Medical Bulletin

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL

SPRING 2019

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Can we turn back the clock on aging?

Senolytic drugs keep people healthy longer by disrupting the aging process

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Still pushing the limits

A world leader for four decades, the U's Center for Magnetic Resonance Research continues to raise the field to higher levels

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Moving up

A good decision is based on knowledge and not on numbers.

– *Plato*

Medical school rankings are one indicator of an institution's perceived quality.

– U.S. News & World Report

AS WE WRAPPED UP the Medical School's 130th anniversary at the close of 2018, years of effort began to bear fruit. We are delighted to see significant improvement in our national rankings. Our Blue Ridge ranking, which measures the amount of National Institutes of Health research funding awarded to our Medical School, rose from No. 33 in 2017 to No. 30 in 2018.

This improvement represents millions of successfully competed for dollars and thousands of hours of work that will eventually result in medical advances. Likewise, our 2020 *U.S. News & World Report* best medical schools research ranking improved, moving up to No. 43 from No. 46. We are also making progress in education and training, as reflected in our *U.S. News* primary care ranking, which climbed two spots to No. 10. Notably, our family medicine specialty came in at No. 5. Rankings are just numbers, but the numbers convey a message about our institution and its reputation. We have renewed our commitment to do the work required to better serve our patients, our students, and our community.

PHOTO: BRADY WILLETTE

James Hereford, Fairview president and CEO, and Jakub Tolar, M.D., Ph.D., Medical School dean and vice president for clinical affairs

HERE ARE A FEW HIGHLIGHTS:

- We have hired impressive new faculty to join our Medical Discovery Teams, which are working to address complex health problems profoundly affecting Minnesotans by delving into the biology of aging, addiction, rural and American Indian health, and optical imaging and brain science.
- I have asked several Medical School faculty members to assume broader responsibilities as associate deans, creating more connectivity between leadership, faculty, staff, and students by distributing responsibility and authority. *Find the current list of leaders at med.umn.edu/about/leadership.*
- Last, but certainly not least, our teams are now working to operationalize the new M Health partnership with Fairview Health Services. Among the partnership's key features are greater financial support for academic medicine and academic physician leadership throughout the system. University of Minnesota Physicians, now led by CEO Badrinath Konety, M.D., M.B.A., remains an independent organization. Aligned with the University's land-grant mission, it will work with other partners and maintain the U of M brand in the market. Additionally, the University and Fairview are working together to create a Wellness Alliance with the goal of restoring well-being and joy to the practice of medicine.

Right now, we are in the early days of putting the plans for our Joint Clinical Enterprise into practice. I look forward to providing future updates on this critical partnership.

Jakub Tolar, M.D., Ph.D.
Dean of the Medical School and
Vice President for Clinical Affairs

New cancer drugs tell patients when it's time for a pill

There's an app for almost anything these days—even cancer care, thanks to a technology that can help to optimize at-home cancer treatment.

Experts from University of Minnesota Health and Fairview Health Services recently partnered with Proteus Digital Health to bring a new type of pharmaceutical called digital medicine to people being treated for cancer.

Digital medicine is already being used in the treatment of conditions like diabetes and hypertension, but the M Health team is the first in the world to use it for cancer.

Here's how Proteus Discover technology works: A pharmacist puts an ingestible, FDA-approved sensor and prescribed chemotherapy into a small capsule. The patient wears a patch on his or her torso that syncs to a secure app. When the patient swallows the capsule and it reaches the stomach fluid, the sensor sends a signal to the patch. The patch records the time the patient took the medicine, as well as the patient's heart rate and activity patterns. This information is sent to the app, which is visible to the patient, his or her care team, and, optionally, a support network of caregivers.

"We've put a lot of time and thought into creating safeguards for chemotherapy over the years," says the University of Minnesota Medical School's Edward Greeno, M.D., also a hematologist/oncologist for University of Minnesota Health, who helped to implement the digital medicine program for cancer patients. "Digital medicine gives us the chance to provide safety oversight when a patient takes oral chemotherapy from home, which leads to better outcomes."

PHOTO: BRIAN PETERSON, COPYRIGHT 2019, STAR TRIBUNE

An ingestible capsule containing a digital sensor and chemotherapy medication allows doctors to monitor their patients' at-home cancer treatment.

Taking oral chemotherapy medicine at home can be easier for patients, but it also can be challenging, Greeno says.

"If a patient doesn't feel well, for example, that person might intentionally decide to skip a pill or take an extra dose," he explains. "This can be problematic when taking oncology drugs. It's also possible for a patient to misunderstand the instructions for their drugs and accidentally take them incorrectly."

Patients can see when they took their medication and get reminders before their next dose. They can also report any problems directly to their doctors through the app.

Proteus Discover can help to avoid some of these problems. Patients can see when they took their medication and get reminders before their next dose. They can also report any problems directly to their doctors through the app.

"It's an additional tool I can use to keep my patients as healthy as possible and avoid potential problems," Greeno says. MB

Robots help U researchers detect autism earlier

Talking robots can help to reveal early signs of autism spectrum disorder.

UNIVERSITY OF MINNESOTA researchers are turning to robots to help children with autism spectrum disorder benefit from early interventions.

The researchers, from the Medical School and the College of Science and Engineering, are using moving, talking robots that interact with children ages 2 to 4 years old and gather data that can reveal early signs of autism. One in 59 U.S. children is on the autism spectrum, but most aren't diagnosed until age 4 or 5. Earlier detection gives health professionals more opportunities to start treatment when children's brains are most plastic, making it easier to change the course of development.

WEB EXTRA

See the robot in action at z.umn.edu/ASDrobot.

In the group were Maria Gini, Ph.D., previously professor of computer science and engineering; Marie Manner, Ph.D., formerly a student in computer science; Amy Esler, Ph.D., assistant professor of pediatrics; and Suma Jacob, M.D., Ph.D., associate professor of psychiatry and pediatrics.

The robot is a tool for seeing how children interact with their surroundings and collecting large amounts of data that can help experts make more accurate decisions about the presence of autism-like symptoms. And because the robots behave in a standardized way, Gini says, they avoid any bias that a human might bring into the assessment.

"Autistic children like to interact with technology more than with people," she says. "The objective of the project is to diagnose autism when the kids are very, very young, because the intervention can be done earlier, and it's much more effective." MB

New device could change concussion diagnoses

Diagnosing concussions and other traumatic brain injuries can be tricky. Current tests don't produce reliable yes-or-no results and are susceptible to manipulation by patients looking to avoid a brain injury diagnosis—such as athletes who want to return to play as soon as possible.

But a new device created by Uzma Samadani, M.D., Ph.D., a neurosurgeon with Hennepin Healthcare and an associate professor of neurosurgery at the University, could change how concussions are identified by providing doctors with quantifiable data, making the diagnosis process much more clear.

The device, called EyeBox, detects signs of concussion by tracking patients' eye movements as they watch a four-minute video.

The EyeBox detects signs of concussion by tracking patients' eye movements as they watch a four-minute video.

The movements allow doctors to assess the nerves in patients' eyes, which are sensitive to potentially elevated intracranial pressure, a telltale symptom of a brain injury.

After years of clinical testing, EyeBox was approved by the U.S. Food and Drug Administration in early 2019 and will be available for physician use from the biomedical company Oculogica.

"Really what we are talking about is changing the way brain injury is diagnosed and defined," Samadani told the *Star Tribune* in January. MB

The device allows doctors to assess whether eye nerves show signs of increased intracranial pressure, a telltale symptom of brain injury.

IMAGE: COURTESY OF OCULOGICA

U investigators find a new way to attack two high-risk viruses

Researchers from the University of Minnesota, the Howard Hughes Medical Institute (HHMI), and the University of Toronto have discovered a possible path toward preventing the development of cancers tied to two viruses that infect millions of people around the globe each year.

Published in *Nature Microbiology*, the research focuses on how the Epstein-Barr virus (EBV), most commonly known for causing mononucleosis, and Kaposi's sarcoma herpesvirus (KSHV) shield themselves from destruction inside the human body.

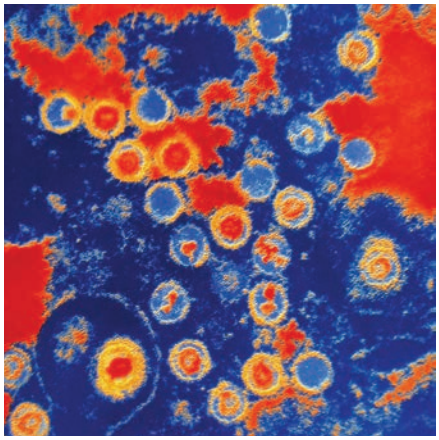


IMAGE: DR. GOPAL MURTI/SCIENCE SOURCE

Magnified and colored transmission electron micrograph of Epstein-Barr virus

"People infected with EBV or KSHV will have the virus for life," says Adam Cheng, a Medical Scientist Training Program student at the University of Minnesota Medical School and the study's lead author. "In most cases, the virus will remain dormant. However, sometimes these viruses can reactivate and lead to abnormal, cancerous cell growth. But now, in the wake of our research, data suggests it may be possible to suppress the virus indefinitely."

Under ideal conditions, a human DNA enzyme called APOBEC3B is capable of mutating and killing EBV and KSHV as they invade and replicate inside the body. However, researchers discovered that both viruses are able to produce defense proteins that bind directly to the APOBEC3B enzyme. When they do, APOBEC3B is unable to mutate and kill the viral DNA.

"Our work suggests that by blocking the viruses' defense proteins, it may be possible to treat mono and prevent the development of cancers caused by EBV and KSHV," says senior author and Masonic Cancer Center member Reuben Harris, Ph.D., who is an HHMI Investigator. "The viral defense proteins are excellent targets for drug development."

Meanwhile, the U's Henry Balfour Jr., M.D., a professor in the Medical School's departments of Laboratory Medicine and Pathology and Pediatrics, is working on bringing an experimental vaccine for EBV to the public. Balfour and his team believe that a vaccine that prevents EBV also holds the potential to prevent mono and other diseases EBV has been linked to, including a variety of cancers and multiple sclerosis. M|B

STUDY LINKS INFECTION WITH HEART ATTACK AND STROKE

High blood pressure, diabetes, high cholesterol, and tobacco smoking are well-known, long-term risk factors for stroke and heart attacks.

But when it comes to short-term risk, other factors might be at play, according to new research from the University of Minnesota Medical School and School of Public Health. The study, published last November in the *Journal of the American Heart Association*, shows that certain infections, such as those in the lungs (pneumonia) and urinary tract, can increase the risk of heart attacks and stroke by acting as "acute triggers."

Led by Kamakshi Lakshminarayan, Ph.D., an assistant professor in the Department of Neurology, the study found that infections substantially increased a person's short-term risk of having a heart attack or stroke. For example, in the two weeks after an infection requiring hospitalization, a patient's heart attack risk increased by 13-fold, and the odds of a stroke increased sixfold.

"The key to explaining the association between acute infections and the short-term increased risk of strokes and heart attacks is inflammation," Lakshminarayan says. "Inflammation promotes plaque buildup in blood vessels and also increases the tendency of these plaques to rupture, thereby blocking blood vessels."

Logan Cowan, a School of Public Health doctoral student involved in the research, says the findings underscore the importance of infection prevention and education.

"Infection prevention is key—so vaccination for influenza and pneumonia is important," he says. "Perhaps we should also consider infection as a 'treatable moment' during which cardiovascular preventive strategies should be implemented." M|B

Experienced coaches offer researchers individualized business advice.

PHOTO: HOLLY SANTIAGO, OFFICE OF THE VICE PRESIDENT FOR RESEARCH

New incubator helps U launch startups

RESEARCHERS AT THE University of Minnesota have a new resource on campus to help them bring their discoveries beyond the lab and into the marketplace.

Discovery Launchpad provides expert coaching and support for researchers who are interested in forming a startup company to commercialize new technology.

The Discovery Launchpad is an incubator program developed by the U's Venture Center to provide expert coaching and support for researchers—including those from the Medical School—who are interested in forming a startup company to commercialize new technology.

The program connects researchers with advisers who coach them through the process of creating business, marketing, and sales plans, as well as working on financial management and developing a business pitch.

"By offering individualized advising from experienced executives and entrepreneurs, we can improve the success of new startup companies based on U of M research, bring new technologies into the market, and increase the overall return on investment for research," says Russ Straate, associate director of the Venture Center. MB

Learn more about the Discovery Launchpad at z.umn.edu/discovery-launchpad.

External funding for U research reaches record level

The University of Minnesota announced in December that it successfully competed for a record $793 million in external research funding in fiscal year 2018. That's according to the 2018 Annual Report on Research and Technology Commercialization released by the University's Office of the Vice President for Research.

The University ranked ninth among the country's public research universities in research expenditures, according to the most recent National Science Foundation Higher Education Research and Development Survey, which compared research expenditure data collected from fiscal year 2017. The Twin Cities campus expended $922 million on research in that period, while the five-campus system expended $948 million.

