and manage delirium in the intensive care unit. Robert Hyzy, MD, the medical director of the Critical Care Medicine Unit and a professor in the Division of Pulmonary & Critical Care Medicine, explains, “We started implementing this bundle in 2010 and it has now become a core element of how we orchestrate our rounds. We’ve got a lot of trainees here, plus nurses, respiratory therapists, nutritionists, family, etc. We were really the first in the nation — as part of the Keystone ICU Collaborative — to recognize the importance of this bundle and to implement it on a broad scale as part of our day-to-day, multidisciplinary care. It’s a great example of how the process of care creates quality of care.”

**The ABCDE(F) Bundle**

- **A** Assess, prevent and manage pain
- **B** Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)
- **C** Choice of analgesia and sedation
- **D** Delirium: assess, prevent and manage
- **E** Early mobility and exercise
- **F** Family engagement and exercise
Health care delivery systems across the country are facing a common challenge: the need to prove they are delivering high-value care that is likely to improve patient outcomes, while avoiding care patients don’t need or that may harm them. The Michigan Program on Value Enhancement (MPrOVE) was launched in November 2016 to help Michigan Medicine meet this challenge.

MPrOVE, a strategic initiative supported by Michigan Medicine and the U-M Institute for Healthcare Policy and Innovation (IHPI), brings together leaders from IHPI and across U-M’s health system to identify, implement and evaluate specific projects focused on improving quality and demonstrating the value of care at Michigan Medicine, while at the same time catalyzing collaborative research efforts to inform state and national policy decisions.

Directed by Eve Kerr, MD, MPH, the Louis Newburgh Research Professor of Internal Medicine and director of the VA Center for Clinical Management Research, MPrOVE’s efforts focus on assessment and enhancement of optimal care by improving the appropriateness of clinical services, concentrating on common and costly areas in which both underuse and over-use are frequent. While there are many current efforts within Michigan Medicine focused on improving care, MPrOVE also focuses on proving, through rigorous evaluations, whether these interventions are effective; and on innovating, by systematically engaging stakeholders in flexible and rapid intervention testing that uses the principles of design thinking.

Among its first projects is an assessment of appropriateness of hi-tech imaging, with the goal of helping clinicians understand when, and how often, tests are ordered that may not be necessary, and developing and evaluating approaches that help to focus on providing the exams patients need while avoiding overtesting.

MPrOVE’s goal is to help establish and highlight Michigan Medicine as an innovator and recognized leader in consistently delivering the right care for the right patient, while avoiding care that is harmful or unlikely to lead to better outcomes. It will also seek to expand IHPI’s visibility as a national leader in research and policy on enhancing value.

Eve Kerr is joined by co-directors Scott Flanders, MD, professor of internal medicine, director of the Hospitalist Program, and vice chair for external relations and quality for the Department of Internal Medicine, and Anne Sales, PhD, RN, MSN, professor and associate chair for educational programs and health systems innovation in the Department of Learning Health Sciences, and research scientist in the VA Center for Clinical Management Research.
Since its inception in 2005, the University of Michigan Center for Value-Based Insurance Design (V-BID) has led efforts to promote the development, implementation and evaluation of innovative health benefit designs that improve quality, enhance the patient experience and lower costs. The center is directed by A. Mark Fendrick, MD, a professor from the Division of General Medicine and the Department of Health Management and Policy, who co-originated the concept of V-BID.

He explains the center’s primary goal as, “We’re trying to shift the focus of health care reform deliberations from how much we spend to how well we spend our health care dollars. If we can align patients and clinicians to do more of the things that make individuals healthier and less of the things that don’t, we will all be much better off.”

Aligning patients’ out-of-pocket costs — such as copayments, co-insurance and deductibles — with the value of health care services is the basic premise of V-BID. This approach to designing benefit plans recognizes that specific health services have different levels of value. Thus, V-BID programs are designed with the tenets of “clinical nuance” in mind, which recognize that 1) medical services differ in the amount of health produced and 2) the clinical benefit derived from a specific service depends on the consumer using it, as well as when, where and by whom the service is provided. V-BID recognizes that the same therapy can be both high-value and low-value depending on patient demographics, presence or absence of specific biomarkers, the disease treated or the stage of a specific clinical condition.

**PRECISION HEALTH MEETS PRECISION BENEFIT DESIGN**

When looking toward the future of health care and internal medicine, V-BID has the potential to make a tremendous impact. “With research advances and technology making health care and treatments much more personalized, the concept of “clinical nuance” to providing the best care will be more important than ever,” Fendrick explains.

Precision medicine — the integration of molecular science into the clinical care of an individual patient — has spurred efforts to develop targeted preventive strategies and disease-specific therapies. This personalized approach to clinical medicine has vast potential to improve quality of care, enhance the patient experience and allow more efficient health care expenditures.

Even as evidence that supports the promise of precision medicine accumulates, several challenges remain that hinder its implementation in clinical practice, including securing consumer trust and investing in the infrastructure required to support the financing and delivery of targeted care. If the full potential of precision medicine is to be realized, system-based reforms must encourage — not deter — the adoption of “personalized” medicine by clinicians and consumers.

“The potentially life-altering clinical innovations that result from the basic science and translational research carried out in our department are often not easily delivered to many Americans who might benefit, due to antiquated reimbursement systems and benefit designs that are lagging behind the science,” says Fendrick. “I like to say that we currently have ‘Star Wars’ science, but ‘Flintstones’ delivery. Clinical care based on V-BID principles can be viewed as the tail of that dog that’s necessary to make sure these amazing discoveries reach the patients. In other words, while we all support scientific breakthroughs, we must also encourage ideas that ensure the patients who benefit receive them.”

Currently, Americans are being asked to pay more for their health care to encourage the use...
of effective, lower-cost clinical services. Such approaches have been utilized for decades with varying effects on spending and patient-centered outcomes. A recommendation that patients are initially prescribed a lower-cost treatment is a reasonable population health strategy, given that a first-line therapy will often be effective and will be considered high-value for that patient and for the payer. However, advances in precision medicine may specify the immediate use of more expensive, targeted therapies, nullifying recommendations for use of standard first-line treatment. Thus, in the increasingly frequent scenario when a person tests positive for a specific marker, a targeted therapy may be indicated to optimize patient-centered outcomes. In these situations, the first-line therapy is no longer high-value, and a clinically indicated, “precision” alternative becomes a higher-value choice.

It is important to note that current cost-sharing levels are generally fixed and do not reflect the varying nature of many clinical conditions. An alternative approach would be to set the level of consumer cost-sharing based on the clinical value — not solely the price — of a therapy when used in a specific circumstance.

Fendrick believes that successful implementation of precision medicine will need to address several system-wide challenges, including administrative complexities, establishing incentives that engage patients and integrating provider- and patient-focused initiatives. By enhancing access to effective therapies when indicated, the application of clinically nuanced cost-sharing commits to established policies that encourage first-line therapies and supports precision medicine initiatives.

Fendrick has been busy sharing these ideas across the country. In February 2016, he testified before the U.S. Senate Committee on Armed Services Subcommittee on Personnel. The committee recommended that V-BID be included in the massive $619 billion defense spending bill. It is also currently being tested in Medicare Advantage (see highlight box).

“We’re gratified to see how this U-M concept is spreading beyond private and public payers into critical federal insurance programs, even as we work to engage with insurers and others in many settings to help them build clinical nuance into their plan designs,” says Fendrick.

**Federal Programs Apply V-BID**

**AFFORDABLE CARE ACT**

Section 2713 of the Affordable Care Act requires that health plans must provide coverage for specific evidence-based preventive services without a patient copayment or contribution toward a deductible. This implementation of V-BID principles has expanded coverage of preventive services for more than 137 million Americans.

**MEDICARE ADVANTAGE**

Starting in January 2017, seniors enrolled in certain Medicare Advantage plans in Massachusetts, Pennsylvania and Indiana who have diabetes, heart disease, depression and certain other conditions will get access to V-BID-style insurance that will lower their co-pays and deductibles for specific services and providers.

More states and more health conditions will be added to the Medicare Advantage demonstration in 2018, under an expansion approved by the Center for Medicare and Medicaid Innovation. Bipartisan legislation supporting a further expansion to all 50 states has been introduced in the US House and Senate.

**TRICARE**

Under a provision in the new National Defense Authorization Act, the TRICARE health insurance program for current and retired members of the military and their dependents will test V-BID in a pilot program.

By January 2018, the pilot will assess whether the V-BID approach helps people with certain conditions stick to their medications, get care that meets specific quality standards and have better outcomes and abetter experience. The assessment of this effort may lead to further rollout of the V-BID approach in TRICARE.
The Department of Internal Medicine has a sizable grassroots effort in immunity. This is hardly surprising, as the more we understand about disease mechanisms, the more we realize that elements of the immune system play a part in all manner of far-flung conditions — and in sometimes-surprising ways. Who would have believed decades ago that the immune system played a role in type 2 diabetes? Or that microbes in the gut could mediate graft-versus-host disease?

Insights like these have turned researchers from many divisions into “inadvertent immunologists.” Thus, in addition to the expected internal medicine footprints in rheumatology, allergy and infectious disease, internal medicine researchers are exploring the role of immune cells in atherosclerosis and dissecting the mechanisms of transplant rejection.

The stories here just scratch the surface. With the advent of immune checkpoint inhibitors and combination therapies, cancer immunotherapy has been reincarnated. Ajjai Alva is helping to test next-generation cancer immunotherapies as part of the Big Ten Cancer Research Consortium (page 37). And new U-M faculty member Daniel Goldstein has upended our understanding of how aging impacts immunity (page 134).
Rheumatology Takes Aim at Autoimmunity

Autoimmunity has been a longstanding strength of the Department of Internal Medicine, and it gained particular momentum in the 1980s when then-Department Chair William Kelley, MD, a rheumatologist, pursued an aggressive campaign to recruit physician-scientists. His goal was the kind of mechanistic understanding needed to one day cure, even prevent, this type of disease.

That goal hasn’t changed, and the Division of Rheumatology remains a powerhouse, evidenced by the fact that U-M is the only university housing two of the 11 NIH Autoimmunity Centers of Excellence. It hosts both a basic science center devoted to the epigenetics of lupus (page 74), as well as a clinical center directed by David Fox, MD, division chief and Frederick G.L. Huetwell and William D. Robinson, MD, Professor of Rheumatology. The clinical center, which focuses on organ-targeted autoimmune diseases, is working to unravel how proposed new treatments work at a cellular and molecular level. It also aims to discover what initiates autoimmune diseases that often appear as clusters within the population.

The center’s first project focuses on secondary progressive multiple sclerosis, a disease with no FDA-approved treatments. Center researchers are examining siponimod, a drug that keeps activated lymphocytes inside the lymph nodes, preventing them from circulating to and attacking the brain. They hope to illuminate how this drug might work in MS.

The second project addresses scleroderma. It is led by Dinesh Khanna, MD, MS, the Frederick G.L. Huetwell Professor of Rheumatology, whose group works to develop and test new treatments for this disease (see box). The project seeks to demonstrate how the rheumatoid arthritis drug abatacept might work in scleroderma by disrupting communication between T cells and antigen-presenting cells.

The final project looks at how three diseases that often cluster epidemiologically are initiated — autoimmune diabetes, rheumatoid arthritis and autoimmune thyroid disease. In these and other organ-targeted autoimmune diseases, unique interactions occur between T lymphocytes and specific cell populations intrinsic to the affected organ. Understanding and disrupting such interactions could offer a new and safer treatment approach to autoimmune diseases compared to current drugs that suppress the entire immune system and increase susceptibility to infection.
The inflammasome is a protein complex that is important for initiating inflammatory cytokines in many diseases. One of them is systemic lupus erythematosus, an autoimmune disease that can cause inflammation in the skin, joints, kidneys, brain and the tissue lining the lungs and heart. Kahlenberg is showing that activation of the inflammasome in the skin of lupus patients can trigger flares in other organs.

While exploring the role of the inflammasome in lupus, Assistant Professor Michelle Kahlenberg, MD, PhD, from the Division of Rheumatology, gleaned an important insight — that inflammation in the skin of lupus patients might be driving other systemic complications, such as kidney disease.

She has used an NIH K08 grant to dig deeper into this connection in the hopes of clarifying the mechanisms at play. Her aim is precision treatments that will prevent disease flares and the organ damage that ensues.

Her research has led to a number of promising insights. Using a mouse model of lupus, Kahlenberg discovered that irritating the skin induces kidney inflammation. Her lab is now exploring how the two systems communicate.