OTHER HIGHLIGHTS FROM THE REPORT:

6.5 percent growth in the University's external research portfolio over fiscal year 2017

12.7 percent increase in federal awards

17.7 percent increase in state awards

8.8 percent increase in National Institutes of Health funding ($22 million) over the previous year

51 percent of all fiscal year 2018 research awards were to the Medical School or other health sciences endeavors

$42.6 million grant—one of the U's largest federal grants ever, from the NIH National Center for Advancing Translational Sciences—to be distributed over five years for the University's Clinical and Translational Science Institute, which helps to move lab discoveries into clinical practice faster MB

WEB EXTRA

To view the 2018 Annual Report on Research and Technology Commercialization, visit z.umn.edu/ResearchAR.

More U students reporting mental health concerns

The number of students coming to college with mental health concerns continues to increase, according to results from a recent health survey of students on the University of Minnesota's Twin Cities campus.

Slightly more than 42 percent of current students reported having a mental health diagnosis in their lifetimes, a 29 percent increase since 2015. The increase was particularly significant for female students, with almost half reporting a mental health condition in their lifetimes compared with 39 percent in 2015.

The data come from the 2018 College Student Health Survey of University of Minnesota Twin Cities students, directed by the U's Boynton Health Service.

Gary Christensen, '86 M.D., Boynton's chief medical officer, says the survey helps U leaders identify health issues affecting students and gives them valuable information to create a healthier campus environment.

"As student mental health needs grow, we have to ask what resources will be needed to keep pace," he says. "The scale of our campus puts us in a better position to provide students a range of resources. But all colleges and universities are struggling to keep up. Our survey should be a clear sign to policymakers, mental health professionals, and public health experts that we urgently need to identify public health approaches to promote good mental health."

Similar to past surveys, anxiety (32 percent) and depression (27 percent) are the most frequently cited mental health conditions among students at the U. MB

WEB EXTRA

Read the full 2018 College Student Health Survey report at z.umn.edu/2018CSHS.

U to lead $9.7M project to improve hearing restoration

The University of Minnesota will lead a research effort to develop a new implantable device and surgical procedure aimed at restoring more natural hearing to people who are deaf or severely hard-of-hearing. The work is funded by a five-year, $9.7 million grant from the National Institutes of Health BRAIN Initiative.

Cochlear implants have long been an effective treatment option for people with hearing loss caused by a lesion or disease of the inner ear or the auditory nerve. Unfortunately, some people aren't able to benefit from cochlear implants because of anatomical variations in their cochlea that limit the ability to implant the device or sufficiently activate the auditory nerve.

The goal of the new grant project is to implant electrodes directly into the auditory nerve, providing access to the hearing pathway and improving activation of the auditory pathway to the brain. Investigators believe this could be helpful for hearing in noisy environments.

"We hope that our proposed auditory nerve implant could lead to a new generation of neural technologies and greatly advance novel treatment options in the hearing implant industry," says Hubert Lim, Ph.D., associate professor in the College of Science and Engineering's Department of Biomedical Engineering and the Medical School's Department of Otolaryngology. MB

U RECEIVES $5.4M TO ADDRESS MEDICINE SHORTAGES

The U's Center for Infectious Disease Research and Policy (CIDRAP) has received a $5.4 million gift from the Walton Family Foundation to address global drug and medical supply shortages.

CIDRAP's work will focus on the supply chains and global disruptions for drugs that provide lifesaving and life-sustaining treatment, with the goal of improving the system's ability to maintain a steady and adequate supply of these critical medications and supplies worldwide. CIDRAP is a global leader in addressing public health preparedness and emerging infectious disease response.

Unexpected yet significant shortages in medical supplies are often due to manufacturing disruptions caused by natural disasters or breakdowns in infrastructure. The disruption makes entire communities vulnerable, especially during public health disasters.

"We know, based on our recent experience, that there will be more and more incidents where necessary drugs or medical supplies will be unavailable to those in crisis and, increasingly, the consequences are truly about life and death," says CIDRAP director Michael T. Osterholm, Ph.D., M.P.H., who will colead the team with Amy Kircher, Dr.P.H., codirector of the U's Strategic Partnerships and Research Collaborative. MB

LOCATION: Rwinkwavu, Rwanda **MISSION:** Addressing global health inequity

Beyond biology

"AS A HUMAN BEING, I cannot say, 'No, go back.' I will see you because I am a community health worker." This is how Jeanne, a CHW in Rwinkwavu, Rwanda, proudly explained that she would never deny health care to her neighbor.

As one of 45,000 CHWs in Rwanda, Jeanne is on the frontline of the country's health system. And in this system, the health of your neighbor is a priority.

Jeanne is also one of many instructors in the social medicine course "Beyond the Biological Basis of Disease." The course is led by SocMed, a nonprofit health-equity education organization based in Minnesota and Uganda. The truly global classroom now has more than 240 alumni from 16 countries, including six medical students from the University of Minnesota.

I took the SocMed course to build my skills in treating systemic health inequities. My experience with medical education before the course largely involved the biological causes of disease; it rarely considered the social structures in which health takes place. Training in social medicine would enable me to dig into inequitable systems and then organize people to respond.

Unlike Jeanne, many forces in the world say, "No, go back," denying people health care. In the United States, this takes the form of copays and high deductibles. In other countries, these barriers were established by multinational lenders who pressured nations to privatize their public health systems.

Such large-scale system failures can appear overwhelming. But the response—and the path toward equity—involves the education of tomorrow's health professionals. If education incites action, which is central to social medicine, that means hope for the future.

Augie Lindmark enrolled in the Medical School's FlexMD program to pursue an Oryema Fellowship in Social Medicine with SocMed. He will graduate from the University of Minnesota Medical School this spring and enter a primary care residency at Yale New Haven Hospital.

SUBMIT YOUR WORK

The *Medical Bulletin* is seeking compelling photos and stories featuring U of M Medical School student, alumni, or faculty experiences abroad. Selected submissions will be published in future issues of the *Medical Bulletin*.

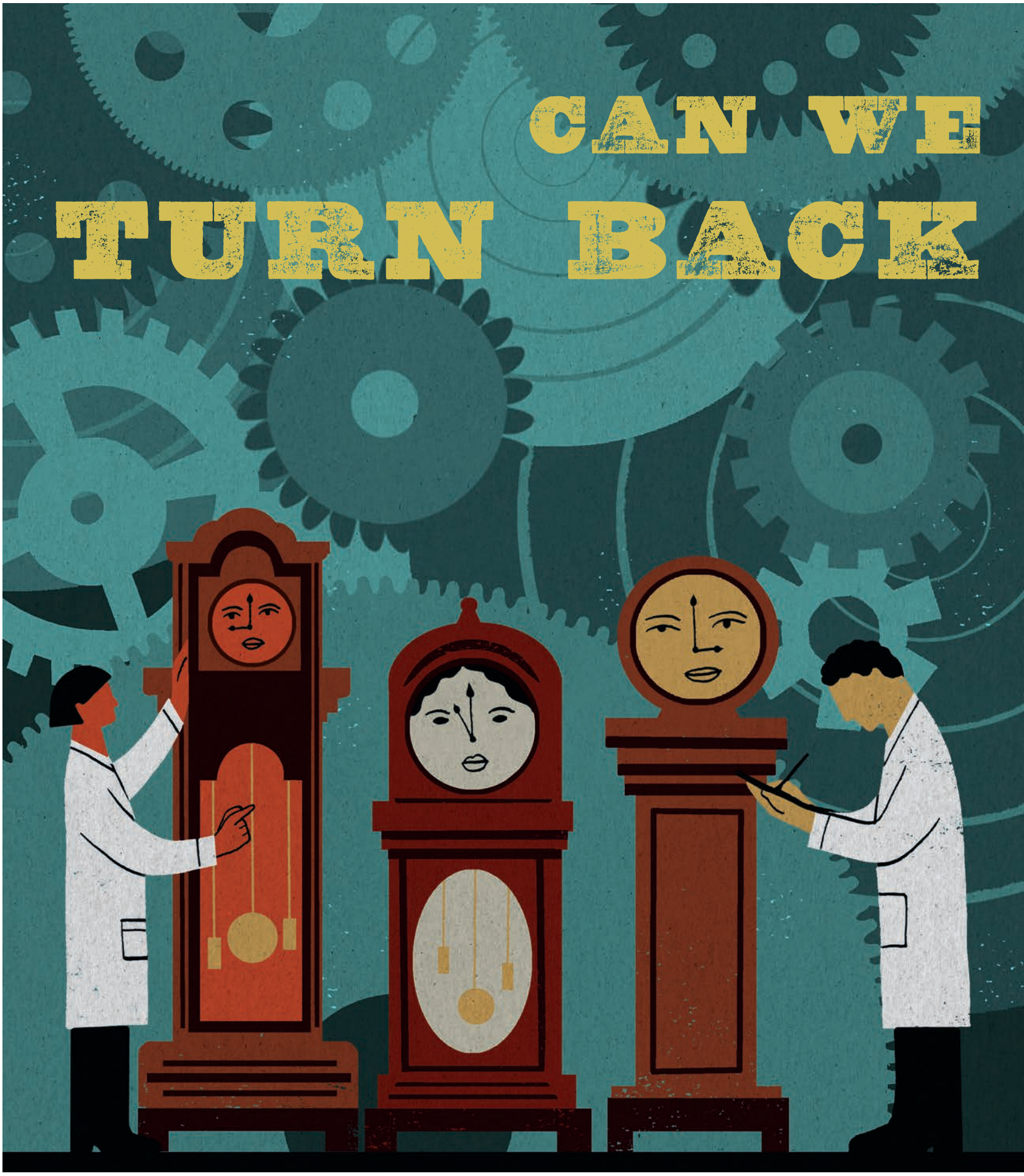
For more information or to submit your photo or story, email managing editor Nicole Endres at nendres@umn.edu.

PHOTO: SARAH GADY

Large-scale system failures can appear overwhelming. But the response — and the path toward equity — involves the education of tomorrow's health professionals.

PHOTO: LEANNE ZHANG

CAN WE TURN BACK



BY EMILY SOHN

THE CLOCK ON AGING?

U scientists are discovering drugs that may keep people healthy and vibrant longer by disrupting the aging process

LIVING LONGER CERTAINLY sounds appealing, unless it simply means more years of dealing with the ills and ailments of old age.

At the University of Minnesota Medical School, researchers are working toward a better option: a prolonged period of healthy life before the onset of diseases commonly associated with aging. Instead of a longer lifespan, this lengthened "healthspan" would mean more years to work, travel, and pursue an active lifestyle. Dementia, cardiovascular disease, osteoporosis, and other disabling conditions would be delayed—or possibly prevented.

A healthier old age is looking increasingly possible, says Laura Niedernhofer, M.D., Ph.D., director of the U's new Institute on the Biology of Aging and Metabolism (iBAM), where she and colleagues are working to develop drugs that slow aging at the cellular level. Called senolytics, these drugs would offer huge benefits across society, Niedernhofer says. More than 90 percent of people over 65 have one chronic disease, she says, and 75 percent have two or more chronic diseases; 10,000 people in the U.S. turn 65 every day.

"That's a lot of sick people and it just robs quality of life, not only for them but for their family members who are caretakers," Niedernhofer says. "What we're aiming to do is work very aggressively on developing therapeutics that target fundamental aging processes with the hope that they would then slow or prevent or attenuate the whole suite of diseases we expect in old age, from cancer to Alzheimer's."

Making 80 the new 60

Historically, research efforts to extend life focused on attacking one aging-related disease at a time, says S. Jay Olshansky, Ph.D., an aging expert at the University of Illinois, Chicago, but discoveries in recent years have started to make biological aging seem like less of an inevitability. Instead, experts are increasingly looking to delay the point at which our bodies begin a rapid decline toward frailty and disease. "We want an intervention that will allow us to take 80 years to become 60," Olshansky says.

Paul Robbins, Ph.D., iBAM's associate director, has seen his career mirror the field's overall shift in thinking—from dealing with aging-related diseases after the fact to slowing their progression before they begin. His early interest was in gene therapy—looking for ways to correct genetic defects or transfer genes to treat diseases like rheumatoid arthritis and diabetes. Then, about

ILLUSTRATION: HANNA BARCZYK

Experts are increasingly looking to

15 years ago, he started to find evidence that similar molecular processes drove the development of all sorts of aging-related diseases.

He switched gears to focus on those molecular processes, which can be tinkered with to cause either age-related diseases or extreme longevity in a variety of animal models, including fruit flies, mice, and worms. "There were certain types of mutations that made their lives shorter," he says, "and certain similar mutations that allowed them to live longer." Those mutations also have parallels in human centenarians, suggesting that senolytic drugs could target the same processes in people, permitting them to live longer, healthy lives.

Over the same period, Niedernhofer's research produced a striking discovery that made an age-slowing approach seem even more feasible. To better understand the health consequences of DNA damage, she knocked out a gene in mice that codes for a DNA-repair enzyme. Without the ability to fix their DNA, the rodents aged six times more quickly than normal. In people, she found, related mutations cause a rare disease of accelerated aging.

Now, Niedernhofer and Robbins had both a feasible idea and an animal model for investigating the biological processes that drive aging. Lured by iBAM's commitment to aging research, the duo, both leaders in their field, moved from the Scripps Research Institute in Jupiter, Florida, to the U of M Medical School, where they are professors in the Department of Biochemistry, Molecular Biology, and Biophysics.

Their recruitment resulted from a $30 million initiative launched by former Gov. Mark Dayton and the state Legislature in 2014–15 that created four Medical Discovery Teams in the Medical School, including iBAM, to improve patient and population health, lower medical costs across the state, and fortify the Medical School's preeminence.

Laura Niedernhofer, M.D., Ph.D., and Paul Robbins, Ph.D., who lead the U's new Institute on the Biology of Aging and Metabolism, believe healthier old age is increasingly possible.

PHOTO: BRADY WILLETTE

o delay the point at which our bodies begin a rapid decline toward frailty and disease.

Targeting troublesome senescent cells

At iBAM, one major focus targets senescent cells, which form in our bodies in response to stress. Senescent cells do the important work of suppressing tumor formation by preventing damaged DNA from replicating, but senescent cells also accumulate with age, as our bodies get worse at getting rid of them. While they hang around, senescent cells release molecules that induce a state of chronic inflammation, which has been linked to many of the health consequences of aging, like slower recovery from surgeries.

For a 2015 study, Niedernhofer and Robbins, along with colleagues at the Mayo Clinic, developed the first drug to kill senescent cells. They gave mice an existing cancer medication called dasatinib, along with a common plant pigment called quercetin, and found that the old rodents maintained a healthy gait, stronger heart function, and the ability to exercise longer. A single dose was enough to slow the aging process.

Since then, the scientists have pushed the possibilities even further. In one study, published in 2018, iBAM researchers and colleagues at Mayo found that transplanted senescent cells caused physical decline in young mice and reduced survival in older mice. But the effect was reversible: a senolytic cocktail of dasatinib and quercetin lowered the load of senescent cells and the inflammatory molecules they produce. The drug also improved physical abilities, such as walking speed and muscle strength. And it lengthened the rodents' lifespans by 36 percent. In another 2018 study, the group reported similarly encouraging findings with another plant compound, called fisetin, even if the medications were given to the mice later in life—the equivalent, Niedernhofer says, of treating a 75-year-old human.

continued

NEW CARE MODELS FOR OLDER PATIENTS

THE MEDICAL SCHOOL is expanding its commitment to educating and training today's physicians to care for tomorrow's geriatric patients—those over age 60.

Jakub Tolar, M.D., Ph.D., Medical School dean and vice president for clinical affairs, says the revitalized relationship between the University and Fairview Health Services provides a prime opportunity to create an integrated system of care for seniors, whose numbers will double by 2030.

"Throughout the University, we have extensive knowledge of the biology, psychology, and other aspects of aging—and we educate 70 percent of the state's primary care physicians," says Tolar. "Our family medicine leaders are collaborating with experts across many fields to develop state-of-the-art geriatrics care training programs and to deliver coordinated care for seniors through our expanded network of primary care sites."

A wider network is just part of the plan, says James Pacala, M.D., a geriatrician and head of the Department of Family Medicine and Community Health. "We need a different approach to adapt to the varying needs of geriatric patients, from the 90-year-old super-athlete to the 60-something patient with 18 medical conditions and 25 drugs."

Tolar and Pacala envision drawing on faculty experts in aging from the University's schools of medicine, public health, and nursing; pharmacology; physical therapy and rehab; dentistry; as well as social work and other programs. This comprehensive effort, says Pacala, will serve as an engine for training and research that will benefit older patients, their families, and caregivers.

$1M BOOST FROM OTTO BREMER TRUST

Though still in the planning phase, the initiative has drawn the support of the Otto Bremer Trust, which recently awarded the University a $1 million grant to develop integrated education for all types of students—not just future geriatricians—who will deliver care to older patients.

The Medical School plans to use the Otto Bremer support to provide geriatrics training for primary care clinics and to develop a telemedicine program that reaches older adults in their own communities, says Tolar. "I'm confident we can transform care for this growing population."

By Mary Koppel

If we don't do something, we're in a world of trouble. There are not enough beds in nursing homes to accommodate all of the aging baby boomers.

Although mice are not people, evidence is adding up to support the powerful potential of new medications to defer aging, Niedernhofer says. She and Robbins continue to work with collaborators at Mayo to develop new drugs that interfere with what Robbins thinks are just a handful of pathways involved in aging. They are also working to fill in more details about the fundamental processes that drive aging in order to collect new insights that will inform drug development. One hope is to create medications that would target specific locations, like the brain or immune system.

TAMING the aging process

The first clinical trial of a different type of drug with anti-aging potential is scheduled to begin this year. Called TAME and developed with guidance from the iBAM directors, the trial is examining whether Metformin, a diabetes drug that has shown promise for delaying the onset of multiple age-related diseases, might be able to delay the development of cancer, heart disease, and cognitive decline in all older adults, not just people with diabetes. The University of Minnesota is one of 14 sites where the TAME trial will take place. Metformin is not a senolytic, as it doesn't target senescent cells, but it could get at the heart of aging. And, depending on its results, the trial could transform old age—and soon. "The first drug for aging could be here in the next five years," Robbins says.

Niedernhofer sees the research as a necessity, not a luxury. "If we don't do something," she says, "we're in a world of trouble because there are literally not enough beds in nursing homes or independent living facilities to accommodate all of the aging baby boomers."

Although hype has been building, it is too soon to recommend that people start self-medicating to fight aging, she adds. Plenty of details remain undetermined about what form the medication will take, how often people will get it, or who will be the target patient population. New medications will also have to be tested exhaustively for safety, but startup companies are increasingly interested in investing in senolytic drugs, says Robbins. One of the first groups to benefit might be cancer patients, who tend to accumulate extra senescent cells and experience accelerated aging from harsh treatments. Initially, the drugs will also likely be geared toward people who already are showing signs of unhealthy aging, having two or more age-related diseases.

Given the cutting-edge research happening at iBAM, the next major breakthrough in senolytics is likely to happen in Minnesota, Olshansky says. The availability of drugs that slow aging, he adds, is a matter of when, not if.

"When it does happen—when some research team somewhere across the globe develops a therapeutic intervention to modulate aging—it will probably become the most important medical discovery in this century because of the breadth of its impact on humanity," he says. "It will make a cure for cancer seem like a minor development." MB

Emily Sohn is a freelance journalist in Minneapolis whose stories have appeared on NPR and in the *Washington Post*, *Nature,* and many other publications.

PHOTO: DEREK MONTGOMERY

Points of pride

Nationwide, schools still struggle to draw Native Americans and Alaska Natives into medicine; here's what's working at our Medical School's Duluth campus

BY JUSTIN HARRIS

Mary Owen, M.D., directs the Medical School, Duluth campus' Center of American Indian and Minority Health, a resource and community hub for Native students.

As a kid, Fredrick Blaisdell saw first-hand some of the all-too-common health challenges facing American Indian and Alaska Native people across the country: insufficient access to health care, a dearth of Native physicians to provide that care, and an overall lack of resources available to the community.

"I saw it as a patient and with my family," says Blaisdell, a member of the Oneida Nation of the Thames who grew up in an urban Native American community near Detroit, Michigan. "We often struggled to get the services we needed."

I wanted to go to a school that included American Indian health as a main focus. When I came to visit campus for my interview, right away it felt like home.

– Fredrick Blaisdell, Medical School, Duluth campus student

That experience was pivotal in his decision to pursue medicine as a career, with the goal of working as a doctor in a Native community. When it came time for Blaisdell to apply to medical school, one place stood above the rest: the University of Minnesota Medical School, Duluth campus.

"I wanted to go to a school that included American Indian health as a main focus," says Blaisdell, a first-year medical student at the Duluth campus and one of six Native American students in his class. "When I came to visit campus for my interview, right away it felt like home."

Since its inception in 1972, the Medical School's Duluth campus has made Native American health a fundamental part of its mission. Over the course of four decades, the Medical School has trained more than 170 Native American physicians—the second-highest number in the country—and become a national leader in addressing health challenges in Native communities.

The Medical School's history of success was highlighted by a report released in October 2018—written by the Association of American Medical Colleges (AAMC) and the Association of American Indian Physicians (AAIP)—that sheds light on the myriad health concerns plaguing American Indian and Alaska Native communities and explores the responsibility that medical schools have to combat these conditions.

"Part of our land-grant mission is to provide care for anyone who lives in Minnesota, and we recognize that some of our greatest health disparities exist within our Native communities," says Paula Termuhlen, M.D., regional campus dean of the Medical School in Duluth. "We want to understand the challenges these communities have and how we can use our resources to help support them."

Understanding the problems

The AAMC/AAIP report outlines the uniquely daunting set of circumstances that contribute to poor health in Native communities. Historical trauma and continued marginalization in American society have made it difficult for Native people to access high-quality care and have contributed to some of the worst health outcomes in the country.

Native people experience higher rates of many chronic and preventable diseases than other Americans and have a life expectancy that is nearly six years shorter. According to the report, about 25 percent of deaths in Native people occur before the age of 45, compared with 15 percent for African Americans and only 7 percent for whites.

Compounding those factors, the report argues, is a lack of Native physicians and medical professionals serving in these communities. Fewer than 1 percent of doctors working in the United States in 2016 identified as American Indian or Alaska Native, and the number of Native students applying to medical school across the country remains relatively stagnant at about 200 a year, despite efforts to improve these numbers.

Mary Owen, '00 M.D., director of the Medical School, Duluth campus' Center of American Indian and Minority Health (CAIMH) and practicing physician for the Leech Lake Band of Ojibwe, acknowledges that the confluence of issues affecting Native health can be overwhelming. But she says the Medical School is in a unique position to help.

"We have complex problems," says Owen, a member of the Tlingit Nation. "But we also have solutions."

Training the next generation

The most obvious solution is an emphasis on recruiting and training Native physicians, a priority that dates back to Duluth's first class of medical students. In that class of 24, two were Native students. All told, the Medical School has graduated 177 Native physicians.

"The school has been committed to supporting Native American students for almost 50 years," says Anna Wirta-Kosobuski, Ph.D., an assistant professor in the Department of Biomedical Sciences on the Medical School's Duluth campus, who contributed to the AAMC/AAIP report and is a member of the Bois Forte Band of Ojibwe. "The longevity and level of commitment set us apart."

Owen says the supportive community on campus is a significant reason for the school's sustained success. CAIMH engages students in Native health issues through programs like the Indian Health Pathway, which supports middle school, high school, and undergraduate students in their pursuit of health-related careers. Another initiative, Native Americans into Medicine, is a six-week summer program for premedical students to collaborate on specific research projects related to Native health.

PHOTO: DEREK MONTGOMERY

PHOTO: COURTESY OF THE CENTER OF AMERICAN INDIAN AND MINORITY HEALTH

TOP Fredrick Blaisdell, a first-year medical student at the Duluth campus, is a member of the Oneida Nation of the Thames.

BOTTOM The Native Americans into Medicine program gives undergraduate students interested in medicine hands-on research experience.

NATIONWIDE

AMERICAN INDIANS AND ALASKA NATIVES IN MEDICINE

4,099
Number of Native physicians practicing in the U.S.—less than 1 percent of the physician workforce

43
Percent of medical schools that had no AI-AN students enrolled in 2016–17

WEB EXTRA

See photos of students in the Native Americans into Medicine program, or read the full report on health concerns plaguing American Indian and Alaska Native communities, at z.umn.edu/CAIMH.

Through such programs, students build relationships with their peers, faculty and staff, and the broader Native community in Minnesota, Owen says.

"We're building a community and we're letting everyone that we come in contact with know about Native health issues and concerns, Native communities, and our culture," she says.

Training more Native physicians is a worthwhile pursuit, Owen says, but it won't overcome the health disparities in Native communities. Federal Indian Health Service clinics across the country—where more than 2 million Native people receive health care—have a 25 percent vacancy rate for physician openings, a number that Owen says cannot be filled solely by Native physicians.

Three years ago, and with that challenge in mind, the Medical School introduced a required curriculum for all students that covers Native history, culture, and identity. The thinking, Owen says, is that the more non-Native students know about Native communities—and the health issues they face—the more motivated they'll be to serve these populations.

Anna Wirta-Kosobuski, Ph.D., leads community-based science programs that encourage elementary school children in Native communities to engage in science at an early age.

PHOTO: DEREK MONTGOMERY

Beyond medical school

Medical School leaders agree that the school's responsibility to Native health goes beyond training the next generation of physicians, because the disparities in these communities go beyond health.

One area that the Medical School has targeted in recent years is early education. Community-based science initiatives led by Wirta have brought fun and engaging science activities to elementary school children in Native communities in Minnesota.

"The thought behind working with the young children is that by the time they reach even middle school, it can be too late to effectively address student needs and provide interventions that promote educational success," Wirta says. "By third grade, many Native American children have not made it to the benchmarks where they need to be in order to move on."

The statistics back up her assertion: In Minnesota, the high school graduation rate among Native American students stands at only 50 percent.