She’s also found that the skin of these patients is highly colonized by Staphylococcus aureus. Furthermore, these bacteria produce toxins that can activate the inflammasome in skin cells and cause significant inflammation.

Her lab is now using bioinformatics and systems biology to try to understand how these insights fit together. Her hope is that as she clarifies the molecular underpinnings of these processes, she’ll learn precisely how to intervene and keep patients with lupus healthy.

Kahlenberg already sees a promising drug target in interferon kappa. “Ideally, we’d like to see it developed as a target for the prevention of skin flares in patients and possibly prevention of systemic flares,” she says. “One of the great things about interferon kappa is that it’s very specific to the skin. We only know of three cell populations that make it, so there may not be a lot of off-target side effects from blocking this pathway.”

This would be a major leap forward for precision lupus treatment and an important means of sparing patients the pitfalls of blunter immune suppression.

“The vision for my lab is a world where patients with autoimmunity don’t get sick. We’re trying to find the switches that turn lupus on and off, and our work suggests that at least one of them is in the skin. Now we’re figuring out how to control it,” — Michelle Kahlenberg, Rheumatology
When AIDS captured the headlines in the 1980s, the vulnerability of the immune system took center stage. Though treatments have turned a once-fatal disease into a chronic one, they have by no means provided a cure.

But researchers in the Division of Infectious Diseases are hoping to change that. One is **Kathleen Collins**, MD, PhD, the Internal Medicine Collegiate Professor in HIV Research, a senior scholar in the Taubman Institute and a 2016 inductee into the National Academy of Medicine. Collins’ lab was the first to identify “reservoirs” of HIV-infected stem cells in the bone marrow. The virus is able to persist in these cells, invisible to the immune system and impervious to the cocktails that keep HIV at bay. Once treatment is stopped, these cells are a potential source of resurgent disease.

Collins’ lab has shown one important way that HIV keeps these reservoirs hidden. It uses the viral protein Nef to disable a key protein cells normally use to alert the immune system to their infection — major histocompatibility complex 1 (MHC-1).

Armed with these insights, Collins teamed up with David Sherman, PhD, the Hans W. Vahlteich Professor of Medicinal Chemistry, to search for a compound that could block Nef.

The team has found promising candidates among the metabolites made by coral-dwelling bacteria called marine actinomycetes. Their experiments in cell lines, primary T lymphocytes and stem cells show these compounds to be the most potent Nef inhibitors ever found.

They are now examining the compounds’ molecular structure in the hopes of learning how to synthesize them for drug production. They are also planning animal studies as a prelude to human testing.

If this approach works, HIV would no longer be able to shield infected cells from the immune system. It would offer, likely in combination with current antiviral therapies, a cocktail that could rid patients of the virus entirely.

Collins thinks this work would not only be transformative in the worldwide fight against HIV, it could translate to other fields, such as the development of vaccines that can seek and destroy cancer cells evading the immune system.
Another member of the Division of Infectious Diseases also had HIV in his sights, but ended up going even further — creating what his lab believes is the first broad-spectrum antiviral agent.

The researcher is Professor David Markovitz, MD. He and then-graduate student Michael Swanson, PhD, achieved this feat by molecularly engineering a sugar-binding protein found in bananas.

The pair already knew that sugar-binding proteins, called lectins, could block HIV transmission by attaching themselves to the sugars on the surface of HIV that the virus would otherwise use to gain entry into human cells. In 2010, they discovered that a lectin found in bananas, BanLec, was especially effective as an anti-HIV agent, and they highlighted its potential as a vaginal microbicide.

“We didn’t think our research would attract much attention,” chuckles Markovitz, “but it ended up capturing worldwide press. I think the combination of HIV, sex and bananas caught the popular imagination.”

The main hurdle in using BanLec clinically was that its antiviral activity came at a cost — an overactive immune response called mitogenicity. So the pair wondered whether they could tinker with the molecule just enough to retain its good qualities while avoiding the bad.

“It was a fairly daring idea,” says Markovitz. “It sounds simple, but no one has ever molecularly engineered a lectin before to separate two disparate functions. Mike was able to do it by mutating a single amino acid in a specific location.”

“We have broad-spectrum antibacterials, but not broad-spectrum antivirals. This discovery raises the possibility that a sick person could be treated with this agent before we know which virus it is. If successfully developed, such an agent would be a huge advance for medical treatment and bioterror defense.”

— David Markovitz, Infectious Diseases

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By replacing a histidine at position 84 with a threonine, they created BanLec H84T.

Now, six years after their initial article, with 26 collaborators from five different countries and a paper in Cell, Markovitz’s lab has shown that BanLec H84T is not only effective at preventing HIV infection, it is also effective against a range of viruses — such as hepatitis C, SARS, MERS, influenza and Ebola.

Animal studies show that BanLec can function both preventively and curatively, though optimal administration will likely depend on the virus type and will need to be clarified in additional animal studies before human testing can occur. In addition, the group wants to better understand how exactly the molecule’s change in structure affects its change in function. This is an ongoing investigation with former U-M chemistry and biophysics Professor Hashim Al-Hashimi, PhD, now at Duke University.

Ultimately, Markovitz believes this work not only could lead to dramatic new treatment possibilities, but may provide insight into both general immunology and the sugar code — the complex system by which sugars influence cell signaling.

And for him personally, the experience has been invigorating. “We are proud of the results, but the best part is that I get to work with an army of incredibly smart, lively collaborators who come at this from different angles and each synergizes with the other,” says Markovitz. “Every time we’ve approached somebody to collaborate, they’ve been excited to do so.”

**FROM INFECTIOUS DISEASES TO AUTOIMMUNITY**

Markovitz’s lab is on the brink of another unexpected breakthrough by digging deeply into a protein that our immune system uses to respond to microbes.

Called DEK, it’s been shown to play a role in innate immunity, cancer development and autoimmunity. Markovitz and collaborators, especially divisional colleague and Research Assistant Professor Nirit Mor-Vaknin, PhD, have helped illuminate the protein’s complex lifecycle and diverse roles in the body.

These include acting within the nucleus to support global chromatin integrity, attracting pro-inflammatory immune cells when secreted, supporting blood-cell development when taken back up by cells, and playing a role in neutrophil extracellular traps, or NETS. These can serve to either kill pathogens or create autoimmunity and blood-clotting problems.

In 2011, Mor-Vaknin and Markovitz published findings that DEK and DEK antibodies were present in the joint fluid of patients with juvenile idiopathic arthritis (JIA). Since then, they’ve been working with collaborators to develop a treatment that could bind to DEK and prevent its inflammatory functions.

The treatment makes use of aptamers, single strands of nucleic acids that can bind to and inactivate specific proteins. Markovitz is working to develop a DEK-specific aptamer that can be delivered by injection directly into joints or in a controlled release formulation that could target multiple joints due to their low-pH environment.

Markovitz is hopeful that this work will result in a mechanism-based treatment for JIA. He also plans to explore DEK’s role in cancer and in hematopoietic stem cell development in the hopes of improving bone marrow transplants.
While the future holds myriad possibilities in areas from precision medicine to health technology, successful clinical care will always focus on the patient, not the disease.

That is the mantra for the Division of Allergy & Immunology, which, because of the meteoric rise in asthma and allergy prevalence, has invested heavily in clinical care. While the division continues to work toward cures, including developing novel allergy vaccines and conducting clinical desensitization trials, compassionate clinical care remains a top priority.

The approach is patient-centered along every dimension. In terms of geography, the division was the first to open off-campus clinics to enhance patients’ access to community-based care. Just recently it partnered with the Corner Health Center in Ypsilanti, Michigan, to do the same for underserved youth.

Patient-centered also means supporting the whole patient. U-M’s Mary H. Weiser Food Allergy Center provides patients with access not only to specialized doctors, nurses and nutritionists, but also to multidisciplinary specialists who can help with the psychosocial issues that can accompany food allergies, such as bullying, anxiety and depression.

“The Comprehensive Food Allergy Service allows us to care for many patients with complex food allergies from around the region whose needs outstrip the services their local physicians can provide,” says Associate Professor Marc McMorris, MD, director of the Food Allergy Service.

Similar issues can be found among severe asthma sufferers, especially the elderly — from depression to reduced activity levels to impaired sleep. These are among the findings of Associate Professor Alan Baptist, MD, MPH, from the Division of Allergy & Immunology.

That is why Baptist has joined with Associate Professor Michael Coffey, MD, from the Division of Pulmonary & Critical Care Medicine to launch the Comprehensive Asthma Management Program. It provides high-risk asthma patients with coordinated access to specialists from both the allergy and pulmonary fields, as well as support from asthma educators, social workers and visiting nurses to meet these patients’ complex and diverse needs.

“The program has a strong educational component that approaches asthma from the patient’s rather than the provider’s perspective,” says Baptist. “We work to help patients identify what is important to them in controlling their asthma and develop strategies for overcoming any barriers to achieving their goals.”

“This is the essence of our approach to clinical care,” says James Baldwin, MD, division chief and professor in the Division of Allergy & Immunology. “Our first focus is always the patient, not the disease.”

**IMMUNOMODULATION RESOURCE**

U-M’s Department of Biomedical Engineering offers collaborative expertise in using nanotechnology and biomaterial technologies to modulate immune responses. They also develop diagnostic and computational tools for the design of immunotherapies.
HUFFNAGLE AND OTHER MICROBIOME EXPERTS BELIEVE IT IS THE METABOLITES PRODUCED BY THESE MICROBES THAT REGULATE OUR IMMUNE RESPONSE.

A U-M internal medicine lab was the first to show, nearly a decade ago, that changing an animal’s microbiome with antibiotics dramatically impacts the immune response in its lungs. Especially with a yeast bloom, the animal becomes prone to developing airway allergies.

Those same researchers believe the microbiome may play a similar role in the development of food allergies. “When food is ingested, it’s broken into all sorts of small components that have the potential to invoke an immune response,” says microbiome researcher and Nina and Jerry D. Luptak Professor GARY HUFFNAGLE, PhD, from the Division of Pulmonary & Critical Care Medicine. “But the GI tract is lined and set up in a way that nothing should get across it to stimulate this immune response. However, we know that the microbiome plays a role in gut permeability and the reactivity of the immune system in the GI tract. Our lab now has data showing that you can change how the immune system sees the introduction of a new food based upon its microbiome.”

His group is working to tease apart just how this happens. He believes that by learning more about which microbes affect this process and how they impact gut permeability, motility, digestion and metabolism, we can ultimately harness the microbiome to make people less reactive to the foods they eat.

DECODING ITS ROLE IN FOOD ALLERGIES

JAMES BAKER, MD, director of the Michigan Nanotechnology Institute and professor emeritus of Allergy & Immunology, pioneered a nano-emulsion-based, non-live-virus nasal vaccine. Later acquired by a pharmaceutical company, the vaccine is effective on a variety of mucosal surfaces, making it suitable for organisms ranging from herpes to inhalational anthrax.

In addition, Lonnie Shea, PhD, chair of the Department of Biomedical Engineering, has co-developed a nanoparticle-based “Trojan horse” allergy vaccine that briefly hides an allergen in the bloodstream until it can be ingested by macrophages and presented to the immune system as harmless. Now in commercial development, it has shown treatment potential for airway and food allergies as well as autoimmune disease.
Tissue and organ transplantation can offer patients a new lease on life. But, especially for certain types of transplant, a major barrier to success is immunologic incompatibility between the donor and host. In the case of lung transplant, the patient’s immune system may see the new lungs as foreign. In the case of bone marrow transplant, the transplanted cells may see the recipient’s body this way. The result too often is an immune attack on healthy tissue.

To prevent this, many patients spend the rest of their lives on immune-suppressing drugs, which leave them vulnerable to infection and sometimes still aren’t enough to halt the attack.

But internal medicine researchers are working to change that. By “listening in” on cell signaling, they’re trying to find ways to halt the destructive signals while retaining the benefits of the transplant process.

**BETTER BONE MARROW TRANSPLANTS: PREVENTING GRAFT-VERSUS-HOST DISEASE**

Bone marrow transplant is a vital treatment for cancers like leukemia and lymphoma, as donor cells are employed to mount an attack on cancer cells. But when that same immune response turns on patients’ healthy tissue, the result is a life-threatening condition called graft-versus-host disease (GVHD).

**IVAN MAILLARD, MD, PhD, the Jeffrey M. Leiden Collegiate Professor of the Life Sciences from the Division of Hematology & Oncology, has exposed a cell-to-cell communication pathway central to GVHD. Known as Notch signaling, it plays a crucial role in regulating the T-cell response that causes GVHD.**

He’s shown that targeting just one of the ligand-receptor pairs important in this pathway can prevent graft-versus-host disease in mice. He was able to do this using a ligand-specific antibody produced by Genentech. This happened without serious side effects and without substantially compromising the cancer-fighting ability of the transplanted cells.

Maillard found that the treatment was long-lasting, yet only had to be administered on a short-term basis immediately following transplant. He’s since applied the approach in a mouse model of heart transplant and shown that it significantly decreased rejection in that setting, as well.

In 2016, Maillard led an international collaboration that lent even more precision to these findings. They found that an unexpected type of cells were the major players in priming donor immune cells to attack their host — making them the key target for Notch inhibition. The critical cells, it turns out, were stromal cells — structural and connective cells in the recipients’ lymphatic system — rather than antigen-presenting cells as it was long presumed.

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Maillard’s group is now working to translate their findings from mice to humans. They’re also probing the mechanism of Notch action in T cells to see whether the pathway might play a role in other T cell-mediated immune disorders like multiple sclerosis.

Maillard’s findings are an important focus, as long-term survival after lung transplant is the worst for all solid organs — less than 20 percent at 10 years, says Lama. The main manifestation of long-term rejection is bronchiolitis obliterans syndrome (BOS), a condition in which fibrosis progressively narrows the airways of the lungs.

By investigating lavage samples from patients with this condition, Lama’s lab discovered the presence of a unique set of donor-derived mesenchymal stem cells in which distinct signaling pathways were activated. Further research indicated that the presence of these cells could identify patients in the process of developing chronic lung rejection.

While Lama immediately saw the makings of a useful biomarker, she continued to study these cells with her sights set on treatment. Her team recently made a major breakthrough in this arena. It started by discovering that, even when removed from the lung, these cells stay activated and continue to produce collagen, which explains their capacity for relentless scarring.

As they dug into the cell signaling at play, Lama’s team found a positive feedback loop that keeps these cells on autopilot. It begins with the enzyme autotaxin, which acts on the cell membrane to generate lysophosphatidic acid, which in turn both signals the cells to produce collagen and increases autotaxin levels.

“This finding is extremely novel,” says Lama. “We’ve never thought of these cells as essentially cancer cell-like in nature, but they are regulating their own behavior like a cancer cell does. It helps us understand why we can’t stop the scarring process by simply changing the environment around the cells — they’ve already begun not listening to anything around them.”

Building on these insights, her team has found in mouse models of BOS that blocking autotaxin and the receptor for lysophosphatidic acid interrupts the rejection process and significantly reduces fibrosis.

Because autotaxin inhibitors and LPA1 receptor antagonists are already in clinical trials for other fibrotic lung conditions, Lama hopes her work will pave the way for clinical trials in BOS to bring much-needed treatments to her lung-transplant patients.

However, Lama is not content to stop at treatment. “For me, a utopian dream would be making a recipient-specific lung in which we could replace some of the donor cells with recipient cells that could play a role in lung regeneration and repair without causing fibrosis or rejection,” she says. “That is connecting us to the world of induced pluripotent stem cells (iPSCs). Perhaps we can turn patient-derived iPSCs into lung-specific cells to make transplantation better and improve the lives of lung-transplant patients in the decades ahead.”
One internal medicine researcher wants to bring precision immune therapeutics to a place they’ve never been — vascular disease. SASCHA GOONEWARDENA, MD, assistant professor in the Division of Cardiovascular Medicine, is using his NIH K08 grant to harness the immune system against atherosclerosis.

People don’t often think of the build-up of cholesterol plaques in the arteries as an “immune” issue. However, there is evidence that macrophages — the immune cells that engulf foreign material such as invading microbes — are essential to the process of removing cholesterol from arteries and delivering it to the liver for disposal.

Goonewardena wants to learn precisely how macrophage dysfunction can impair this process of “reverse cholesterol transport.” He also plans to develop a precision drug-delivery system to correct the dysfunction. His goal is to attack atherosclerosis at its source — with no side effects.

He’ll do this with a nanoparticle drug carrier called a dendrimer. These water-soluble branched molecules can hold not only drugs but also ligands that can specifically target surface receptors unique to macrophages.

Goonewardena has already shown that methotrexate, a powerful anti-inflammatory, can induce macrophages to carry out reverse cholesterol transport. He plans to use his K award to engineer a two-stage targeted delivery system for the drug.

“First, we’ll target the dysfunctional macrophages through a surface receptor,” says Goonewardena. “Then, the drug will be released from the dendrimer by a macrophage-specific enzyme that is activated in cardiovascular disease.”

This precise targeting means that the drugs should be able to rid arteries of excess cholesterol without producing side effects like the pain that can happen when statins act on a patient’s muscles. It also means that dosing should be much more forgiving, since the drugs would only be released in the cells that need them and at a time when the body needs it. Any unused drug complexes would simply be shuttled out of the cell and excreted in the urine.

Goonewardena is enthusiastic about the potential of his work for atherosclerosis, but says this two-step targeting approach has the capacity to turn any drug into a precision therapeutic. “The most exciting thing is we’re developing an enabling technology that allows us to take existing drugs that we know work and just target them to the right cells, so we can get all of their upsides without the side effects.”

IMPLICATIONS FOR AGING

GOONEWARDENA BELIEVES HIS MACROPHAGE-TARGETING PLATFORM WILL HAVE MAJOR IMPLICATIONS FOR OTHER AGING-RELATED DISEASES THOUGHT TO BE DRIVEN BY DYSFUNCTIONAL MACROPHAGES, SUCH AS ARTHRITIS, ALZHEIMER’S AND DIABETES.

“BY TARGETING THESE CELLS, WE CAN POTENTIALLY CREATE A ‘PLUG AND PLAY’ PRECISION SYSTEM,” HE SAYS. “WHERE WE USE DRUGS WE ALREADY HAVE TO DIRECTLY TARGET MACROPHAGES DRIVING A PATIENT’S DISEASE.”

“We’re developing an enabling technology that allows us to take existing drugs that we know work and just target them to the right cells, so we can get all of their upsides without the side effects.”

— SASCHA GOONEWARDENA, CARDIOVASCULAR MEDICINE
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If we’ve learned anything from decades of battling our most formidable health foes — obesity, cancer, dementia — it’s that tackling them once they’re established is not to our advantage.

Indeed, the key to our future lies, to a large extent, in our successes of the past. We bent the curve in cancer, lung disease and cardiovascular disease by reducing smoking, cleaning our air and treating high blood pressure and cholesterol before they led to a heart attack. We’ll need that same emphasis on lifestyle, the environment and early intervention in the years ahead.

Thankfully, we now know — and are increasingly pushing to learn — more about the risk factors for disease and how they vary among individuals, allowing us to be more strategic in our approach. We’re developing new biomarkers to detect the earliest signs of disease — and stepping in quickly to halt its progress. We’re identifying innovative ways to support behavior change and foster healthier lifestyles. And we’re learning why aging predisposes us to disease in an effort to turn back our molecular clocks.

The internal medicine faculty featured in this section say emphatically that prevention and healthy aging are the ways of the future. That managing disease is out and managing health is in. And that it’s our health span, not just our life span, that’s the true measure of success.
When envisioning the future of cardiovascular medicine, thoughts can instinctively turn high-tech — from pill-sized pacemakers to custom artificial hearts.

This will be part of the picture, say those in the Division of Cardiovascular Medicine, but most believe the biggest gains will be made in a single area — prevention.

“One of the principal ways we’ve improved cardiovascular health to date has been a decline in smoking,” says Professor Hitinder Gurm, MD. “We went from smoking is bad for you to smoking is no longer socially ‘cool.’ What if we could add that ‘coolness’ factor to exercise and healthy eating? This is what it will take to be able to live the kind of record-breaking life spans that are predicted — for our cardiovascular health to be optimal.”

His colleagues agree; some shared their perspectives on what it will take to unlock optimal cardiometabolic health for the population, at home and abroad.

**THE ENVIRONMENT**

One foundational aspect of good cardiovascular health is all around us, yet it’s invisible — both literally and in most discussions of the major risk factors for cardiometabolic disease.

It’s air quality. Research by Professor Robert Brook, MD, has shown that air pollution causes a host of cardiometabolic changes, such as impaired blood vessel function, increased blood pressure, changes in blood clotting and inflammation — and over the long term contributes to conditions such as atherosclerosis and diabetes. His findings revealed that even at the relatively low levels of air pollution we have in the U.S., these changes can contribute to arrhythmia, heart failure, heart attack and stroke among susceptible individuals.

In fact, the air pollution-related risk of dying from cardiovascular disease is as great if not greater than it is for pulmonary disease.
“People clearly know that lifestyle factors like exercise and avoiding salt and trans-fatty acids impact our cardiometabolic health,” says Brook. “What’s generally not thought about are the effects of changes in the climate, air and water. But if you look globally, indoor and urban air pollution are among the top ten causes of mortality. In the future, environmental factors will no doubt be of growing importance to our health outcomes.”

Brook believes the best approach to improving our cardiometabolic health in the decades ahead will be a multi-pronged one. First, he says, we must target disease much earlier. “One thing we’ve learned is that small increases in blood pressure or cholesterol lead to marked increases in disease risk over a lifetime,” he says. “So I hope we will prioritize learning how to safely and cost-effectively treat the very earliest stages of common conditions like dyslipidemia, hypertension, obesity and diabetes — ideally even before they’re present.”

This is where Brook sees a role for precision medicine in population health. “This may be where genetic profiling, advanced atherosclerosis imaging and other predictive, precision medicine efforts may help identify people who are at a greater lifetime risk for heart disease, so that we can employ medical and lifestyle approaches to protect them.”

Another prong in Brook’s prevention plan addresses the risks his own research has identified. He’s now studying the use of practical, cost-effective tools to reduce personal and community exposure to air pollutants, such as air purifiers and inexpensive face masks.

In addition, Brook stresses the importance of sound environmental policy. “Our research shows the link between environmental policy and health,” he says. “The good news is that, in North America, we’ve made progress in general since the 1970s on our air and water quality. But we need to make sure that we don’t head in the wrong direction for the sake of economic expediency. Given the tens to hundreds of millions of people who are exposed, small increases in pollutants translate to significant increases in death and disease across the population.”

HEALTHY LIFESTYLES

The more widely discussed contributor to cardiometabolic disease is, of course, lifestyle — and internal medicine faculty are hard at work on this challenge.

One example is Kim Eagle, MD, the Albion Walter Hewlett Professor of Internal Medicine and director of the Samuel and Jean Frankel Cardiovascular Center.

“People clearly know that lifestyle factors like exercise and avoiding salt and trans-fatty acids impact our cardiometabolic health,” says Brook. “What’s generally not thought about are the effects of changes in the climate, air and water. But if you look globally, indoor and urban air pollution are among the top ten causes of mortality. In the future, environmental factors will no doubt be of growing importance to our health outcomes.”

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Eagle helped launch Project Healthy Schools, which aims to change the culture in which sixth graders form habits that will shape their cardiometabolic health. It uses a fun, interactive approach to get kids to eat more fruits and vegetables; exercise; and reduce sugary drinks, fatty foods and screen time.

Piloted in 2004 in one Ann Arbor middle school, the program is now in 70 middle schools across the state, with longitudinal data showing that it improves both self-reported behaviors and cardiovascular risk factors.

Much as with environment health, researchers say thoughtful programming is only part of what’s needed for large-scale impact. “I think in addition to great programs like Healthy Schools, there has to be policy change,” says Hitinder Gurm. “It’s in the taxpayer’s interest to ensure that government policies support the health of the population, so I’d like to see us creating cities where it’s safe and inviting to walk. I’d like to see taxes on unhealthy foods and drinks, with the money used to subsidize healthier foods, making it easier for farmers to sell their produce locally. These things would make a difference, and I have faith that we can do it. When America makes up its mind, this country does amazing things.”
The Division of Gastroenterology already offers multidisciplinary care for functional bowel disorders that is among the most progressive and comprehensive in the country — from state-of-the-art diagnostics to custom dietary interventions to psychosocial approaches aimed at reducing hypersensitivity in the gut.

But this is just the start, says functional bowel disorders expert WILLIAM CHEY, MD, the Timothy T. Nostrand MD Collegiate Professor of Gastroenterology. Chey has taken a leadership role in expanding the division’s nutrition and behavioral medicine footprint to reach more patients with an even broader array of services.