"That's what pushed me toward working with the young children. They have a natural curiosity, and, ideally, we can reach them before they start to lose interest in the excitement of learning," Wirta says. "The goal is that they'll graduate from high school, and move on to postsecondary education. The long-range goal is that they go into some sort of science career, which would be a huge bonus."

Termuhlen calls the idea of addressing education shortcomings at the earliest opportunity an "aha moment" for the Medical School.

2
Nationwide ranking in number of AI-AN graduates (177)

2
Number of AI-AN students in the Duluth campus' first enrolled class of 24 students, in 1972

46
Years Native Americans into Medicine, a summer enrichment program at the Duluth campus for Native American and Alaska Native premedical students, has been held

13
Percent of Duluth campus faculty who are AI-AN individuals

Source: Reshaping the Journey *(October 2018) from the Association of American Medical Colleges and the Association of American Indian Physicians*

"We realized we have to take a step even further back and start to engage," she says. "If we were to follow those students into the future, how many of them get through high school? Can we start to budge that high school graduation rate? We know educational successes will translate into economic successes, and that supports improvement in health outcomes."

And, as Owen notes, if more Native students are going to college, how many might pursue careers in health-related fields?

"We need more Native pharmacists, more Native nurses, more Native public health specialists, more Native dentists," she says. "That's why these community-based science activities are so important."

'Nobody gets here on their own'

For all of the innovative programs the Medical School has developed to address Native health issues, it's how the Native community has become an integral part of Duluth campus' DNA that makes Owen most proud. It's a community that embodies Native values, she says.

"We want this to be like a Native community, which is not built on individualism, but just the opposite," she says. "It's built on supporting one another, believing that we're all connected, and that we all help one another. Nobody gets here on their own."

That full-circle ethos is evident in efforts like Wirta's early education outreach initiative. It's also reflected in mentorship opportunities that offer medical students a chance to shadow and work alongside practicing Native physicians in those communities.

Lacey Running Hawk, '13 M.D., a member of the Standing Rock Lakota and a family medicine physician for the Mille Lacs Band of Ojibwe, says those experiences in medical school continue to shape who she is as a doctor today.

PHOTO: COURTESY OF ANNA WIRTA-KOSOBUSKI, PH.D.

Students at Nett Lake Elementary School build DNA models using candy as part of a community education program.

"The strong community on campus and that cultural connection reminded you why you were meant to do this, and it motivates you to keep going," recalls Running Hawk, who shadowed Native physicians and volunteered in Native communities while in medical school. "Having the mentorship from Native physicians, it also gives you the heart to want to be that mentor to others."

And that's exactly what Running Hawk has done. She's now a community preceptor for the Medical School's Rural Family Medicine, Native American and Minority Health Scholars Program.

"We have this idea that you are where you are because somebody reached back and helped you," Running Hawk says. "And now it's my responsibility to do that for the next generation." MB

Justin Harris is an editor-writer with the University of Minnesota Foundation.

WEB EXTRA

Watch Wirta lead Nett Lake Elementary School kids through hands-on science experiences at z.umn.edu/CAIMH.

Going cell-to-cell with ovarian cancer

Masonic Cancer Center researchers evaluate a unique immunotherapy designed to keep this wily disease from coming back

BY BARBARA KNOX

Melissa Geller, M.D., M.S., was still a new doctor completing her fellowship at the University of Minnesota in the early 2000s when she resolved to spend the rest of her career helping people who face the grimmest of cancer diagnoses.

"Having to tell a patient with ovarian cancer that there is no cure for her disease is incredibly difficult," says Geller, now associate professor and division director of Gynecologic Oncology in the Medical School's Department of Obstetrics, Gynecology, and Women's Health. "I knew then that, someday, I wanted to be able to say to these women, 'You will never have a recurrence of this cancer.'"

And today she's optimistic about a form of immunotherapy originally developed by her Masonic Cancer Center, University of Minnesota colleague and mentor Jeffrey Miller, M.D., a professor of medicine in the Medical School. Through a partnership with the biotechnology company Nant, Geller and her team are now treating women who have recurrent ovarian cancer in two early-phase clinical trials.

While Miller has used this type of immunotherapy to treat people who have blood-related diseases, Geller's studies are the first to explore whether it can be effective against solid tumors.

Promise of cell therapy

The stakes are high. More than 22,500 women are diagnosed with ovarian cancer every year in the United States, according to the American Cancer Society. The majority have a recurrence within two years, and, despite the best efforts of doctors like Geller, five-year survival rates for ovarian cancer are less than 50 percent.

While current treatments for ovarian cancer—surgery to remove the tumor followed by six months of chemotherapy—attack the disease from the outside, the cell therapy trials underway now take the fight to the cancer's front lines: inside the body, where the battle is being waged on a cellular level.

Immunotherapy treatments—including cell therapies—are designed to harness the power of the body's immune system to kill cancer cells by either delivering new cells to the fight or revving up the ones already there. Both of Geller's trials hinge on natural killer (NK) cells.

In a healthy body, NK cells rally to the site of infection or disease and call other cells to come to that location and help beat back the infection. But cancer cells are wily and elusive. And researchers now know that women with ovarian cancer have fewer NK cells in the peritoneal area—and the ones they do have function poorly, which allows cancer cells to flourish.

In the first trial, Geller is administering a cell therapy called FATE-NK100, developed by investigators at the University in collaboration with Fate Therapeutics, directly into each patient's peritoneal cavity through a port in the abdomen. The treatment is derived from the blood of a related donor. Six patients have been

ILLUSTRATION: KEITH NEGLEY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EXPLORING THE CMV–OVARIAN CANCER LINK

CYTOMEGALOVIRUS, or CMV, infects more than half of all adults by the time they turn 40. For most people with healthy immune systems, the virus causes no signs or symptoms.

But for women who have ovarian cancer, the virus has unknown—and potentially important—effects on their treatment and quality of life. Researchers suspect that CMV reactivation may be an unrecognized complicating factor in the treatment of ovarian cancer that could affect both immune function and outcomes.

Rachel Vogel, Ph.D.

Now, with support from two Department of Defense grants, researchers at the University of Minnesota are investigating how CMV reactivation affects women who have ovarian cancer during the course of their disease.

Rachel Vogel, Ph.D., assistant professor in the Medical School's Department of Obstetrics, Gynecology, and Women's Health and researcher at the Masonic Cancer Center, received a $1.1 million grant to study how CMV affects patients' symptoms during ovarian cancer treatment. She'll be working with Masonic Cancer Center colleagues Melissa Geller, M.D., and Heather Nelson, Ph.D., on the study.

The same team, this time led by Nelson, was also awarded a $385,000 pilot grant to study the CMV–ovarian cancer interaction over an extended period of time.

"By understanding how the virus is impacting symptoms and treatment, we can design interventions to improve outcomes and quality of life," Nelson says.

PHOTO: BRADY WILLETTE

Melissa Geller, M.D., leads two clinical trials using natural killer cell–based immunotherapy to knock out recurrent ovarian cancer.

treated so far, and, Geller reports, she's finding that those donor NK cells are still at work more than a month later.

"The longer those NK cells stick around," Geller explains, "the more—hopefully—we will see the disease stabilize, so we can keep the patient off chemotherapy."

That trial, which is focused on establishing optimal dosing for the FATE-NK100 treatment, will go on for another year.

In the second trial, Geller uses the drug developed by Miller's team in its partnership with Nant. Geller describes it as a "souped-up agonist that sends in a combination of NK cells and T cells to attack the cancer cells where they grow." (T cells are also key players in a healthy immune system.) Again, the treatment is delivered directly into the abdomen—a first for this drug—on a four-weeks-on/four-weeks-off schedule.

"Our goal is to prevent cancer recurrence and, if it works, that ultimately this will become a treatment that women could give themselves at home," she says.

With only four women in the trial so far, Geller continues to recruit additional patients.

Geller credits the U's unique blend of translational research laboratories, a pharmaceutical-grade manufacturing facility, and dedicated oncology clinics for not just developing the treatments and bringing them to patients, but also for changing and adapting the treatments quickly as researchers make new discoveries in the lab.

The next big push

While immunotherapy has fundamentally changed the landscape of cancer treatment, it's massively expensive to develop personalized cell therapies derived from donors for every patient. So researchers have been busy in recent years trying to create a one-size-fits-all treatment that is both effective and affordable.

According to Miller, who is director of the Masonic Cancer Center's Cancer Experimental Therapeutics Initiative, that's the next step—and it's already well underway at the University.

"Working with Fate, our next big push is to develop an off-the-shelf NK cell therapy product," he says. "We know how to make pluripotent stem cells (adult cells that are genetically reprogrammed) into NK cells, so now we have the opportunity to make a big batch of hundreds of doses."

Using that approach, Miller explains, doctors could simply go to the freezer, remove a dose, and administer it to a patient: faster, cheaper, and, ideally, every bit as effective as those painstakingly manufactured personalized treatments. That's what Miller aims to confirm when

While current treatments for ovarian cancer attack the disease from the outside, trials underway now take the fight to the front lines: inside the body, where the battle is being waged on a cellular level.

he treats his first patient in a new trial that he expects to start later this year.

Meanwhile in the lab, Miller's next major project is creating a new type of NK cell that is hyper-focused on ovarian cancer. Will NK cells designed to have extra specificity be even more effective in their search-and-destroy mission? That's what Miller and his team aim to find out.

After more than two decades in the field and a lot of pioneering research behind him, Miller believes this work can spur a revolution in cancer treatment.

"One thing I've seen in my many years doing this work is that pharmaceutical companies only invest with a goal of commercializing treatments if they think it'll be a game-changer," he says. "And they're investing."

If all goes well in the upcoming trial, Miller says, best-case scenario, they could have a commercial cell therapy ready to be used in the clinic in five years.

"Five years is quick," he cautions, "but this field is moving quickly."

For the ovarian cancer patients that Geller sees in clinic every day, the prospect of an effective cell therapy is a ray of hope.

"I'm so grateful for the mentorship I've gotten from Jeff [Miller] and all the work he and his team have done to develop this cell therapy," says Geller. "And I'm especially grateful that now women with ovarian cancer can benefit, too." MB

Barbara Knox is a freelance writer and editor and a frequent contributor to the *Medical Bulletin*.

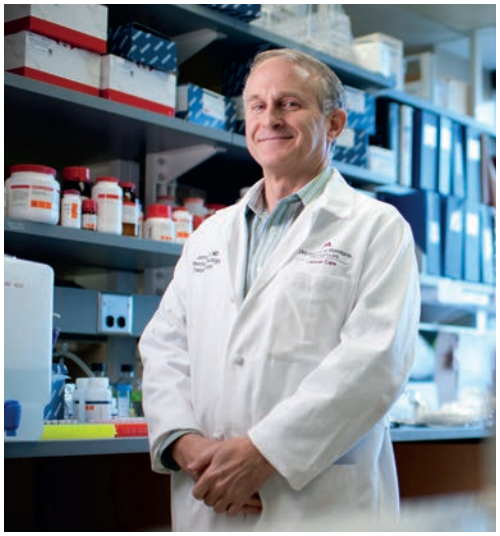


PHOTO: SCOTT STREBLE

Jeffrey Miller, M.D., has found success in employing natural killer cells against blood cancers and is hoping the success translates to solid tumors like ovarian cancer as well.

WEB EXTRA

Masonic Cancer Center researchers are developing a blood test to screen for ovarian cancer. Learn more at z.umn.edu/ovariancancertest.

BUILDING A BETTER APP

HOW DO YOU GET women who've been diagnosed with ovarian cancer to undergo genetic testing? It's a surprisingly hard sell, says University of Minnesota Health gynecologic oncologist Melissa Geller, M.D.

Sometimes women are concerned that their insurance won't pay for genetic counseling, while others are fearful of what they might discover. What if they find out that they carry gene mutations like BRCA1 or BRCA2, which increase risk of breast and ovarian cancer? And, if they do carry a mutation, they fear they may have passed it along to their children. Sharing that news with your kids is tough.

Geller decided to tackle the information barrier with an app. With funding from the Department of Defense, she developed mAGIC (mobile application for genetics in cancer), a seven-day educational app designed for women who have ovarian cancer who haven't gone through genetic counseling.

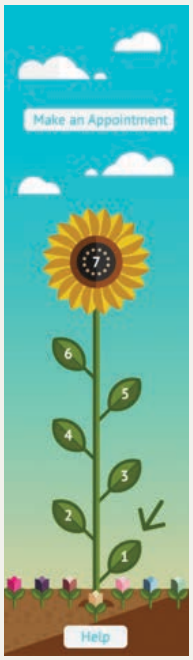


IMAGE: SOFTWARE FOR GOOD

To determine whether the app was effective in convincing women to seek genetic testing, Geller gave one group of women an informational pamphlet, while the other group had access to the app.

"Women who used the app learned more about hereditary ovarian cancer and were more apt to talk with family members about it," Geller says. "It's a potentially very powerful tool."

It's also more important than ever to get women tested. "We now have drugs that have been shown to improve survival in women who are BRCA-positive," she says, "so testing is critical."

While the first version of mAGIC performed well, Geller now wants to take it to the next level. With the help of philanthropy, she plans to update it to keep getting information out to at-risk women and their family members.

Find out how your gift can help to develop the next-generation mAGIC app by contacting Lacy Moser of the University of Minnesota Foundation at 612-625-6495 or lmoser@umn.edu.

ILLUSTRATION: DAN WOYCHICK

GETTING IT

How doctors in training can learn to avoid making the wrong diagnosis

BY GREG BREINING

Diagnosing illness is one of the most important things doctors do. Yet they get it wrong a small but significant part of the time.

"We are not nearly as good at diagnosis as we thought we were," says Andrew Olson, M.D., assistant professor of medicine and pediatrics in the University of Minnesota Medical School. "We produce people who are right 85 to 90 percent of the time in the hospital and 95 percent of the time in outpatient settings. That's not good enough."

To improve doctors' skills, Olson has been spearheading efforts in the Medical School's undergraduate and graduate programs to teach diagnosis more systematically and comprehensively.

"In my opinion, the most promising strategy is to improve education," he says. "If I teach a student who is then going to practice for 40 years and see thousands and thousands of patients, the impact potentially is huge."

Though fundamental, diagnosis is one of the most complex things a doctor does; it's based on a combination of subjective information, objective tests, rational thought, and no small amount of intuition that defies easy explanation.

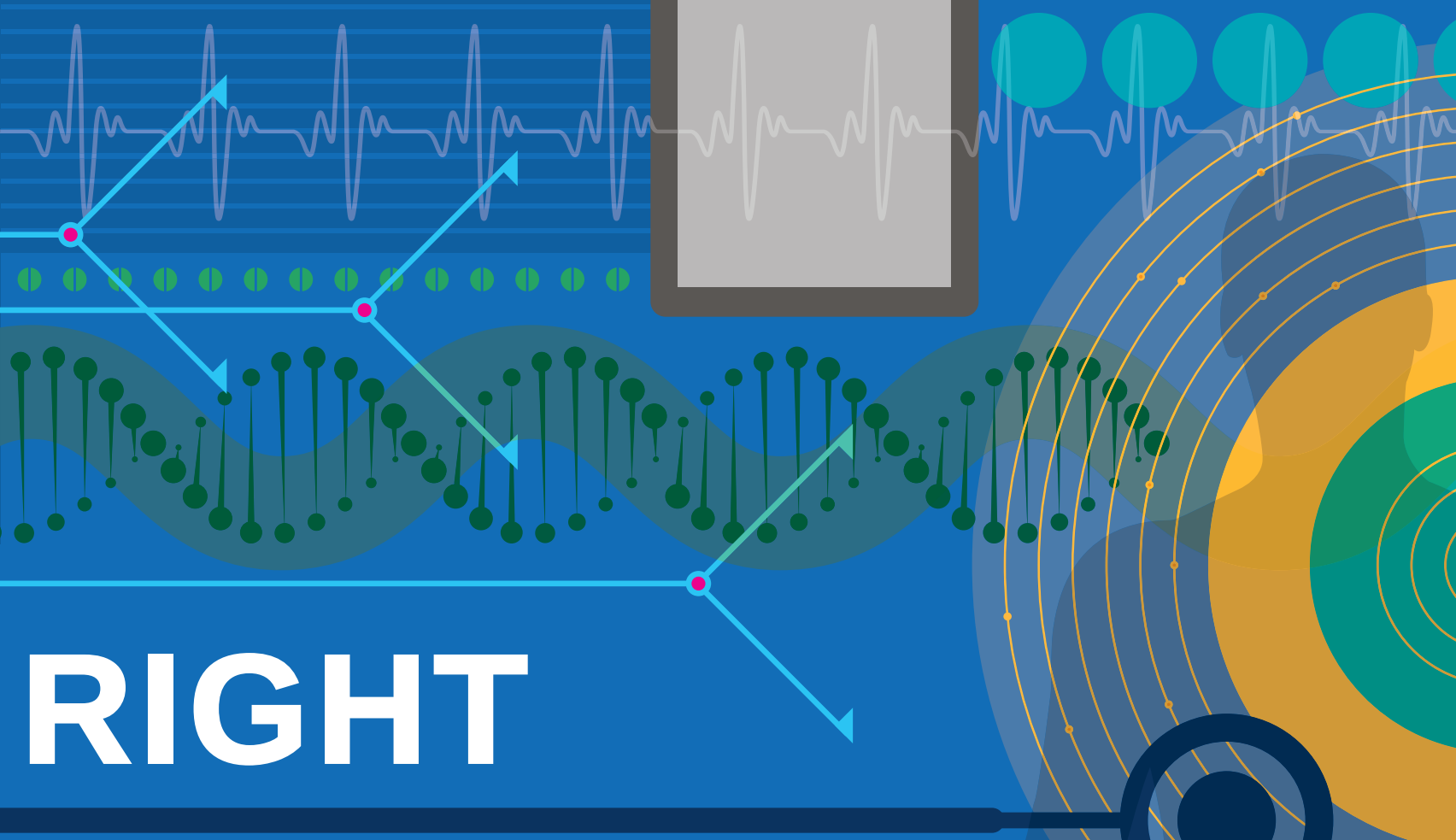
"Until recently, we have not understood terribly well the processes we use to make diagnoses," says Olson. "When we don't understand the process very well, how do we teach it?"

As a result, diagnosis has been taught more implicitly than explicitly. Young doctors learn to take medical histories and then follow more experienced mentors who impart—clearly or not—their own diagnostic methods. That sort of learning leads to uneven results. And, research shows, reliance on intuition and mental shortcuts at the wrong times leads to errors.

COGNITIVE BIAS

Medicine has treated knowledge as the basis of good diagnosis. But, as Olson and colleagues recently noted in the journal *Diagnosis*, "knowledge is necessary but not alone sufficient."

"The reasons I err aren't necessarily that I didn't know a fact," says Olson. "If you look at what gets missed in the hospital, it's things



RIGHT

like sepsis, strokes, heart attacks. What gets missed in outpatients? Cancer, most commonly. Why is that? We know a lot about all those things. It's not a knowledge problem alone. It's that I put the pieces together the wrong way."

That happens because doctors rely on intuition when circumstances require more deliberation, explains Pat Croskerry, M.D., who leads the Critical Thinking Program in the Division of Medical Education at Dalhousie University in Halifax, Nova Scotia.

"In an emergency setting, I can see one problem after another, and I can function at an almost intuitive level and say this almost always turns out to be that, and that's how I'm going to treat it," says Croskerry, a coauthor of the *Diagnosis* paper. "A patient may come in who is constipated. Constipation is pretty straightforward in 99 percent of cases." A laxative solves the problem. But infrequently, constipation may be caused by a growing tumor or neurological problem.

Doctors must "be alert to the possibility that what you're seeing may not be routine," says Croskerry. "That's the real trick in being a good diagnostician—keeping an eye on what your intuitive system is doing."

Writing in the *New England Journal of Medicine*, Croskerry described a patient who came to the hospital with stab wounds to his arm, back, and chest. After ascertaining that the wound to his back did not penetrate the chest cavity, doctors patched him up and sent him home. Five days later, the man went to another hospital in the area complaining of vomiting and blurred vision. A CT scan revealed a knife wound several inches into his brain.

"Anchoring bias" led the resident to focus on the most obvious injuries, to the exclusion of the head wound. "Even though you think you may be being vigilant and careful, you can still get caught on these biases," says Croskerry.

Scientists have written about biases for 40 years, but medicine has largely overlooked the research because it is so intangible (see sidebar, page 27).

"It's something that goes on between the physician's ears," says Croskerry. "Anybody observing my behavior from the outside

The human brain is wired to believe we're correct. Being right and being wrong feel exactly the same until someone tells you you're wrong.

– Andrew Olson, M.D.

doesn't really know what my brain was going through when I made that decision. But cognitive scientists do. And medicine really hasn't embraced cognitive science and asked questions about how we think."

BETTER STRATEGIES

Olson agrees that cognitive shortcuts lead to errors, but he questions whether simple awareness will lead to dramatic improvements.

"Maybe that is the problem, but addressing it might not be the solution," he says. "I think what we're all working on now is what strategies may be helpful to avoid some of those cognitive errors? We all know the worst strategy in the whole world is to 'try harder.'"

What might work?

Developing skills in "reflective practice" is one possible strategy, says Olson. Making a grid of possible diagnoses—"What's for it? What's against it?"—can force a physician to reason more deliberately.

Another is feedback. "The way training is now, a student or resident admits a patient at night, they go home, they don't find out what happened to that patient. So they think they're right. The human brain is wired to believe we're correct. Being right and being wrong feel exactly the same until someone tells you you're wrong," says Olson. The Medical School participated in a recent study with six institutions to bring feedback into training programs. "We found that the diagnosis changed about 40 percent of the time—a lot."

Doctors should also be willing to admit they don't know. Pressure to diagnose leads to "premature closure" and can stymie further inquiry, says Olson. "I think a lot of the reason we label stuff early on is because we are uncomfortable saying, 'I don't know, but I'll be with you.' That's probably one of the most important things that we can do as clinicians."

Teamwork can improve diagnosis as well. Medical teams, which are often hierarchical, can learn from aviation. Air crews, from pilots to copilots to flight attendants, speak up if something doesn't seem right.

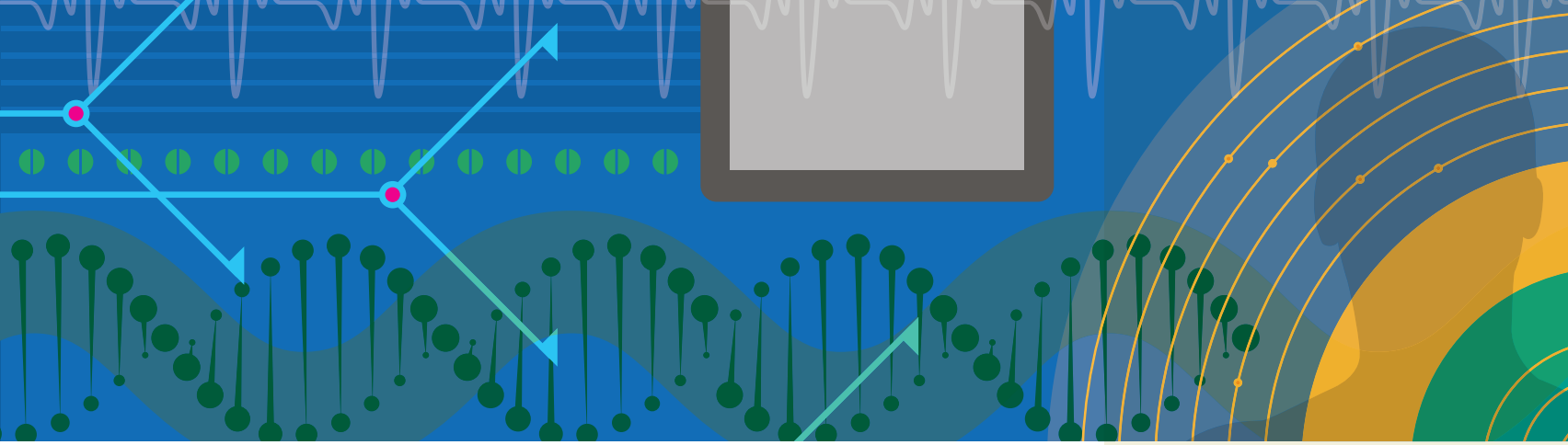
WOVEN INTO THE CURRICULUM

A more systematic approach to teaching diagnosis has been creeping into medical school curricula as practitioners and faculty realize the shortcomings of learning diagnosis strictly by doing.

"The notion even that there was a science around clinical diagnosis is a relatively new concept," says Robert Englander, M.D., associate dean for undergraduate medical education. "It's moving from an implicit approach to an explicit approach around clinical reasoning. Only in the last 10 to 15 years has there been an exploding focus on patient safety and quality. The attention to clinical diagnostic reasoning has sprung out of that movement."

To help students develop these skills, the Medical School weaves in lessons in diagnostic thinking right from the start and throughout the undergraduate and graduate experiences, says Englander.

A course called Foundations in Clinical Thinking spans the first two years of medical school and allows students to work with clinical problems and generate differential diagnoses. At the Medical School's Duluth



campus, a problem-based learning thread during the first two years helps students think about diagnosis.

There's also a greater emphasis on teamwork, Englander says. Students are engaged in collaboration with students in nursing, pharmacy, dentistry, and public health.

In Olson's Advanced Physical Diagnosis course, fourth-year students study research literature to evaluate aspects of physical examination that are most useful in making diagnoses. Erica Levine, M.D., an internal medicine resident, says the course developed her physical examination skills and ability to evaluate evidence-based medicine.

"We definitely looked a lot at uncovering some myths the medical community holds true," says Levine. "We focused a lot on the data behind different findings."

"I think the main takeaway is to think critically, because that separates doctors from computers," adds Gretchen Colbenson, M.D., who also took the class. "One of my biggest takeaways is that diagnoses are much grayer than anyone would tend to believe before any medical training."