“Right now, we’re very much an outlier in the infrastructure we’ve created at Michigan, which integrates dieticians and behavioral psychologists into the routine care of patients with digestive disorders,” says Chey. “Going forward, we’re including treatment for other things that can amplify a patient’s illness experience like sleep disorders and we’re integrating alternative medicine tools like acupuncture and select herbal therapies. In addition to elimination diets, we’ll also increasingly incorporate so-called ‘functional foods’ — foods that offer therapeutic benefit beyond their nutritional value, often by manipulating the microbiome and, through it, our metabolome.”

U-M’s microbiomics and metabolomics infrastructure, says Chey, will help enable the precision treatment of GI disorders in the years to come. He expects we’ll be able to use insights from these platforms both to reverse-engineer medications and also to move beyond the use of clinical symptoms in classifying patients. “I think 20 years down the road, we’ll be using microbiomic or metabolomic fingerprints to identify subgroups of patients that are more likely to respond to various targeted therapies,” he says.

E-HEALTH: NEW APPS FOR HEALTH AND NUTRITION

Another aspect of Chey’s vision is bringing patient support and education beyond the clinic walls. One way is through a telemedicine platform his division is creating and testing (page 93). He’s also made substantial progress in developing mobile and web-based apps for GI health and nutrition (page 126).

The first, My GI Health, uses an adaptive interview process to probe patients’ symptoms prior to their office visit. The aim is to generate a medical history that sets the stage for a more effective encounter, along with a set of educational materials tailored to patients’ symptoms and their causes.

The second, My Nutrition Health, is designed to help patients with irritable bowel syndrome (IBS) identify the relationship between their diet and GI symptoms. It includes a food and symptom tracker along with educational materials about the low-FODMAP diet to help patients pinpoint and eliminate the FODMAPs that trigger their symptoms. (FODMAPs are short-chain carbohydrates and sugar alcohols that can contribute to IBS; the term stands for Fermentable Oligosaccharides, Disaccharides, Mono- and Polyols.)

Chey developed both apps in partnership with U-M’s Center for Health Communications Research and Cedars-Sinai Medical Center in Los Angeles. The GI app was sponsored by Allergen and Ironwood Pharmaceuticals, and the nutrition app by Nestle — a model of academic-industry partnership that Chey believes will be increasingly important to the future of health care.
TEST KITCHEN AND FODMAP LAB
Chey is relying on similarly productive partnerships to support two additional innovations scheduled to roll out this year.

The first is a test kitchen designed for cooking classes and health-themed dinners addressing conditions from IBS to diabetes to heart disease. It will be a multidisciplinary space with participation from the Division of Gastroenterology; Frankel Cardiovascular Center; Division of Metabolism, Endocrinology & Diabetes; MHealthy and the Department of Nutrition Sciences, where patrons as well as graduate and medical students can learn about healthy cooking from experienced chefs and U-M physicians, dieticians and health educators. “We hope to prove that we can create a self-sustaining, high-value enterprise that offers a fun and delicious dining experience while engaging and improving the health of the community,” says Chey. “My vision is to see it morph into an independent amphitheater with a media center to televise these cooking shows and extend our reach even further.”

Chey is also helping to build at U-M the first FODMAP-analysis lab in the United States, a project informed by his recent mini-sabbatical to Australia’s Monash University, where the low-FODMAP diet was developed. Having the ability to carefully determine the FODMAP content of foods is important, both to companies developing low-FODMAP food options and to his GI colleagues who use these diets clinically and are studying how best to selectively reintroduce FODMAP-containing food groups to individuals who’ve improved on a full FODMAP-exclusion diet.

This multi-faceted, integrated approach is what is positioning the GI Division to lead in the decades ahead, says Chey. “The model we’re building at Michigan is one that others can recreate in the coming years,” he says. “I believe it will go from being an interesting curiosity to the national standard of care.”
Jessica Mellinger, MD, MSc, clinical lecturer in the Division of Gastroenterology, believes the most important tool for clinical hepatologists in the decades ahead will be one they often feel least prepared to use — words.

“The thing I find most exciting about behavioral health is that words are often the intervention,” says Mellinger. “But many hepatologists find that words fail us when we try to encourage patients to seek alcohol use treatment for their liver disease. My goal is to transform the conversations we have with our patients, so that we say the right things and involve our patients in a way that gives them the boost they need to make a change.”

Mellinger’s research focuses on alcoholic liver disease (ALD), which comprises roughly half of all liver disease cases in the U.S. If uninterrupted, ALD can progress from fatty liver disease to chronic hepatitis to cirrhosis to liver failure. The way to prevent progression is to stop drinking, but, says Mellinger, most hepatologists aren’t trained to help patients do this. “We make a referral to an addiction treatment facility and tell the patient, ‘You need to get help. You need to stop drinking,’ and often that’s it.”

Mellinger says hepatology is somewhat behind the curve in adopting a behavioral health approach, but that this will need to change as the disease landscape changes. “For a long time, our field has been focused, and rightly so, on developing basic knowledge of disease processes: What does a virus do in the liver, what are the mechanisms of fibrosis, what medical targets can we hit for different hepatitis viruses and so on. Now that we have a cure for hepatitis C, the next most prevalent liver diseases are alcoholic liver disease and non-alcoholic fatty liver disease, and they are both caused by — and best treated by — behavior.”

Mellinger believes she can help bridge the gap between patients’ needs and providers’ behavioral health preparedness with an interactive online tool that can inform and structure their conversations. The tool will educate patients about their condition and match them with treatment programs based on their preferences. It could be completed by patients in advance and the results shared with providers for a richer, more productive clinic visit.

“The tool could help us address common misconceptions among ALD patients — such as the belief that only liquor, not beer, is dangerous to their liver,” she says. “And it could help identify patients who may prefer the social support of group therapy and those who may want more individualized help changing the thought patterns that reinforce their drinking through an approach like cognitive behavioral therapy.”

Patients and providers are both hungry for solutions, says Mellinger, and she hopes her tool will be a meaningful start. She’s now conducting mixed-methods research to probe patients’ understanding of the risk of alcohol consumption in their disease, why they drink and their barriers to stopping — information that will guide the development of her tailored online tool.
In 2016, U-M was awarded a six-year, $8.2 million grant from the National Institutes of Health to investigate the molecular changes that occur during and after physical activity. U-M is one of five chemical analysis sites within the new Molecular Transducers of Physical Activity Consortium. The consortium was created to assemble a comprehensive map of the proteins, peptides, circulating nucleic acids, lipids, hormones and other molecules that change with exercise and have the potential to cause a positive metabolic effect. With thousands of participants and samples, this is the first large-scale, systematic study designed to answer this question. All data will be publicly accessible.

Led by Charles Burant, MD, PhD, the Dr. Robert C. and Veronica Atkins Professor of Metabolism, and Jun Li, PhD, associate professor in the Departments of Human Genetics and Computational Medicine & Bioinformatics, the Michigan research team will help analyze plasma and tissues collected from human participants and animals undergoing physical activity. It will make use of the infrastructure and expertise of the NIH-funded Michigan Metabolomics and Obesity Center, which Burant directs.

“This collaborative effort will help us discover how different individuals respond to exercise and then predict the right amount and type of exercise to improve their health,” says Burant. “It may also help us develop ways to mimic the beneficial effects of exercise in those who are not able to exercise to obtain health benefits.”
Each week it seems there’s a new superfood or compound with cancer-prevention claims. From acai berries to zinc, they all have their proponents. But do they work? And, if so, how, for which cancers and at what doses?

These are the questions that captivate DEAN BRENNER, MD, the Kutsche Family Memorial Professor of Internal Medicine in the Division of Hematology & Oncology and the Department of Pharmacology. He’s spent the last 25 years developing tissue- and blood-based cancer-prevention biomarkers and using them to determine various compounds’ efficacy, optimal dosing and safety.

He’s also become increasingly interested in how obesity drives cancer — particularly colon cancer — with an eye toward using natural preventive compounds to interrupt the process.

He and a series of expert collaborators from across campus are exploring how fatty acid biochemistry is altered in obesity and how this in turn stimulates the eicosanoid system, drives inflammation and predisposes the colon’s stem cells to cancerous changes.

They’ve begun testing an omega-3 fatty acid regimen on humans to identify the precise doses required to reverse this process. “We recently finished a clinical trial and found that overweight and obese people had different effects of omega-3 fatty acid intake compared to normal weight people,” says Brenner. “When we looked at fat samples from obese rats in culture, we saw enormous changes in many of the molecules that we think are driving these processes. Recently, we have collected fat samples from obese women before and after 12 weeks of omega-3 fatty acid administration.”

They’re now working to quantify the molecular changes in the human samples and connect them to the stem-cell alterations that herald cancer. He says his work would only be possible at a place like Michigan.

“People all over this place are just so darn good that we get a huge amount of help,” says Brenner. “Bill Smith from biological chemistry brings expertise in fatty acid biochemistry, Duxin Sun is a fabulous analytical pharmacy scientist, MAX WICHA from hematology & oncology has been instrumental in helping us understand how stem cells work and Jim Varani in pathology can grow just about anything in culture. It’s just an enormously strong environment.”

CHUCK BURANT from MEND has great lipodomics tools, Duxin Sun is a fabulous analytical pharmacy scientist, MAX WICHA from hematology & oncology has been instrumental in helping us understand how stem cells work and Jim Varani in pathology can grow just about anything in culture. It’s just an enormously strong environment.”
There are currently about 7,000 geriatricians in the country, according to the National Academy of Medicine. It estimates that we actually need 17,000 — and with our aging population, this will rise to 30,000 by 2030.

This disconnect in supply and demand means huge opportunities for up-and-coming trainees with an interest in aging. Leaders in the Division of Geriatric & Palliative Medicine say their field offers nearly unrivaled potential for game-changing research, care innovation and collegial leadership, all while allowing them to make the kind of impact that fills their careers with purpose.

“When I started training, I sought out national leaders for guidance about what I should specialize in,” says Professor RAYMOND YUNG, MB, ChB, chief of the Division of Geriatric & Palliative Medicine and director of the Institute of Gerontology and the Geriatrics Center. “A single question from one of them has driven my whole career: ‘Where do you think you can do the most good?’”

That geriatricians are indeed “doing good” is evidenced by how much the field has evolved in just the last two decades. “When I started my fellowship, I saw substantial disability in patients in their 70s,” says LONA MOODY, MD, MSc, the Amanda Sanford Hickey Collegiate Professor of Internal Medicine. “But today, I have 95-year-old patients who are active in the community and are undergoing preoperative evaluations for minor surgeries. In my short career, the field’s moved that much.”

And the pace of change will only accelerate, they say, in large part because of a major shift in focus — from disease management to healthy aging.

**RESEARCH: FROM EXTENDING HEALTH SPAN TO BETTER PALLIATIVE CARE**

This change in emphasis has been made possible in part by the significant insights coming from aging-related research.

“We now know from animal studies that there are potentially dozens of different ways to extend life span and health span, from calorie restriction to use of the diabetes drug metformin,” says Yung. “The excitement ahead is that we’re at a stage where we can start translating these insights to people.”

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**THE ALLURE OF AGING**

**PARADIGM SHIFTS AND COMPPELLING QUESTIONS MAKE GERIATRICS A HUB OF INQUIRY FOR THE DECADES AHEAD**
The search for some version of the fountain of youth has been irresistible since long before the days of Ponce de Leon, and now it appears we’re on the cusp of real progress. Finding effective compounds or strategies to stave off the health effects of aging holds the promise of addressing multiple diseases common to the aging process at once, which according to Yung, puts geriatrics and gerontology in the midst of an impending revolution in preventive medicine.

The focus on prevention has also been driven by the need for earlier intervention in the more intractable diseases of aging. “In dementia, as with various types of cancer, if we wait until the patient has clinical evidence of disease, we’ve probably lost the battle,” says Professor Emeritus JEFFREY HALTER, MD. “The brains of people with clinical dementia are riddled with amyloid material; the likelihood of reversing it with some magic medication isn’t great. The emphasis now is on earlier identification and prevention, seeking the kinds of strategies that have made such a big impact on heart disease and diabetes.”

Michigan is well-poised to impact the course and outcomes of dementia and other age-related diseases thanks to leadership roles in research such as the Health and Retirement Study (page 133). KEN LANGA has used the HRS to generate important insights about dementia and other aspects of aging,” says Halter. “In recent years, the study has become more and more biologically oriented with the analysis of blood and other samples to look for potential biomarkers. Because the HRS follows a representative sample of the U.S. population as participants age and develop disease, I think it will lead to even more insights in the years ahead.”

U-M geriatrics faculty approach health and aging research from a variety of other angles as well. For example, Yung explores the relationship among aging, inflammation and immunity. Mody develops strategies to prevent infections and antibiotic-resistant bacteria in institutional settings. And Professor NEIL ALEXANDER, MD, MS, conducts sophisticated mobility studies that help us understand, measure and treat biomechanical changes linked to aging and age-related diseases.

In addition to work like this, says Yung, there is much to be done to advance research related to precision medicine and palliative care.

“As we learn more and more about age-related physiological and immunological changes, we’ll be better able to predict our patients’ response to medicine and prescribe it in a more precise way that minimizes the risk of side effects,” he says.

Of course, even with our best efforts to extend our health span and offer more precise treatment, eventually we will die. Our challenge is learning to do it well.

“The world of palliative research is wide open,” says Yung. “It’s in its infancy, like geriatrics was 30 years ago. There is so much we need to know — from best practices in symptom management to how to support the psychological and biological resiliency of loved ones after a patient’s death. The opportunities for research are unlimited.”

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Geriatrics is also in many ways the heartland for those interested in developing, implementing and testing new models of care. “We’ve developed several models that inform today’s health care policy and delivery,” says Mody. “Concepts such as readmission reduction, care transitions and multidisciplinary care are all mainstream now, but they started in geriatrics.”

The last decade has seen numerous care innovations, such as Acute Care for Elders (ACE) units, featuring interdisciplinary team-based care, watchfulness for geriatric syndromes, early transition planning and senior-friendly facilities; the Program of All-Inclusive Care for the Elderly (PACE), connecting nursing home-eligible patients with comprehensive medical and social day services that allow them to continue living at home; the Hospital Elder Life Program (HELP), designed to prevent delirium in the hospital; and many, many others.

Geriatrics is a good fit for those interested in building community partnerships to support health, says Yung. “We’re thinking more and more about the relationships among mind, body and community,” he says. “For example, I’m the university representative to the Osher Lifelong Learning Institute at the University of Michigan. We offer classes and lectures to some 1,500 local retirees to keep their minds active and keep them socially engaged. This kind of programming is going to be increasingly important as we think about extending health.”

Geriatrics is also ripe for technological innovation. Elderly patients are among those who can benefit most from tele-health platforms, where webcams and sensors allow them to be monitored and cared for without having to travel to appointments in poor weather or with limited mobility.

LEADERSHIP: “GERONTOLOGIZING” FELLOW DISCIPLINES

Yet another area that offers rich opportunities for the geriatricians of tomorrow is helping to “gerontologize” other disciplines — teaching colleagues how to integrate the principles of geriatrics and aging into their work.

From a care standpoint, this will be essential to addressing the growing needs of an aging population, most of whom won’t have direct access to a geriatrician.

“Right now, I have two mentees who are in colorectal surgery,” says Mody. “They came to me and said, ‘How can we integrate how you think as a geriatrician, about multiple morbidities and about function in an aging body, into our practice so that we can enhance outcomes after colorectal surgery?’ I’m excited that they will be able to go out and integrate these concepts into their care.”

This type of mindset is also important in research. “We need to increasingly include age as an important variable as we build evidence-based approaches,” says Yung. “We need to help our fellow researchers understand that an 80-year-old is not just an older 60-year-old.”
Clinical research is often not as relevant as it could be to clinical practice because studies either don’t include the elderly at all or have exclusion criteria that eliminate the majority of “real-world” patients. “I often call the older adults in these studies ‘elderly-like creatures,’” says Yung. “They may be similar in age to some of the patients we see, yet they are nothing like them because they have none of their co-morbidities.”

The same is true for pre-clinical research. “We generally study diseases in young animals,” says Yung. “This is one of the reasons that many promising animal trials fail in humans. Our group has shown, for example, that the efficacy of cancer immunotherapies in young animals is significantly different than in old animals. This has huge implications for translation, and it’s something we have to help the research community address.”

The opportunities for leadership, care innovation and translational research in geriatric and palliative medicine make the field an exciting place to be in the years ahead. This is particularly true at Michigan, say members of the division, because they are well-supported and work hard to pay this support forward. “Dr. Carethers is a strong advocate for our division,” says Mody, “and as faculty, we want to have new, dynamic, brilliant people entering our field, so we work hard to be mentors and role models to them.” This is how the division believes it will help redefine the experience of aging in the decades to come.

The U-M Health & Retirement Study

A HIGH-VALUE RESOURCE FOR RESEARCH ON HEALTH & AGING

U-M is home to a powerful tool in the development of evidence-based approaches to senior health care: the U-M Health and Retirement Study (HRS). The HRS is a nationally representative, ongoing study launched in 1992 and funded by the National Institute on Aging and Social Security Administration. It collects wide-ranging data every two years from approximately 20,000 people in the U.S. over age 50, and also gathers information from those individuals’ loved ones after their deaths.

Information is collected on areas such as participants’ labor force participation, economic status, family structure and health. The health data includes physical and psychological self-reports, biomarkers and genetics, cognitive testing, health behaviors and health services utilization.

The study’s associate director is KENNETH LANGA, MD, PhD, the Cyrus Sturgis Professor of Internal Medicine from the Division of General Medicine. He and colleagues use the survey to probe issues such as the causes, prevalence and economic impact of dementia; long-term effects of acute illnesses on the brain and body; and the role of Medicare and Medicaid policies on health outcomes for older adults. His work is consistently covered in the national press and has informed congressional discussions about funding for dementia care and research.
U-M hopes to make major leaps in our understanding and treatment of age-related cardiovascular disease with the launch of the Michigan Biology of Cardiovascular Aging Program. MBOCA for short, it aims to stimulate multidisciplinary, collaborative research that will generate breakthroughs along the basic-translational-clinical continuum.

Its director is new faculty member DANIEL GOLDSTEIN, MD, the Eliza Maria Mosher Collegiate Professor in Internal Medicine from the Division of Cardiovascular Medicine. Goldstein’s own work has helped reveal how aging fosters inflammation, and ultimately, disease. He’s been working to unravel the cellular and molecular processes involved, with an eye toward enabling the development of future therapies.

Goldstein has focused on the role of aging in three inflammatory disease processes: the chronic inflammation of atherosclerosis and transplant vasculopathy, and the acute inflammation of respiratory viral infections.

Among his more provocative findings is that — in contrast to the adaptive immune system, which has been shown to decline with aging — elements of the innate immune system can show exaggerated responses as we age. It is this over-exuberant response that can make respiratory viruses so deadly to older patients and causes the vascular inflammation that can drive atherosclerosis. Using mouse models, he’s revealed some of the cell types and inflammatory mediators involved, and he’s hoping to expand this work within the collaborative environment of the MBOCA program.

Goldstein has already begun collaborating with U-M’s arrhythmia group to understand how aging, atrial fibrillation and atherosclerosis interact. “Working with arrhythmia experts like JOSÉ JALIFE and HÉCTOR VALDIVIA, we’ve generated data that potentially connects these issues, which could lead to new therapeutic options,” says Goldstein. “This is exactly the kind of synergistic collaboration we hope to catalyze through MBOCA.”

“BY BRINGING TOGETHER RESEARCHERS WITH COMPLEMENTARY EXPERTISE, WE HOPE TO FILL IN PARTS OF THE PUZZLE AS TO HOW AGING IMPACTS THE CARDIOVASCULAR SYSTEM.”
—DANIEL GOLDSTEIN, CARDIOVASCULAR MEDICINE

THE MICHIGAN BIOLOGY OF CARDIOVASCULAR AGING (MBOCA) PROGRAM

THE NEWLY CREATED MBOCA PROGRAM ALREADY HAS SEVERAL AFFILIATED LABS AND IS ACTIVELY RECRUITING NEW MEMBERS TO CREATE A CRITICAL MASS OF COMPLEMENTARY EXPERTISE RELATED TO CARDIOVASCULAR AGING. IT AIMS TO ENHANCE MULTIDISCIPLINARY RESEARCH COLLABORATIONS AND PROVIDE EDUCATIONAL FORUMS, INCLUDING AN ANNUAL SYMPOSIUM.

MBOCA IS ALSO COMMITTED TO HELPING JUNIOR FACULTY THROUGH ENHANCED MENTORING AND PILOT FUNDING. THE PROGRAM IS CURRENTLY PARTNERING WITH THE CLAUDE D. PEPPER OLDER AMERICANS INDEPENDENCE CENTER ON A PILOT GRANT PROGRAM.

MBOCA RECEIVES SUPPORT FROM U-M’S FRANKEL CARDIOVASCULAR CENTER AND THE NATIONAL INSTITUTE ON AGING.
Michigan Medicine is participating in an important multi-center clinical trial through the NIH-funded Autoimmunity Centers of Excellence designed to prevent rheumatoid arthritis (RA). Called StopRA, it aims to determine whether an existing, first-line RA medicine called hydroxychloroquine can prevent disease onset. The trial enrolls people who have no clinical signs of the disease but who do have elevated anti-CCP antibody levels, a biomarker that predicts future development of RA. U-M’s participation is being coordinated by ELENA SCHIOPU, MD, assistant professor in the Division of Rheumatology.

“WE HOPE THIS IS JUST THE FIRST STEP TOWARD ONE DAY BEING ABLE TO IDENTIFY PEOPLE WHO ARE AT RISK FOR RHEUMATOID ARTHRITIS AND TO COMPLETELY PREVENT THE DEVELOPMENT OF THIS AUTOIMMUNE DISEASE.”
—DAVID FOX, RHEUMATOLOGY
The medical school experience has changed dramatically from the way that education reformer Abraham Flexner envisioned it in 1910. Even today’s faculty, who were educated in the 1980s and ’90s, are amazed by all that has transpired during their tenure.

And the changes keep coming. As Cyril Grum, MD, the senior associate chair for undergraduate medical programs, notes, “There’s an explosion of new medical information every six months.”

How can we help students thrive in this fluid, fast-paced environment? The continuing rollout of Michigan’s revolutionary new curriculum is key, as are evolutionary changes planned for graduate education. Competency must be proven, but so must the development of critical skills, such as communication and collaboration. And we must treat our students as the individuals they are.

The Department of Internal Medicine is leading on all of these fronts.
Implementing the New
Input-Driven Curriculum

The class that entered U-M in 2016 is a historic one: the first to experience the full program of curricular changes that were initiated in 2014. Shaped by input from faculty, staff, students and patients, these changes differ from past educational practices in seven important ways.

**Education is More Fluid**
What used to be a fixed “2+2” curriculum, two years of basic science and two years of clinical rotations, has been radically reengineered. U-M educators now lay a science-based foundation in year one, then integrate science into clinical settings over the next three years. On the flip side, students get to jump into patient care almost from the start. “In year one, we teach a clinical reasoning course and initiate a four-year doctoring course,” notes Associate Dean for Medical Student Education RAJESH MANGRULKAR, MD. “Our aim is to make the practice of medicine relevant from the beginning and gradually increase students’ exposure to it.”

**Learning Can Happen Anywhere**
The once-common experience of joining hundreds of other students in lecture halls is increasingly being replaced by online lectures that students can access anytime. And anywhere — from a study carrel to Starbucks. “But,” notes former Dean JAMES WOOLLISCROFT, MD, “the online experience can be isolating for some students. We compensate for that by providing small-group sessions that are led by faculty.” There’s a give-and-take in these groups, as educators encourage students to think critically about the knowledge they’ve just absorbed.

**Memorization is Out**
Physicians who trained in previous generations were expected to memorize massive amounts of information: the names of bones, potential drug interactions or the six things that might cause a spike in blood pressure. Today’s students aren’t required to do that; they have instant access to much of what they need on their mobile devices. U-M trains them to sort through the noise (volume) of all that information to find what is truly useful.

**High-Tech Tools Are In**
No more fretting over that first intubation or catheterization. U-M has developed a state-of-the-science simulation center that enables students to practice procedures on lifelike mannequins. Courses at the center are offered at designated times, and — since 2016 — students have been granted 24-hour access to the space to gain even more experience.

Software — especially mobile apps — also plays a part in educating future physicians. One app called “Nerve Whiz,” developed by U-M’s Zachary London, MD, enables users to view the muscles on a screen, tap which ones the patient identifies as weak and receive possible diagnoses, complete with relevant pictures and diagrams. “There are also some serious video games out there that encourage learning,” affirms Woolliscroft.

**Individuality is Encouraged**
It used to be that all medical school applicants wanted to become practicing physicians. Now some are interested in earning an MD to complement knowledge in their primary field, such as engineering, business or law. U-M works with those students to customize the program to fit their needs.