The Medical School is looking for better tests to gauge how well students and residents are learning. Multiple-choice exams are "a pretty bad indicator of diagnostic ability," Olson says. "We need to move to something called a workplace-based assessment, which is our ability to actually assess a learner's ability to do something in a real-world environment with real-world patients. A lot of that is focused on the process they use."

Olson is particularly proud of the pediatrics residency program, which pairs resident doctors with role-playing patients in ambiguous situations. Residents explain the diagnostic process to patients and discuss why a diagnosis may have to wait. Additionally, faculty discuss errors they have made in diagnosis, "which is really a powerful thing to hear," he says.

To minimize such errors, the Medical School will continue to hone its curriculum aimed at strengthening diagnostic skills, develop assessment tools to gauge students' abilities, and conduct research to determine how well students are learning.

"There is no one answer and there are no easy answers," says Olson. "If there was an easy answer, we would have found it already." MB

Greg Breining is a journalist and author based in St. Paul, Minnesota.

WHAT IS BIAS?

Bias influences how and why we make decisions—and it's no different for doctors. According to a report by Pat Croskerry, M.D., in *Academic Medicine*, common cognitive biases that affect physicians' diagnoses include:

- **Availability bias**, which occurs when recent similar examples (immediately available in the physician's memory) unduly influence a decision about a current patient's diagnosis.
- **Gambler's fallacy**, which is the opposite of availability bias and occurs when a physician doubts the current patient's diagnosis based on similar diagnoses of other patients, i.e., gambles that the trend will not continue.
- **Confirmation bias**, which occurs when a physician forms an early opinion about a patient's diagnosis and consequently looks for and favors evidence that confirms that diagnosis.
- **Anchoring bias**, which occurs when a physician locks on to particular symptoms and signs in a patient's initial presentation and fails to adjust that initial impression as new data become available.

A storybook solution

Alumnus promotes health equity by making books a standard feature of pediatric care

PHOTO: BRADY WILLETTE

ONCE UPON A TIME, there was a bow-tie-clad doctor who believed deeply in the power of books to give babies, toddlers, and preschoolers their best chance in life. That doctor's devotion to early childhood literacy steadily grew, and soon led him to advocate for equity and justice for all.

His snappy wardrobe—the colorful bow ties "are part of my look, and they're also clinically better than neckties" (studies show that neckties harbor germs)—and his apparently boundless energy make Nathan Chomilo, M.D., seem a bit like a storybook character himself. The Park Nicollet pediatrician and internal medicine hospitalist serves as medical director for Reach Out and Read (ROR) Minnesota, which incorporates books and reading into pediatric care, and is a go-to source for media on the vital importance of early childhood literacy.

THE POWER OF EARLY READING

An alumnus of the University of Minnesota Medical School (Class of '09), Chomilo was appointed to the Governor's Early Learning Council in 2016, is active in the Minnesota chapter of the American Academy of Pediatrics (including serving as an AAP Early Childhood Champion), and is cofounder and vice president of Minnesota Doctors for Health Equity. Those activities reflect his keen interest in social determinants of health—the conditions into which people are born, grow, work, and age, and which largely account for health inequities. Reading, he says, is a proven way to influence the trajectory of a child's life.

Chomilo's involvement with ROR Minnesota began in 2009 when he was in the second week of his internship and ROR's then-medical director, Laurel Wills, M.D., came to speak at a lunchtime lecture he attended.

"She talked about this simple intervention done during pediatric well-child checks, where the doctor talks about the importance of books and gives a book that's appropriate for that child's age and developmental stage," recalls Chomilo.

The participating physician also gives parents tips for making story time more engaging and interactive, such as emphasizing rhyming or, for older children, asking open-ended questions. The "how" is important and it varies by age, he says. "And there's evidence behind it—this isn't just a feel-good thing."

The program capitalizes on a critical window of brain development—during a child's first three years—and the unique physician-patient relationship to give kids a foundation for success. Chomilo was captivated; after the lecture, he asked how he could get involved. Today, he is the state chapter's medical director.

Evidence of the program's impact continues to mount: families served by ROR are 2.5 times more likely to enjoy reading together or have books in the home, and their children's language development advances by three to six months on average, according to data from the national organization. One study published in *Clinical Pediatrics* found that participating toddlers scored higher in receptive and expressive vocabulary, regardless of parental education, parental language proficiency, or foreign-born status.

THE READ-ALOUD HABIT

Today, one in three children in Minnesota between 6 months and 5 years attends a clinic that participates in Reach Out and Read (ROR). Two-thirds of those children live in the Twin Cities metro area. "My goal, and ROR's goal, is to make this the standard of care for pediatrics in all of Minnesota," says Nathan Chomilo, M.D., medical director of the Minnesota chapter. Because about 90 percent of children will be seen at least once by a pediatrician in the first year of life, he says, doctors have the chance to help families set the read-aloud habit early on.

Poverty, racism, discrimination, those are all stressors. But there are also experiences that buffer that. The time that you feel safe and loved with a trusted adult is one way to buffer against that toxic stress.

– Nathan Chomilo, M.D.

OFFSETTING STRESSORS

That's a big deal, Chomilo explains, because low literacy is linked to poverty, substance abuse, and crime later in life. And reading together as a family also has been shown to increase parents' confidence in their parenting abilities – and help offset anxiety for both child and parent.

"Poverty, racism, discrimination, those are all stressors," Chomilo says. "But there are also experiences that buffer that. The time that you feel safe and loved with a trusted adult is one way to buffer against that toxic stress.

"This is why I wanted to become a doctor, to help improve my community," he says.

ROR is one promising, relatively low-cost path to decreasing the state's vast racial disparities – what Chomilo calls "gaps in opportunity" – but it requires buy-in from doctors and policymakers, Chomilo says. Physicians, already squeezed to do more in less time, sometimes hesitate to add ROR to their practices. "But almost universally, they find that it just fits seamlessly with their visits."

Speaking of time, the self-described "citizen-physician" appears to manage it well. Besides his many other roles, Chomilo finds time to spend with family, serve as an adjunct assistant professor at the U of M Medical School, play adult league soccer, attend Vikings games, travel, and devour comic books. "I'm a big comic book nerd," he admits.

Not surprisingly, reading is a favorite pastime for the whole family. Chomilo's 2-year-old son, Nchare, is currently into *Please, Baby, Please* by Spike Lee and a picture book about trucks. "One of my proudest moments in the past year was when he was around 16 months, he went to the bookshelf, grabbed a book and brought it to me," says the friendly doctor, as a broad smile appears just above his bow tie. M|B

By Susan Maas, a Minneapolis writer and editor and a regular contributor to the *Medical Bulletin*

PHOTO: LYNDSAY STEVENS

Jack Weston and his daughter, first-year medical student Julia Weston, enjoyed Family Weekend festivities last fall.

Family Weekend (second annual!): August 22–23

The Medical School invites students' parents and other family members to attend a series of informative and entertaining events August 22–23 during Family Weekend. It's a great time for families to connect with their students in their new surroundings at the Medical School while hearing from faculty members and exploring the Twin Cities campus. The event culminates in the White Coat Ceremony, during which new students receive their first white coats, at 2 p.m. Friday, August 23, in Northrop Auditorium. M|B

To learn more about Family Weekend, visit med.umn.edu/family-day. To find out more about the White Coat Ceremony, contact Rachel Rudeen at rude0105@umn.edu or 612-626-4519.

CELEBRATING 50 YEARS OF FAMILY MEDICINE

Join us on Friday, October 11, as we celebrate the 50th anniversary of the Department of Family Medicine and Community Health. M|B

Visit z.umn.edu/FMCH50 for more information.

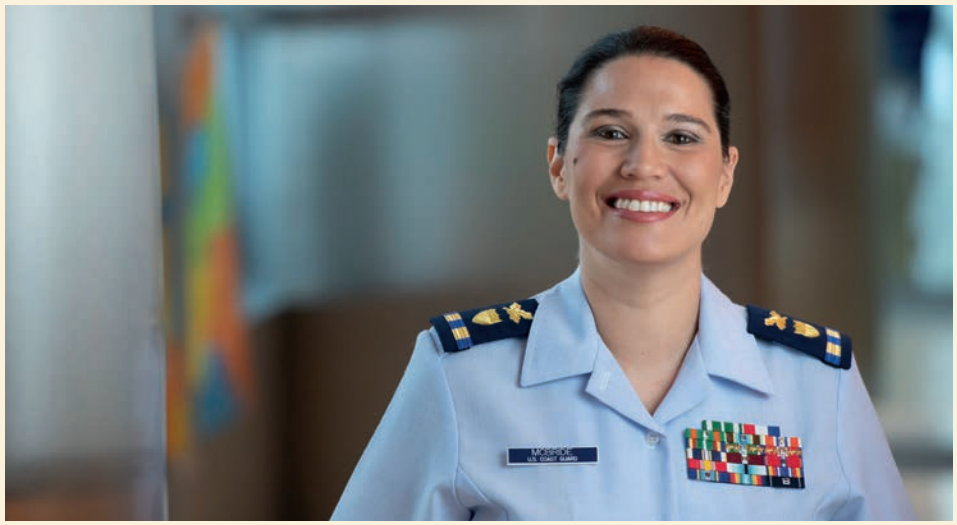


PHOTO: SCOTT STREBLE

Charting her own course

TERRI McBRIDE GREW UP in San Antonio, Texas, but she always dreamed of traveling the world. So in 1999, after joining the U.S. Coast Guard as an active-duty member, she was excited to accept a post as a boat crewman and watchstander on Long Island in New York.

Her duties were rigorous.

"It was a hard job," McBride recalls. "We cleaned the boats. We sanded and painted the boats. Our 24-hour watch days alternated with 9-to-5 workdays."

Plus, she learned a lot about discipline. In some ways, you might say, it was perfect preparation for the challenges of medical school.

FROM SEA TO SCHOOL

For McBride, joining the Coast Guard was a means to end. She had grown up in a poor community and, after graduating high school, decided to pursue a degree, becoming the first in her family to attend college. But she soon found that balancing her studies with a full-time job was difficult.

"The hours that I needed to work as a waitress to make rent and pay tuition interfered with the time I needed for classes and homework," McBride says.

She quit school and enlisted with the Coast Guard, eventually intending to take advantage of the GI Bill to finance her education. "The Coast Guard sounded attractive to me because their missions are not combat-oriented," McBride says. "They're involved with search and rescue. They help protect the environment. Those things are in line with my values."

She also got to travel the world – visiting Alaska, Mexico, Indonesia, Thailand, and many other places – as part of the job.

In 2009, McBride left active duty and began work on a bachelor's degree in nutrition science/dietetics at San Jose State University in California. She had been trained as a cook during her time in the Coast Guard, but academia introduced her to the science of nutrition – and it fascinated her.

I've always wanted to serve the underserved because of my background. I have a natural empathy toward what some people may consider "hopeless" patients. – Terri McBride

She changed her major to biology and shortly thereafter was recruited into the Maximizing Access to Research Careers (MARC) and Research Training Initiative for Student Enhancement (RISE) programs, which give students from minority backgrounds research experience and mentor them toward careers in research.

Among other things, the program supported her attendance at a science conference where she presented a poster that caught the attention of Casey Dorr, Ph.D., a U of M graduate who is now an assistant professor in the Medical School and a researcher at Hennepin Healthcare Research Institute. That connection ultimately brought McBride to Minnesota for medical school.

SERVING THE UNDERSERVED

And she's still happy about her choice. "The administration has really been reaching out to students, getting feedback, and implementing it," notes McBride, who is now in her third year of medical school. "They've reduced the lecture hours, which sounds like a minor thing, but it's huge for medical students, who can get really burned out.

"I'm also impressed by how open-minded the faculty are as far as things that they incorporate into their curriculum. We've had a curriculum about race and medicine that I thought was very helpful. Faculty have brought in LGBT and transgender community [members], and they talk about things that you wouldn't necessarily think of in the health care setting."

McBride has also benefited from financial support through medical school, including from the Alpha Epsilon Iota Endowment Fund, which supports diversity in the student body.

"Being an independent student, every dollar counts for me," she says. "Especially when I started medical school, I had so much debt just from all the testing fees, tutoring fees, traveling."

McBride still serves in the Coast Guard reserves as a finance and supply chief warrant officer and spends a good portion of her breaks from medical school at the USCG Base Detachment St. Louis. She is currently thinking about a career in forensic psychiatry—a path that often involves working in the legal system with people who have mental illnesses and with other underserved populations.

"I've always wanted to serve the underserved because of my background," she says. "I have a natural empathy toward what some people may consider 'hopeless' patients due to their lack of medical compliance and self-harming behaviors, because I have experienced the same frustrations with many of my family members.

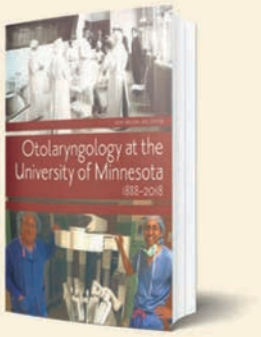
"Looking back, I can see that when people in our family or neighborhood got sick, they didn't get top-notch care because of our financial status. I want to serve those people." M|B

By Joel Hoekstra, a Minneapolis writer and editor

To make a scholarship gift or to learn more, please contact Carrie Albers with the University of Minnesota Foundation at albersc@umn.edu or 612-626-8481.