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Another way for students to tailor their education to their personal interests is by pursuing a specialization through the Paths of Excellence program. These paths include:

- Ethics
- Global Health and Disparities
- Health Policy
- Innovation and Entrepreneurship
- Medical Humanities
- Patient Safety/Quality Improvement/Complex Systems
- Scholarship of Learning and Teaching
- and Scientific Discovery.

After selecting one of the paths, students connect with an advisor, engage in specialized experiences, develop knowledge through informational sessions, field trips and lectures, network with peers and professionals, and complete a capstone project.

Medical student Megan Lane chose Ethics. From this starting point, “I ended up getting interested in the ways we use and acquire bodies for anatomy laboratories,” she explained.

Lane’s capstone project focused on issues of post-mortem decision-making and the ethical use of deceased individuals in educational and clinical settings. Now in her third year, Lane continues to research ethics and is exploring the possibility of pursuing another degree in this area.

“It isn’t just about doing a capstone project; it is about deeper-dive learning and about being part of a community and connecting [to other students],” said Heather Wagenschutz, co-director of the PoE program. “These connections can last a lifetime.”
GRADUATE EDUCATION CHANGES: IN THE PLANNING STAGES

As noted earlier, changes to the undergraduate curriculum have been revolutionary in nature. In describing similar efforts underway for the Internal Medicine Residency Program, administrators use the word “evolutionary.”

The person leading the charge is Director John Del Valle, MD. “My vision is to continue to build flexibility into training to meet the individual needs of our learners,” he explains, citing new curriculum initiatives that focus on topics such as residents as teachers and narrative medicine. “We are also enhancing the ability of residents to pursue scholarly projects that range from basic science to clinical studies,” he notes. “Fellowship programs and future employers will want to see a scholarly product.”

A third focus of the program addresses resident wellness: “Now’s the time to ensure that burnout doesn’t become an issue, to help residents find their work-life balance.” To that end, Del Valle says, “We’ve gone beyond limiting hours worked and are now focusing on creating time and space for individuals to meet their personal health needs.”

Helping residents develop a clear career path for the future is another important service that the program provides. “We mentor them through the process of identifying their personal and professional goals, and encourage them to take advantage of targeted retreats that focus on topics ranging from leadership to applying for fellowships to finding their first jobs.”

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Says Cyril Grum, MD, the senior associate chair for undergraduate medical programs, “We’re very open to ‘individualizing’ education, especially for those who plan to go right into research or consulting work.”

Another way to individualize education is to recognize that people learn at different speeds. As Michael Lukela, MD, director of the Medicine-Pediatrics Residency Program, explains, “There’s been a national shift away from a time-based notion of readiness — that everyone has to finish in four years — to the idea that mastering certain competencies is the better metric.” Under testing or observation, it may be revealed that one student can finish in three years while another requires an additional semester of experience. With a competency-based system like this, notes Wooliscroft, “the focus is on getting everyone to the same place, no matter their ability.”

TEAMWORK HAS ITS PLACE

The medical school has always encouraged its students to become strong leaders. Now it expects them to be team players as well. Why? “The sole practitioner is a thing of the past,” explains Grum. “Today’s doctors have to be able to work well within a team — with nurses, social workers, pharmacists and other professionals — to deliver the best possible care to patients.”

The Center for Interprofessional Education makes that goal a reality by bringing together students from all of the university’s health science schools for common study opportunities. Launched in 2015, the center has already developed such offerings as an award-winning, team-based decision-making course that involved 250 students and 11 faculty members from five schools.

PATIENTS GAIN A VOICE

There was a time when doctor-patient communications were lopsided, with the doctor doing most of the talking. Today’s medical students are trained to listen intently to uncover any factors that might be contributing to their patients’ conditions (or impeding their recovery) and to decide with them the best way forward. As Joseph Kolars, MD, senior associate dean of education and global initiatives, notes, “The approach we now take is, ‘How can I help you achieve your health goals?’”

Also, for the first time in the university’s history, patients are involved in assessing students and recommending additional curricular changes. A communication loop has been formed, and that bodes well for quality improvement in the future.
Molding young minds: That used to be the sole focus of medical education. But a new generation is looking for more from medical schools, more focus on the whole student: mind, body and spirit.

To address this challenge, the U-M Medical School has devised a variety of solutions, many of them connected with its Professional Identity and Balance efforts. These include mindfulness workshops, wellness weeks and participating on an Active U team. The most popular solution of all, however, may be the one that borrows a bit from the Harry Potter books. Its name? M-Home.

The spark for M-Home came from students who expressed concern to the dean that clinical rotations — some off campus — were leaving them feeling detached from their peers. The dean turned to Medicine-Pediatrics Residency Program Director MICHAEL LUKELA, MD, for help. After researching different ways to solve the problem, Lukela led a group in organizing students into “houses” to help build a feeling of connectedness and camaraderie. “Through these houses,” Lukela explained, “students can engage in a variety of team-building activities: some social, like the M-Home Olympics; some altruistic, like volunteering at a local food bank; and some educational, like participating in the Healer’s Art course.”

Lukela continues: “Although a wonderful experience, medical school is demanding. It’s important for students to find a place that is intellectually challenging and inspiring, and makes the successes and setbacks more manageable. We hope M-Home is that place.”

Since launching M-Home, Lukela has stayed involved with the program: he serves as a house director, along with ANDREW BARNOSKY, DO, MPH, Rachel Glick, MD, and Eric Skye, MD. RAJESH MANGRULKAR, MD, associate dean for medical student education, calls these four faculty members “role models, and an invaluable source of knowledge, encouragement and support for our students as they follow their paths.”
What skills are most important in the “making” of an MD? Different experts will give you different answers.

“In my generation, a lot of work went into memorization,” says Senior Associate Dean of Education and Global Initiatives JOSEPH KOLARS, MD. “Now, most of the knowledge a doctor needs can be accessed through a smartphone. That means the skill we most need to emphasize to our students is critical thinking, deciding which data is most reliable.” He draws a comparison to lawyers, saying medical students also need to “follow the evidence.”

Associate Dean for Medical School Education RAJESH MANGRULKAR, MD, believes in leadership. “Every student must learn to effect change in health care,” he says, adding that “leadership is a central tenet for the new curriculum.” In what at first blush might seem a contradiction, he also champions teamwork. “We don’t want to put individuals on pedestals or encourage them to make decisions in isolation. Students must be able to work together [with other health care professionals] in a team.”

Teamwork naturally involves communication, and that is the skill that MICHAEL LUKELA, MD, is most eager to impart. “We do a good job working physician to physician,” he explains, “but we need to enhance our communication with other members of the health care team and with patients and their families.” Such discussions may reveal issues that get in the way of good health habits. “For instance,” he says, “we tell diabetics to eat well-balanced meals made with fresh ingredients. But what if our patients have transportation challenges, can’t afford to buy the proper food or live in a ‘food desert’ with no grocery store?” This kind of information can significantly impact a treatment plan.

Hand in hand with communication, Lukela notes, is empathy: the ability to appreciate another’s feelings and experiences. Lukela, who directs U-M’s Medicine-Pediatrics Residency Program, helps his charges develop this skill through required rotations caring for vulnerable patients at such sites as Hope Clinic in Ypsilanti, Michigan, and the Community Health and Social Services Center in Detroit.

The ability to converse with and care for people from all walks of life is one sign of a student’s or resident’s adaptability. Another sign is the enthusiastic embrace of new technologies as they are released into the marketplace. “Just a decade ago, our patient notes were on paper and our X-rays were on film,” says CYRIL GRUM, MD, senior associate chair for undergraduate medical programs. “Both are digitized now, and we’re better off for it because of the accessibility that digitization provides.” Keeping one’s mind open to emerging technologies and techniques in medicine is a skill Grum would like to instill in the students he encounters. Thankfully, he notes, “This generation may be the best equipped of all to do that.”
Continuous Quality Improvement in Education

The curriculum has been revamped, and implementation is in progress. But how can U-M maintain that momentum over time, ensuring that succeeding students receive the best education possible? The answer, to borrow a phrase from industry, is to commit to “continuous quality improvement.”

“A site visit by our accrediting body occurs every eight years, and we used to time our curricular changes to match that,” explains Joseph Kolars, MD, senior associate dean for education and global initiatives. “But not anymore. [From this point forward,] the review process will be constant, and change will be motivated by that.”

The primary source of input will be the faculty committees that spearheaded the original changes. “During the initial process, we invited patients, staff and students to join us on the committees,” says Rajesh Mangrulkar, MD, who serves as associate dean for medical student education. “With these additional voices at the table [in the future], we won’t lose our way.” Kolars adds, “We’ve even asked students to assemble their own committees and report on their progress.”

Input can also come from outside the university, as faculty meet with colleagues at conferences and consortia. Michigan is a charter member of the American Medical Association’s Accelerating Change in Medical Education Consortium, whose hallmark is a free-flowing exchange of ideas. Schools such as Harvard, North Carolina and the University of California, San Francisco share policies and practices that have worked well at their institutions. “We share with them, too,” notes Kolars, “as well as with other schools in our state.”

Cynics might say that continuous quality improvement is just a gimmick to gain higher rankings. But Kolars rejects that idea: “We’re doing this because it’s our basic mission as a university: to be accountable to society. There’s an undeniable link between how well we educate our students and the health of the people we serve.”

“We’re doing this because it’s our basic mission as a university: to be accountable to society. There’s an undeniable link between how well we educate our students and the health of the people we serve.”

—Joseph Kolars, Gastroenterology
Long hours, lots of paperwork, a lifetime of friendships and an education that helped them exceed their career expectations: That’s what past chief medical residents remember most about their experiences at U-M.

JEOFFREY STROSS, MD, who served in the 1970s, recalls working every other night for the first two years as a resident. “It was exhausting work,” he says. “I would come home to my wife, sit down to read a newspaper or watch the news, and fall asleep in the chair before dinner was even served.” Also, he explains, “There were just 16 in our class. You knew everybody; there was a lot of camaraderie.” For Stross, some of those relationships still continue: He recently traveled to Chicago to celebrate the 50th wedding anniversary of one of his co-interns.

When Stross became chief resident, the hours improved: “I didn’t have to be in the hospital all the time; I could handle residents’ questions over the phone from home at night.” There was more administrative work: e.g., making up the residents’ work schedules and running the house staff program. But that was balanced by more time spent at patients’ bedsides. “Supervising residents in patient care really helped me decide to be a teaching doctor,” he explains.

In 1974, Stross’ experience led to a position as assistant professor in internal medicine, where he steadily rose up the academic ranks. Later in his career, he served as chief of the Division of General Medicine.

MARK MCQUILLAN, MD, a resident during the early 1980s, also appreciated the greater role that CMRs played in patient care. “During morning reports, we would go over every admission, learning about the most challenging cases in the hospital. We’d then walk the floors, stopping to do things like change IVs. As the patients prepared to leave, we became involved in discharge planning, too,” he explains.

After McQuillan completed his residency, he moved on to a rheumatology fellowship — also at U-M — then joined the school’s clinical faculty. He now also serves as a Michigan Medicine hospitalist, inspired by the experiences he had in his training.

A graduate of Dartmouth and Penn, Kathleen Cooney, MD, came to Michigan for her residency in the late 1980s. “At that time, you were expected to work in three hospitals: U-M, the VA and Wayne County General Hospital,” she notes. “It was an intense period; our class really bonded. We taught each other, as peers and chief residents.”

Former Department Chair WILLIAM KELLEY, MD, made it a point to provide leadership opportunities for Cooney and the other two CMRs. “When the university opened the new main hospital, we three were supposed to organize the moving of internal medicine patients to the facility. When I tried to do my job, I experienced a huge pushback from one attending physician. He got scolded by the chair, and I got a pep talk. ‘Do what I ask you to do with confidence,’ Kelley said. ‘I will always support you.’”

After completing a fellowship in medical oncology at Michigan, Cooney confidently entered the research ranks at the university. Over a period of 20 years, she served in a variety of capacities, culminating in the positions of deputy director of U-M’s Comprehensive Cancer Center and chief of the Division of Hematology & Oncology. In 2016, she left to become chair of internal medicine at the University of Utah.

The loss of Cooney was not unexpected. “We have been fortunate to attract talented residents who, in addition to having performed in outstanding fashion academically, have tremendous qualities as individuals,” explains JOHN DEL VALLE, MD, the residency program director. “We expect them to be highly valued by other institutions in the health care community.”

Del Valle continues: “We appreciate the contributions that Kathleen and other former CMRs have made to our department, and are proud to have played a part in their development.”
The Department of Internal Medicine has trained approximately 175 chief medical residents since the institution of the CMR program in 1962. Highlighted individuals are currently serving in academic or administrative roles within the Medical School.
10. PROFESSORSHIPS

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What does it take to recruit and retain high-caliber faculty who excel at research, are eager to work with patients, and are enthused about educating the next generation of physicians? In a word, professorships.

A professorship brings many practical benefits to the recipient, such as a stipend, lab funding or a travel budget to attend conferences. There is also an intangible benefit associated with this honor, and its value is inestimable. Explains geriatrician/epidemiologist Lona Mody: “Professorships and the funds that come with them set us free — free to pursue the dreams that we accumulate over time, but are unable to act on because we are bound by our everyday responsibilities. Now I can step back and say, I’ve wanted to drive the agenda this way, and this will give me the leeway to do it.”

Read how the Department of Internal Medicine is supporting faculty in this way, and how Chair John Carethers is hoping to triple the number of professorships in the coming years — allowing us to not only realize but to excel at our vision.
The highest honor that a department can bestow upon a faculty member is a named professorship. Within the Department of Internal Medicine, the tradition of such honors began almost 50 years ago with a gift from a Michigan alumnus.

Chicagoan John Gideon Searle prepared for his career by graduating from U-M’s School of Pharmacy in 1922. This background, plus years of working his way up the chain of command, helped him to successfully lead his family’s pharmaceutical business for more than 35 years. In his retirement, he contributed a significant amount of his wealth to philanthropic causes, in his hometown and elsewhere. The John G. Searle Professorship at Michigan, established in 1968, is part of that philanthropy. This position is currently held by Department Chair JOHN CARETHERS, MD, who focuses his research on the intersection of cancer and genetics.

For more than two decades, the Searle Professorship stood alone among charitable gifts to the department. Then state funding for universities began to decline — precipitously. This spurred a significant effort to raise private funding in support of faculty salaries, resulting in the establishment of 10 named professorships in the 1990s. Four of these funded general research in internal medicine, with the department free to designate the monies where needed. The other six professorships reflected donors’ interest in seeing their contributions directed toward sub-specialties such as hypertension, gastroenterology, rheumatology and cardiovascular medicine. The Emanuel N. Maisel Professorship in Oncology, held by ERIC FEARON, MD, is also an example of this.

In 2000, the first of a series of even more specialized professorships was established. That was the year that the Millie S. Schembechler Professorship in Adrenal Cancer came into being. Schembechler, the late wife of U-M’s celebrated football coach, had died of this disease, and her family asked that the professorship be given to someone whose research would advance the chances for finding a cure. GARY D. HAMMER, MD, PhD, currently holds the chair. Hammer studies the cellular and molecular mechanism by which signaling pathways and downstream transcription factors coordinate the specification of adrenocortical cells within the adrenal gland.

In 2001, with donors’ help, the Department of Internal Medicine launched its first interdisciplinary chair: the Ruth Dow Doan Professorship in Biologic Nanotechnology. The study of this topic, which promises to revolutionize the delivery of medicines, genetic materials and vaccines, requires an understanding of both medicine and engineering. The inaugural recipient, JAMES BAKER, MD, had just the right background for the professorship, holding joint appointments in the Medical School and College of Engineering. He now leads the Michigan Nanotechnology Institute for Medicine and Biological Center at U-M.

The year 2008 marked a change in the administration of named professorships, which greatly enhanced internal medicine’s ability to disburse more funds to its faculty. During that year, the endowment for a professorship named in honor of H. Marvin Pollard, a long-serving division chief of gastroenterology, had reached a point where the principal exceeded the amount of money needed. The department then split the endowment into seven distinct professorships. JUANITA MERCHANT, MD, PhD, whose research contributes to our understanding of the gastric response to chronic inflammation, is the holder of one of those chairs.
Through the end of 2008, 28 named professorships had been established. With the arrival of John Carethers, MD, who made faculty funding one of his top administrative goals, the pace of this effort quickened.

Since his arrival, a dozen professorships have come into being with a combination of donor and department funds; eight more were funded entirely by the department, signaling Carethers’ commitment to professional development. Additionally, an entirely new category of professorships emerged to support the work of educational administrators. In 2012, the Senior Associate Dean of Education and Global Outreach, Joseph Kolars, MD, was awarded the Josiah Macy, Jr. Professorship in Health Professions Education. 2015 saw the development of the Marguerite S. Roll Professorship in Medical Education; the recipient of that honor was Associate Dean for Medical School Education Rajesh Mangrulkar, MD. With the time afforded them by their professorships, these two men recently spearheaded the development of a new curriculum for undergraduates. (See the Education section starting on page 136.)

Are there other categories of professorships that should be developed? David Ginsburg, MD, who holds the Warner-Lambert/Parke-Davis Professorship of Medicine in the Division of Molecular Medicine & Genetics, sees one possibility. Ginsburg is a bit of a rarity in today’s academic medical center environment; he’s a clinician-scientist who moves from bedside to bench and back again, and strongly believes that one activity informs the other. “I’d like to see a prestigious professorship that requires a person to engage in patient care and perform cutting-edge laboratory research,” he says, “I think it’s important to maintain that connection, a major challenge in this time of increasing specialization.”

At the end of 2016, there were 91 professorships associated with the department. That represents significant progress, but Carethers would like to see more. “We have 814 faculty members in the department,” he notes, “and about 270 of them are on the instructional track. I’d like to see every one of those 270 with a professorship some day.

“Ideally, I’d love to have 814 professorships.”

One of the newest named scholarships at U-M honors an alumna of great historical importance: Amanda Sanford Hickey, MD. “Sanford Hickey was the first female to graduate from U-M Medical School, back in 1871,” explains the professorship’s recipient Lona Mody, MD, MSc, from the Division of Geriatric and Palliative Medicine. “She was the only woman in her very competitive academic environment, which made her bring excellence every day to her field, her life, her work.”

Mody added, “She also married, raised two children and was very well-known as a speaker in her community [of Auburn, New York]. She achieved a work-life balance — an achievement I admire. This professorship gives me a model, a moral support, a framework to follow in my own life.”

Sanford Hickey also inspires a group of medical school students who are part of the M-Home experience. The Amanda Sanford House is one of four learning communities meant to help students feel connected and supported through their undergraduate years at U-M — goals that the school’s first female graduate would likely have embraced.
What exactly does the funding for a named professorship support? The answers may surprise you.

Traditionally, it pays the faculty member’s salary, and also provides discretionary funding to be used in whatever way he or she deems necessary to the work of advancing their research. For example, “They could use it to further their education by attending a national meeting of their professional organization,” notes Department Chair \textbf{JOHN CARETHERS, MD}. “Or they could purchase a new computer or piece of lab equipment,” \textbf{DAVID PINSKY, MD}, the division chief of cardiovascular medicine, affirms the importance of the latter: “Good research is expensive. Endowments give our professors the resources to afford reagents, scanner time, statistical support and computer infrastructure and to pay the highly trained personnel needed to help us in our research.”

Another use for endowment funding is to support novel or early areas of inquiry — something that traditional grantors, such as the National Institutes of Health — are reluctant to do.

If funding is the number-one benefit of holding a named chair, a close second is something called “protected time.” Faculty members with professorships are excused from many day-to-day departmental responsibilities, leaving them free to spend more time in deep, uninterrupted thought. “We want them to think outside the box, be more creative and come up with wild ideas — informed wild ideas,” explains Pinsky. “Those ideas can sometimes develop into completely new discoveries.”

Protected time can also be spent on thoroughly investigating and acting on funding possibilities. “Many people don’t realize how long it takes to prepare a grant application,” says Pinsky. It’s a process that is best not rushed — not with millions of dollars at stake.

Time also plays a part in the professor’s ability to coach younger colleagues and students, who represent the next generation of medical professionals. To fully understand the satisfaction this brings to the mentor, see the profile of \textbf{KIM EAGLE, MD}, the Albion Walter Hewlett Professor of Internal Medicine, on page 152.

As evidenced from these examples, much is given to named professors to allow them to perform research in the most supportive setting possible. But the relationship is a reciprocal one: what is expected of professors in return is that the knowledge they gain from their work brings help and hope to the patients they serve.

\textbf{PINSKY, DAVID}
The benefits that faculty enjoy in the context of their professorships — more time to plan, more funding to support their research, more opportunity to lift up younger colleagues and students — have been detailed earlier. But what about the benefits that donors receive? Though harder to measure, they are no less meaningful.

JAMES WOOLLISCROFT, MD, had a firsthand view of this, when he served as dean of the Medical School from 2007 to 2015. “For some donors,” he notes, “establishing a professorship is an opportunity to ‘pay it forward’ — to use the fruits of their labor to recognize the university [or a specific program or professor] for the impact it had on their careers.” For others, the experience is a very personal one. “Once, I worked with a husband who funded a chair in the hope that others wouldn’t have to go through the trauma his wife had in battling cancer;” he says. On another occasion, a grandfather was comforted by the knowledge that his contribution would support a faculty member who was committed to fighting a devastating disease affecting his grandchildren. “He left our meeting with new-found confidence that a cure might be found,” says Woolliscroft.

In several circumstances, the act of creating a professorship has brought families in turmoil together. “I’ve seen some who were quite divided be able to turn their relationships around to meet this common goal,” Woolliscroft explains, proving that healing doesn’t just happen in the hospital.
KIM EAGLE, MD, is a well-known cardiologist. Since his recruitment to the University of Michigan in 1994, he has overseen a vigorous outcomes research program focusing on quality, cost effectiveness, the evaluation and management of acute coronary syndromes and aortic diseases, heart disease in special populations, and the fight against childhood obesity. It’s evident that he has a unique set of credentials. But that’s not the only unique thing about him. Eagle is one of just a handful of faculty members who have the distinction of being the recipient of one named professorship and the inspiration for another.

Eagle came to U-M from Massachusetts General Hospital, and a few years later, was awarded the Albion Walter Hewlett Professorship in Internal Medicine. “I feel very fortunate to have been given this professorship, which honors the chief of medicine who served here from 1908 to 1916,” explains Eagle. “Dr. Hewlett was an early cardiovascular scientist who studied arrhythmias and hypertension, and was a real leader in the early years of the medical school. I find his work inspiring.”

Eagle is effusive in his appreciation of the value of professorships: “First, they allow the recipient to spend some of his/her time performing early research and to involve junior colleagues or students in that effort.” A second advantage involves the stipend attached to the professorship. Eagle has used part of his funding to support a summer internship program in his outcomes research laboratory. “In recent years, we’ve had 35 to 40 undergraduates working with us from many different universities,” he noted.

Eagle’s program is very hands-on. “The students shadow us in patient care, both inpatient and outpatient. They do
volunteer work with us at World Medical Relief in Detroit. Most importantly, they get a chance to see what a life in health care would be like,” he says.

“Among other benefits, the Hewlett Professorship has afforded me the flexibility to devote time to the young people in our midst,” Eagle continued. “Now, when a student comes through my door, I can say yes to thinking about how I can help them on their journey.”

Eagle’s students appreciate his commitment to their development. And former patients appreciate his dedication to their well-being — so much so that, in 2014, they joined with the department to establish the Kim A. Eagle Professorship in Cardiovascular Medicine. “I was deeply moved by the outpouring of support that led to this event,” notes Eagle. “It is very humbling to realize that my name will be linked to an outstanding faculty member here in perpetuity.”

The inaugural recipient of this chair, VALLERIE MCLAUGHLIN, MD, has proved more than worthy of the honor. McLaughlin is a noted researcher and principal investigator of drug therapies to ease the symptoms of pulmonary vascular disease. She also directs the division’s Pulmonary Hypertension Program, where she treats both inpatients and outpatients and oversees operations for high-intensity patient care sections in the only accredited PH center in the state.

What benefits has the Eagle Professorship brought to her? “Professorships have a profound impact on the academic environment,” she says, “one that extends well beyond the boundaries of the campus and lasts far into the future. We’re not just teaching students: We’re molding future generations of physicians, and I am fortunate to be able to direct philanthropic funds toward providing learning opportunities for them.”

Kim Eagle is thrilled to have such a colleague serve as the first person appointed to his named professorship. And he hasn’t been surprised about her success. “I helped recruit Vallerie to Michigan,” he says, calling her a “superstar” — a title that could easily be applied to him as well.