New book marks ENT's 130 years at the U

A new book, *Otolaryngology at the University of Minnesota: 1888–2018*, chronicles the history of ear, nose, and throat medicine and surgery and celebrates the specialty's 130-year history at the U of M—an anniversary that coincided with the Medical School's founding in the same year.



The book describes the evolution of the specialty and the Department of Otolaryngology–Head and Neck Surgery, highlighting the program's rise to regional and national prominence. It was edited by ENT specialist Kent Wilson, M.D. (a 1966 graduate of the Medical School), with assistance from Robert Maisel, M.D. (1967), and Thomas Christiansen, M.D. (resident alumnus, 1974).

What began as a specialty devoted to the health of eyes, ears, noses, and throats now includes expertise in facial plastic and reconstructive surgery, pediatric otolaryngology, and neurotology. M|B

Read the book for free online at z.umn.edu/ENThistory or buy the print edition at z.umn.edu/ENTbuy.

Capitol engagement

The University of Minnesota's $87 million biennial budget request to the Legislature this session focuses on attracting and keeping the best faculty, improving equipment in research facilities, and supporting U of M outreach across the state.

Topping the list is a requested $28 million state investment in the Institute of Child Development, built on the Twin Cities campus in 1913. The $42 million bonding plan, which calls for the U to contribute $14 million, will turn the building into a modern research and training hub for this top-ranked program.

To maintain its 29 million square feet of physical space, the University has requested an additional $200 million for asset repair and renovation. These "HEAPR" funds allow for system-wide updates to improve campus safety, accessibility, and energy efficiency.

With a new governor in place and the launch of a new budget cycle, the University needs your help. Advocacy remains a key component of our support: advocacy contacts made to elected officials in 2018 increased by 94 percent over the previous year. Clearly, our elected officials are hearing from you about the importance of the University to Minnesota. M|B

Please remain engaged and, if you haven't done so already, join UMN Advocates at advocates.umn.edu/join.

A century of discovery

SCIENCE FICTION AUTHOR Isaac Asimov once wrote, "Everything about microscopic life is terribly upsetting. How can things so small be so important?"

But "important" is almost too timid a word to describe the powerful microbes responsible for some of humankind's most devastating diseases—tuberculosis, diphtheria, influenza, polio, HIV/AIDS, and staph and fungal infections, to name just a few.

Since the University of Minnesota's Department of Microbiology and Immunology was established in 1918–1919, scientists there—and in other departments, too—have contributed mightily to the world's store of knowledge about the bacteria, fungi, and viruses that teem within and on humans, animals, and plants. In fact, the American Society for Microbiology recently recognized the University for its accomplishments over the past century with a prestigious "Milestones in Microbiology" award.

Many talented individuals across the University have contributed seminal discoveries over the past 100 years. Here are a few standouts:

- Arthur T. Henrici, M.D. (1889–1943), called "America's bacteriologist" in his day, did pioneering work on bacterial growth and structure, and provided one of the earliest descriptions of the biofilms that play key roles in dental plaques, infectious diseases, and antibiotic resistance.
- Robert G. Green, M.D. (1895–1947), is credited with saving the Midwest fur industry through his studies of viral infections in silver fox and mink, and for discovering the first adenovirus, canine hepatitis virus, and the vaccine that protected dogs and foxes from it.
- Robert A. Good, M.D. (1922–2003), helped lay the foundation for the first successful human bone marrow transplant, performed at the U of M in 1968.
- Lewis W. Wannamaker, M.D. (1923–1983), developed the strategies to prevent rheumatic fever and kidney disease following a strep infection that remain the standard of care today.
- Dennis W. Watson, Ph.D. (1914–2008), developed the anthrax vaccine used to protect soldiers in World War II, and was the first to identify the toxic component of Gram-negative bacteria, which can cause fever, diarrhea, and toxic shock.
- Martin Dworkin, Ph.D. (1927–2014), a pioneer in understanding how multicellular bacteria communicate and behave together, was among the first to apply mathematics modeling to microbial research.

Current department chair and Regents Professor Ashley Haase, M.D., two-time recipient of a National Institutes of Health MERIT Award for his work on HIV/AIDS, praises what he calls "a history of faculty excellence" in a department designed to teach students at every level, from undergrads to medical and graduate students.

Now at home in a new building in the U's Biomedical Discovery District, the department prepares students to take on the 21st century's greatest infectious diseases.

"Our rich, distinguished past has prepared us well to work on the great killers of our time," says Haase, "including HIV/AIDS, TB, antibiotic resistance, and influenza." MB

PHOTO: COURTESY OF THE CENTER FOR THE HISTORY OF MICROBIOLOGY/ASM ARCHIVES

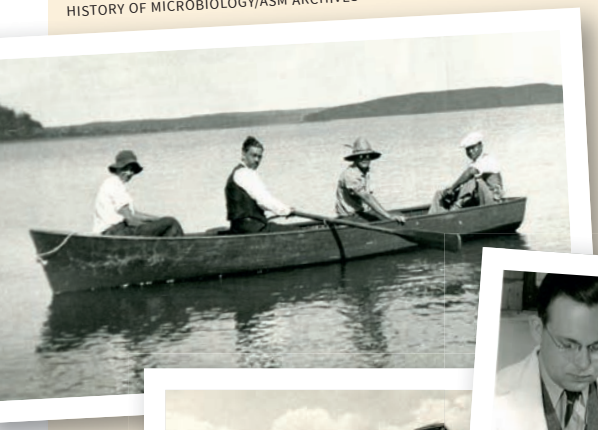


PHOTO: UNIVERSITY ARCHIVES

PHOTO: UNIVERSITY ARCHIVES

CLOCKWISE, FROM TOP LEFT
Arthur T. Henrici, M.D. (third from left), and students take samples from Lake Alexander to study the bacterial ecology of lakes in 1932.

Virologist Robert G. Green, M.D., in his lab circa 1940.

The department found its first home in Millard Hall.

A CENTENNIAL CELEBRATION

JULY 19, 2019

100 years MICROBIOLOGY & IMMUNOLOGY MEDICAL SCHOOL

Join us for a research symposium, luncheon, "Milestones in Microbiology" presentation, and celebratory dinner.

McNAMARA ALUMNI CENTER

Learn more at z.umn.edu/microbiology100.

A quality stethoscope for $5?

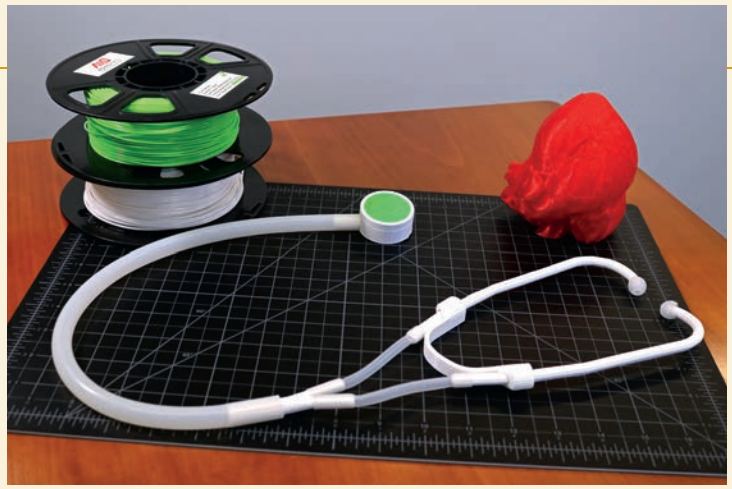


PHOTO: ALLISON THOMPSON

Research teams have 3D-printed functional stethoscopes comparable to the Littmann Cardiology III for a small fraction of the price.

If it seems like 3D printing is everywhere these days, that's because it is. And it's good for more than simple modeling, as the U's Bio-Medical Library Makerspace is demonstrating.

Last year *PLOS One* published an article by researchers who 3D-printed a functional, low-cost stethoscope. The research team says their 3D-printed stethoscope was comparable to the Littmann Cardiology III—which retails for about $100 and was the industry standard until the newest model was introduced in 2016—and can be made for about $5.

They designed the stethoscope components using open-source computer-aided design tools and made all the project files—from the original models to the printable parts to sound files used to test the stethoscope—freely available via a GitHub repository. The effort was part of a larger research project to design open, printable, and validated devices, including otoscopes, tourniquets, and pulse oximeters.

Parts for the stethoscope were printed at Makerspace using an Original Prusa i3 Mk3 printer. The stethoscope took about four hours to print and used 57 grams of PLA plastic that cost $1.72. The nonprinted parts (earbuds, silicone tubes, and a thin plastic sheet) were all generally inexpensive and easily found. Assembly took less than 15 minutes.

"Some of the greatest challenges in health care today are access and affordability. Our students (and future physicians) need to learn to think critically and creatively, question assumptions, and find new solutions," says Jonathan Koffel, a member of the U Libraries team that 3D-printed and assembled a stethoscope. "This is a great example of taking an iconic tool and using off-the-shelf technology to make an on-demand version that gives most of the functionality at a small fraction of the price."

The plans are freely available online and could be especially useful in resource-poor settings, Koffel adds. MB

WEB EXTRA

Find the printing instructions at z.umn.edu/stethoscope.

Henry Buchwald, M.D., Ph.D.

ACS HONORS U SURGEON

Henry Buchwald, M.D., Ph.D., a longtime professor in the Department of Surgery and a Class of 1966 resident alumnus, will be honored in June with the 2019 Jacobson Innovation Award for his groundbreaking work in metabolic/bariatric surgery.

The award, bestowed by the American College of Surgeons (ACS), honors physicians who have developed field-changing surgical advances. Buchwald is renowned for his surgical innovations, including the introduction of the partial ileal bypass procedure to treat hyperlipidemia, or high cholesterol levels.

An accomplished researcher, Buchwald in 1973 received the largest National Institutes of Health multicenter grant at the time, which funded a long-term study that proved a link between high cholesterol levels and heart disease.

Buchwald is also a professor of biomedical engineering at the University; his work developing implantable medical devices has resulted in 17 patents.

He was the first to hold the Owen H. and Sarah Davidson Wangensteen Chair in Experimental Surgery, and in 2002 he received the Harold S. Diehl Lifetime Achievement Award from the Minnesota Medical Alumni Society.

In 2020, the University of Minnesota Press plans to release a memoir by Buchwald, tentatively titled *A New Way*. The book will explore the life and work of Buchwald's mentor, Owen H. Wangensteen, M.D., Ph.D., the legendary surgeon who chaired the Department of Surgery at the Medical School from 1930 to 1967. MB

Meeting their matches

THE McNAMARA ALUMNI CENTER buzzed with excitement March 15 as 230 University of Minnesota Medical School students anxiously waited for the clock to hit 11 a.m. It was Match Day, a culmination of four years of hard work and determination—and the day they'd find out what's next on their journey to become doctors.

This year, a whopping 52.1 percent of the class matched to primary care residencies—a five-year high for U of M Medical School graduates. Following suit, the most popular specialties were family medicine (20.4 percent), internal medicine (19.1 percent), pediatrics (8.3 percent), and emergency medicine (7.4 percent), followed by psychiatry, obstetrics and gynecology, general surgery, and internal medicine–pediatrics.

More than 43 percent of those who matched will stay in Minnesota residency programs. MB

WEB EXTRA

See more photos from the big event at z.umn.edu/2019matchday.

PHOTOS: JOEL MOREHOUSE

LEFT Caitlin Bell celebrates her match in internal medicine at the University of Colorado School of Medicine in Denver.

BOTTOM LEFT Nermine Abdelwahab, here with her mother, Ekram Ahmed, matched to an internal medicine residency at the U of M.

BOTTOM RIGHT Jonathan Roberts and Sarah Kemp pause for a photo op.

Mark your calendars

ALUMNI CELEBRATION: OCTOBER 11–12

Join fellow alumni, faculty, and current students at this year's Alumni Celebration, featuring a full day of tours and Medical School updates. Reunion dinners will be held for the classes of 1959, 1964, 1969, 1979, 1989, 1994, and 2009. Watch for more details in the coming months. To update your contact information, visit med.umn.edu/alumni/stay-connected.

Help make your reunion memorable! The Medical School is seeking alumni to serve on the reunion planning committee or as reunion gift volunteers. MB

To learn more about the Alumni Celebration and opportunities to get involved, please contact Maureen Long at mlong@umn.edu or 612-626-8045.

INVEST IN THE NEXT GENERATION

Help us extend the University of Minnesota Medical School's legacy to the next generation of students by making a reunion gift or pledge in honor of your class.

All gifts and pledges to the Medical School made between January 1 and December 31 by members of your class will count toward your class' scholarship gift total. You can also participate by documenting or updating a planned or estate gift commitment this year. MB

For more information about making a reunion gift, updating your plans, or starting your own scholarship fund, please contact Elsa Scheie at escheie@umn.edu or 612-625-7947. To make a gift online, visit z.umn.edu/reuniongift.