“AMONG OTHER BENEFITS, THE HEWLETT PROFESSORSHIP HAS AFFORDED ME THE FLEXIBILITY TO DEVOTE TIME TO THE YOUNG PEOPLE IN OUR MIDST. NOW, WHEN A STUDENT COMES THROUGH MY DOOR, I CAN SAY YES TO THINKING ABOUT HOW I CAN HELP THEM ON THEIR JOURNEY.”

— KIM EAGLE, CARDIOVASCULAR MEDICINE
When division chiefs use the acronym “R&R,” they’re not talking about taking a vacation. They’re referring to “recruitment and retention,” the process of building a faculty that contributes to U-M’s reputation as the leaders and best in health care.

CHUNG OYWANG, MD, should know. His Division of Gastroenterology employs 10 of the named professors in the Department of Internal Medicine. He can easily explain how such professorships help him bring the physicians he wants to Michigan.

“In the mid-2000s,” he recalls, “BISHR OMARY was a division chief at Stanford and also the digestive disease research center director. When I heard that he had stepped down from these responsibilities, I quickly developed a plan to bring him to Michigan. I approached him, and he indicated that he had a very high regard for U-M and would seriously consider coming. But he would need an endowed chair to make the move. Fortunately, we happened to have a vacant chair, so we offered that to him as part of the recruitment package.”

Owyang continues: “He’s been here for about eight years now, and certainly has done wonders to the physiology department. The department is now almost double in size compared to before he came, rising in ranking from number 10 to number one during his tenure. At the same time, he has served as the editor-in-chief for our specialty’s journal, Gastroenterology. These are the kinds of things that bring prestige to the university. Bishr is just one example where an endowed chair can do wonders for recruitment.”

“Juanita has made fantastic contributions to the Medical School, to her department and to the division ever since,” he adds. At the moment, her research is centered on stem cells: What makes a cell decide to divide, to differentiate and to die? The answers to those kinds of questions are critical for developmental biology, and also important for regenerative medicine. Because of her endowed chair, she is performing this groundbreaking research at Michigan.”
What do you do when an opportunity to stop and really think about your work comes along? If you’re like LONA MODY, MD, MSc, you embrace the freedom that has been given to you and open your mind to dreaming.

“Often when we write grant applications for federal or foundation funding,” Mody notes, “we are bound by the granting organization’s rules, regulations, review criteria, funding priorities, even national priorities. With endowed professorships and the funds that come with them, we are set free — free to pursue the dreams that we accumulate over time, but are unable to execute because of other responsibilities.”

Mody was recently rewarded for past performance with the gift of a professorship: one that is named for the first female graduate of the Medical School. (See page 149 for details about this historical figure.) The accompanying funding will enable her to explore new areas of endeavor, starting with expanding her research. “My career has been built around preventing infections in aging populations,” she explains. “I have focused on studying seniors in nursing homes, but now I can broaden that scope to include other settings.”

“For example,” she notes, “let’s follow the case of a 65-year-old patient, who gets a hip replacement at the hospital. After surgery, he will need three weeks to recover in a rehabilitation facility. While there, he will visit physical therapy and related departments, taking his meals and socializing in common areas. When he is released, he may still require PT that is delivered at a community clinic. Eventually, he comes back to the hospital to see his surgeon, who will evaluate how he is doing. There, it is revealed that he has developed an infection.”

Mody’s goal is to trace the path of that health event. “In which setting did he pick up the organisms that contributed to his infection?” she asks. “Did he inadvertently spread them as he made his way throughout the hospital, rehab facility and clinic? And, most importantly, what interventions can we develop to prevent future migrations of these organisms and their resulting infections?”

One intervention that Mody plans to investigate relates to hand hygiene. She says: “The hand-washing guidelines established for health care workers have been proven to reduce the spread of disease in patients. What would happen if we engaged patients and their family members in preventing pathogen transmission as well?” Mody submitted a grant application to the Centers for Disease Control and Prevention to study this idea, but the agency only funded a piece of it. “I’ve used some of my professorship funding to cover the rest,” she explains. This includes defraying the travel costs of international leaders to come to U-M and advise Mody and her researchers on the best way to approach their work. “After we finish our study,” she says, “We will travel abroad to share our findings and increase our visibility as leaders in the field.”

Tangentially, Mody would also like to fund professional development for the junior faculty she works with. “When we go to medical school,” she explains, “we are not trained to manage research teams. I want to do something to change that.” Mody’s vision includes instruction in grant writing, academic writing and time management as well as advice on how to handle employee issues, career advancement hurdles and the challenges of maintaining a good work-life balance. This concern for others and a cohesive plan to respond to it mark a milestone in her own development as a professional who is well worthy of the professorship honor she has received.
Since 1968, 91 professorships have been established in the Department of Internal Medicine. As seen below, the pace of establishment has increased over time, with the majority coming in this decade.

### Named Professorships 1968–2016

<table>
<thead>
<tr>
<th>DATE</th>
<th>PROFESSORSHIP</th>
<th>FACULTY</th>
<th>DEPARTMENT</th>
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<tr>
<td>1968</td>
<td>John G. Searle Professorship in Internal Medicine</td>
<td>John M. Carethers, MD</td>
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<td>Eric Fearon, MD, PhD</td>
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<td>E. Gifford and Love Barnett Upjohn Professorship in Internal Medicine and Oncology</td>
<td>Stephen J. Weiss, MD</td>
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<td>1993</td>
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<td>M. Bisnh Ornary, MD, PhD</td>
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<td>1994</td>
<td>Warner Lambert/Parke-Davis Professorship in Medicine</td>
<td>David Ginsburg, MD</td>
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<td>1995</td>
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<td>Millie Schembechler Professorship in Adrenal Cancer</td>
<td>Gary D. Hammer, MD PhD</td>
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<td>Victor Vaughan Collegiate Professorship in the History of Internal Medicine</td>
<td>Joel D. Howell, MD, PhD</td>
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<td>William K. and Delores S. Brehm Professorship in Type 1 Diabetes Research</td>
<td>Peter Arvan, MD, PhD</td>
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<td>J. Griswold Ruth, MD and Margery Hopkins Ruth Professorship in Internal Medicine</td>
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<td>Hakan Oral, MD</td>
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CONTINUED ON PAGE 158
<p>| Year | Professorship Title                                                                 | Name                                           | Department                              |
|------|------------------------------------------------------------------------------------|                                                |                                        |
| 2012 | H. Marvin Pollard Collegiate Professorship in Gastroenterology                     | Grace Elta, MD                                 | Gastroenterology                       |
|      | H. Marvin Pollard Collegiate Professorship in Gastroenterology II                  | Open                                            | Gastroenterology                       |
|      | H. Marvin Pollard Collegiate Professorship in Gastroenterology III                 | Open                                            | Gastroenterology                       |
|      | H. Marvin Pollard Collegiate Professorship in Endoscopy Research                   | Thomas D. Wang, MD, PhD                        | Gastroenterology                       |
|      | Thomas H. Simpson Collegiate Professorship in Cancer Research, Medical School      | James M. Rae, PhD, MD                          | Hematology &amp; Oncology                  |
|      | Thomas H. Simpson Collegiate Professorship, Medical School                          | Ronald J. Buckanovich, MD, PhD                 | Hematology &amp; Oncology                  |
|      | Ray and Ruth Anderson-Laurence M. Sprague Memorial Research Professorship          | Muneesh Tewari, MD, PhD                        | Hematology &amp; Oncology                  |
|      | Frederick G.L. Huetwell Professorship in Rheumatology                              | Dinesh Khanna, MD, MS                          | Rheumatology                           |
|      | Frederick G.L. Huetwell Research Professorship in Rheumatology                     | Bruce C. Richardson, MD, PhD                   | Rheumatology                           |
|      | Josiah Macy, Jr. Professorship in Health Professions Education                     | Joseph C. Kolars, MD                           | Gastroenterology                       |
|      | Jerome W. Conn Collegiate Professorship                                             | William E. Rainey, PhD                         | Molecular &amp; Integrative Physiology     |
| 2013 | Cis Maisel Professorship in Oncology                                              | Open                                            | Hematology &amp; Oncology                  |
|      | Moshe Talpaz, MD, Professorship in Translational Oncology                          | Open                                            | Hematology &amp; Oncology                  |
|      | Jeffrey M. Leiden Collegiate Professor of the Life Sciences, Medical School        | Ivan Maillard, MD, PhD                         | Hematology &amp; Oncology                  |
|      | Alice Hamilton Collegiate Professor of Medicine, Medical School                    | John Z. Ayanian, MD, MPP                       | General Medicine                       |
| 2014 | Kim A. Eagle, MD, Endowed Professorship in Cardiovascular Medicine                | Vallerie V. McLaughlin, MD                     | Cardiology                             |
|      | Department of Internal Medicine Collegiate Professorship in HIV Research            | Kathleen Collins, MD, PhD                      | Infectious Diseases                    |
|      | Department of Internal Medicine Collegiate Professorship in Diabetes Complications | Rodica Pop-Busui, MD, PhD                      | MEND                                   |
| 2015 | Eliza Maria Mosher Collegiate Professorship in Internal Medicine                   | Daniel R. Goldstein, MD                        | Cardiology                             |
|      | Timothy T. Nostrand, MD, Collegiate Professorship in Gastroenterology              | William D. Chey, MD, MD                        | Gastroenterology                       |
|      | Cyrus Sturgis Research Professorship in Internal Medicine                           | Kenneth M. Langa, MD, PhD                      | General Medicine                       |
|      | Louis Newburgh Research Professorship in Internal Medicine                          | Eve A. Kerr, MD, MD                            | General Medicine                       |</p>
<table>
<thead>
<tr>
<th>Year</th>
<th>Professorship</th>
<th>Professor</th>
<th>Department</th>
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<tbody>
<tr>
<td>2015</td>
<td>Amanda Sanford Hickey Collegiate Professorship in Internal Medicine</td>
<td>Lora Mody, MD</td>
<td>Geriatrics &amp; Palliative Medicine</td>
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<tr>
<td></td>
<td>William Henry Fitzbutler Collegiate Professorship in Internal Medicine</td>
<td>Vincent B. Young, MD, PhD</td>
<td>Internal Medicine Department</td>
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<td>Norman Radin Professorship in Nephrology</td>
<td>Subramaniam Pennathur, MD</td>
<td>Nephrology</td>
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<td>Alan B. Leichtman, MD, Collegiate Professorship in Transplant Nephrology</td>
<td>Milagros D. Samaniego-Picota, MD</td>
<td>Nephrology</td>
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<td>Madeline and Sidney Forbes Professor of Oncology</td>
<td>Max S. Wicha, MD</td>
<td>Hematology &amp; Oncology</td>
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<td>Betram Pitt, MD, Collegiate Professorship in Cardiovascular Medicine</td>
<td>Keith D. Aaronson, MD</td>
<td>Cardiology</td>
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<td>Agnes C. and Frank D. McKay Professorship</td>
<td>James A. Shuyman, MD</td>
<td>Nephrology</td>
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<td></td>
<td>Nina and Jerry D. Luptak Research Professorship</td>
<td>Gary B. Huffnagle, PhD</td>
<td>Pulmonary</td>
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<td>Melvyn Rubenfire Professorship in Preventive Cardiology</td>
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<td>Galen B. Toews, MD, Collegiate Professorship in Pulmonary &amp; Critical Care Medicine</td>
<td>Bethany B. Moore, PhD</td>
<td>Pulmonary</td>
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<td>Robert H. Bartlett Collegiate Professor of the Life Sciences</td>
<td>Cheng-yu Lee, PhD</td>
<td>Molecular Medicine &amp; Genetics</td>
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<td>2016</td>
<td>Marguerite S. Roll Professorship in Medical Education</td>
<td>Rajesh S. Mangrulkar, MD</td>
<td>General Medicine</td>
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<td>Henry Sewall Research Professorship in Pulmonary and Critical Care Medicine</td>
<td>Vibha N. Lama, MD, MS</td>
<td>Pulmonary</td>
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<td>Giles Bole, MD, and Dorothy Mulkey, MD, Research Professorship in Rheumatology</td>
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<td>Rheumatology</td>
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<td>Ivan Duff Collegiate Professorship in Geriatric and Palliative Medicine</td>
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<td>Collegiate Professorship in Geriatric and Palliative Medicine</td>
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<td>Jeffrey B. Halter, MD, Professorship in Geriatrics</td>
<td>Raymond L. Yong, MB, ChB</td>
<td>Geriatrics &amp; Palliative Medicine</td>
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<tr>
<td>2017</td>
<td>Edward T. and Ellen K. Dryer Early Career Professorship In Rheumatology</td>
<td></td>
<td>Rheumatology</td>
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</table>
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