In Memoriam

EDITOR'S NOTE: The *Medical Bulletin* now handles obituaries for Medical School alumni in a new way. We are including simple announcements in print with a link to each person's public obituary notice, when available, online. We provide links to published obituaries because they offer readers the information families have chosen to share to honor their loved ones. Full obituaries can be found at z.umn.edu/memoriam-spring19.

CHARLES V. ALLEN, M.D., Class of 1958, Modesto, Calif., died Jan. 19 at age 85. Dr. Allen practiced internal medicine.

ALAN M. AVRICK, M.D., Class of 1943, La Cañada Flintridge, Calif., died Jan. 12 at age 101. Dr. Avrick specialized in surgery and family medicine.

MALCOLM N. BLUMENTHAL, M.D., Class of 1958, Minneapolis, died Nov. 14 at age 85. Dr. Blumenthal was an allergy and immunology specialist.

JON E. BOLINE, M.D., Class of 1960, Highlands Ranch, Colo., died Sept. 15 at age 82. Dr. Boline was a pathologist.

EUNICE A. DAVIS, M.D., Class of 1954, St. Paul, Minn., died Jan. 28 at age 89. Dr. Davis was a pediatrician.

JAMES H. DOBIS, M.D., Class of 1976, Lake Nebagamon, Wis., died Nov. 30 at age 69. Dr. Dobis practiced family medicine.

RICHARD A. EDLUND, M.D., Class of 1956, Muskegon, Mich., died Jan. 31 at age 88. Dr. Edlund practiced obstetrics and gynecology.

GILBERT H. FRIEDELL, M.D., Class of 1949, Charleston, S.C., died Sept. 23 at age 91. Dr. Friedell was a pathologist.

A. WILLIAM GEHRING, M.D., Class of 1965, Hazen, N.D., died Jan. 15 at age 79. Dr. Gehring was a pathologist.

DANIEL J. HANSON, M.D., Class of 1953, Toledo, Ohio, died Nov. 2 at age 90. Dr. Hanson was a pathologist.

KENNETH G. HENRY, M.D., Class of 1952, Bloomington, Minn., died March 12 at age 98. Dr. Henry practiced family medicine.

DOUGLAS L. HOM, M.D., Class of 1974, Seattle, Wash., died Jan. 25 at age 69. Dr. Hom practiced internal medicine.

LESLIE W. JACOBSON, M.D., Class of 1957, Minneapolis, died Sept. 17 at age 86. Dr. Jacobson was an ophthalmologist.

WAYNE H. JARVIS, M.D., Class of 1982, Duluth, Minn., died Nov. 15, at age 65. Dr. Jarvis was a general surgeon.

LAWRENCE J. KLECATSKY, M.D., Class of 1967, Myrtle Beach, S.C., died Dec. 13 at age 77. Dr. Klecatsky practiced emergency medicine.

LOWELL H. KLEVEN, M.D., Class of 1958, Minneapolis, died Oct. 2 at age 85. Dr. Kleven was an orthopaedic surgeon.

RANDALL A. LAKOSKY, M.D., Class of 1962, Faribault, Minn., died Dec. 30 at age 82. Dr. Lakosky was a psychiatrist.

CHARLES N. MARVIN JR., M.D., Class of 1981, Wayzata, Minn., died Oct. 7 at age 64. Dr. Marvin was a plastic surgeon.

DUANE E. NESS, M.D., Class of 1958, Wadena, Minn., died Nov. 10 at age 91. Dr. Ness practiced family medicine.

S. SCOTT NICHOLAS, M.D., Class of 1961, Minneapolis, died Oct. 17 at age 81. Dr. Nicholas was an allergy and immunology specialist.

WILLIAM F. NUESSLE, M.D., Class of 1946, St. Cloud, Minn., died Dec. 7 at age 94. Dr. Nuessle practiced internal medicine.

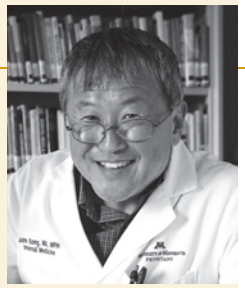
ROBERT J. OLSON, M.D., Class of 1957, Williston, N.D., died Nov. 6 at age 87. Dr. Olson was a radiologist.

WARREN F. OSTLUND JR., M.D., Class of 1968, Oakmont, Pa., died Sept. 26, at age 75. Dr. Ostlund was a radiologist.

JOHN A. PETERSON, M.D., Class of 1957, Rio Verde, Ariz., died Aug. 20 at age 87. Dr. Peterson was an anesthesiologist.

DEAN B. PRATT, M.D., Class of 1963, Elkhart Lake, Wis., died Oct. 29 at age 80. Dr. Pratt was a general surgeon.

GEORGE E. REISDORF, M.D., Class of 1960, Inverness, Fla., died Jan. 11 at age 83. Dr. Reisdorf was an orthopaedic surgeon.



JOHN SONG, M.D., an associate professor in the Center for Bioethics and in the Medical School's Division of General Internal Medicine, died Feb. 27 in Minneapolis. Dr. Song was a talented teacher, researcher, and clinician who was dedicated to health justice and equity and passionate about addressing the needs of disadvantaged people. He founded the Phillips Neighborhood Clinic in Minneapolis, a free clinic staffed by volunteers and students that serves those without insurance.

Read more at z.umn.edu/johnsong.

BRIAN D. SAINE, M.D., Class of 1967, Granger, Ind., died Jan. 16 at age 76. Dr. Saine was an otolaryngologist.

JOHN M. SCANLAN, M.D., Class of 1963, St. Paul, Minn., died Oct. 26 at age 81. Dr. Scanlan was a psychiatrist.

MONICA A. SHERIDAN, M.D., Class of 1983, Walnut Creek, Calif., died Nov. 24 at age 66. Dr. Sheridan specialized in physical medicine and rehabilitation.

JOSEPH L. SPRAFKA, M.D., Class of 1945, St. Paul, Minn., died Oct. 14 at age 96. Dr. Sprafka was a surgeon.

ANTON F. SPRAITZ JR., M.D., Class of 1957, St. Paul, Minn., died Sept. 16 at age 87. Dr. Spraitz practiced obstetrics and gynecology.

BARBARA H. SUBAK, M.D., Class of 1955, Minneapolis, died Oct. 29 at age 92. Dr. Subak practiced family medicine.

FRANK A. UBEL JR., M.D., Class of 1946, St. Paul, Minn., died Jan. 9 at age 94. Dr. Ubel specialized in internal medicine and occupational medicine.

DAVID A. VAN BOCKEL, M.D., Class of 1972, Louisville, Ky., died Dec. 2 at age 71. Dr. Van Bockel was an anesthesiologist.

STANLEY C. VON DRASHEK, M.D., Class of 1947, Rio Verde, Ariz., died Dec. 19 at age 93. Dr. Von Drashek was a radiologist.

JEFFREY C. YUE, M.D., Class of 1986, Medina, Minn., died Jan. 10 at age 59. Dr. Yue was an anesthesiologist.

Still pushing the limits

Center for Magnetic Resonance Research director reflects on four decades of advancements

IN DECEMBER 2017, Kamil Ugurbil, Ph.D., and his team at the University of Minnesota's Center for Magnetic Resonance Research (CMRR) produced the world's first MRI of the human body at 10.5 Tesla – a magnetic field strength 3.5 to 10 times greater than today's standard clinical MRIs.

In the early years of MRI, four decades ago, magnetic fields higher than approximately 0.25 Tesla were thought to be difficult and suboptimal. Even when 1.5 Tesla was proven feasible, many scientists thought the technology would top out there.

Not Ugurbil, who in May will receive the 2019 Institute of Electrical and Electronics Engineers Medal for Innovations in Healthcare Technology for his groundbreaking imaging research. We caught up with Ugurbil recently and asked him to reflect on the advancements he's seen – and pioneered – over the years.

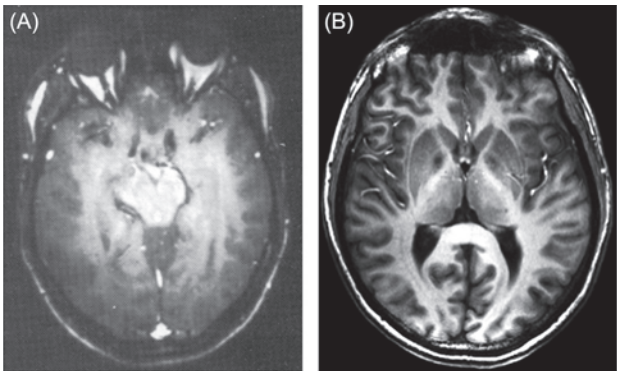


IMAGE: COURTESY OF KAMIL UGURBIL, PH.D.

Proof that scientists can make the difference: These are early 4 Tesla MR images taken by the manufacturer, at left, and the CMRR, at right.

MB: What made you think that high-field human imaging was possible when others said it wasn't?

UGURBIL: Before I came to academia, I worked at Bell Labs in New Jersey, where we pioneered the use of nuclear magnetic resonance to study metabolism inside a living cell, demonstrating the ability to detect metabolites in vivo for the first time. We used very high magnetic fields, albeit in small samples, with magnets typically used by chemists and biochemists. But we were always thinking, "Wouldn't it be nice to develop this technology to apply to humans?"

Difficulties predicted for human imaging were based on simulations and theoretical considerations that were not experimentally proven. Magnetic resonance techniques are extremely dynamic, extremely versatile. There was no reason to think that someday we wouldn't be able to apply them to humans.

MB: Tell us about your first foray into human high-field imaging.

UGURBIL: We were lucky that, in the mid-1980s, the U was looking to invest in some new areas and solicited ideas from the faculty, analogous to what the Medical Discovery Teams program [a state-funded Medical School initiative] looks like today. We applied for and got that funding. That's how we got the 4 Tesla scanner.

CMRR Milestones

1982
Kamil Ugurbil, Ph.D., arrives at the University of Minnesota and starts his laboratory (initially located on Lake Minnetonka) focused on using magnetic resonance technology that would eventually evolve into the Center for Magnetic Resonance Research (CMRR) on the Twin Cities campus.

1990
CMRR produces the world's first high-contrast, high-resolution images of the human brain at high magnetic fields (4 Tesla and above).

1992
CMRR introduces functional brain imaging for the first time, together with independent and concurrent work by investigators from Massachusetts General Hospital, showing neuronal activity in the human brain.

1998
CMRR is first in the world to demonstrate that breast tumors can be detected through high-field magnetic resonance imaging and spectroscopy.

1998
CMRR moves to its new home, a 36,000-square-foot facility in the University's then-new Biomedical Discovery District.

The Center for Magnetic Resonance Research's first 4 Tesla scanner now only functions as art in the building's courtyard. "That's the magnet that started this whole endeavor," says longtime director Kamil Ugurbil, Ph.D.

PHOTO: SCOTT STREBLE

Before the magnet came to Minnesota, Michael Garwood, Ph.D., from CMRR already showed that, contrary to expectations, one can get excellent anatomical images of the human brain at 4 Tesla.

After the system arrived in Minnesota, the first thing we attempted was functional brain imaging, which was successful. That was not only one of the first applications of human imaging on the 4 Tesla magnetic field, but also a new discovery—one that could actually image brain activity. This was a major development, a revolution.

MB: Then you started working on the 7 Tesla technology, which you literally built from the ground up.

UGURBIL: Today, the 7 Tesla is an instrument you can buy. It wasn't when we started. We were the first in the world to put it together. The 7 Tesla is now FDA-approved for clinical diagnosis and is really the most advanced platform for human imaging that exists.

MB: Which of the CMRR's achievements are you most proud of?

UGURBIL: Generally speaking, we are very proud of our efforts to push to higher magnetic fields. We developed the understanding of the physics of imaging at high fields and the physics of functional imaging, which is intricately linked to magnetic field strength. We developed technologies to overcome difficulties at high fields. We introduced 7 Tesla, and finally, today, we are at 10.5 Tesla. We developed the whole field, essentially.

We used to be the only ones doing this type of research. Today it's a burgeoning research area.

So a lot to be proud of, I guess! It's a good way to start my day, talking about this! MB

Interview by Nicole Endres

HOW MRI WORKS

A powerful magnetic field and radio waves generate signals from hydrogen atoms in the body. Those signals are detected by a radio antenna and then translated by a computer into clear, 3D images of the scanned area.

WEB EXTRA

View more brain images from the CMRR's 7T scanners at z.umn.edu/7T.

1999

CMRR experts introduce the 7 Tesla MRI scanner they developed for human studies.

2009

16.4 Tesla scanner arrives at the U for animal studies.

2009

CMRR is named a coleader of the National Institutes of Health's Human Connectome Project (HCP), the most ambitious brain imaging study conducted to date; CMRR develops all image acquisition and reconstruction techniques employed in the HCP and its subsequent follow-up grants.

2010

CMRR expands to 75,000 square feet, providing researchers and physicians with new space.

2013

The 110-ton 10.5 Tesla magnet arrives at the CMRR.

2013

BRAIN Initiative launches, with many studies using imaging expertise developed at the CMRR.

2017

CMRR produces the first-ever 10.5 Tesla image of the human body.

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