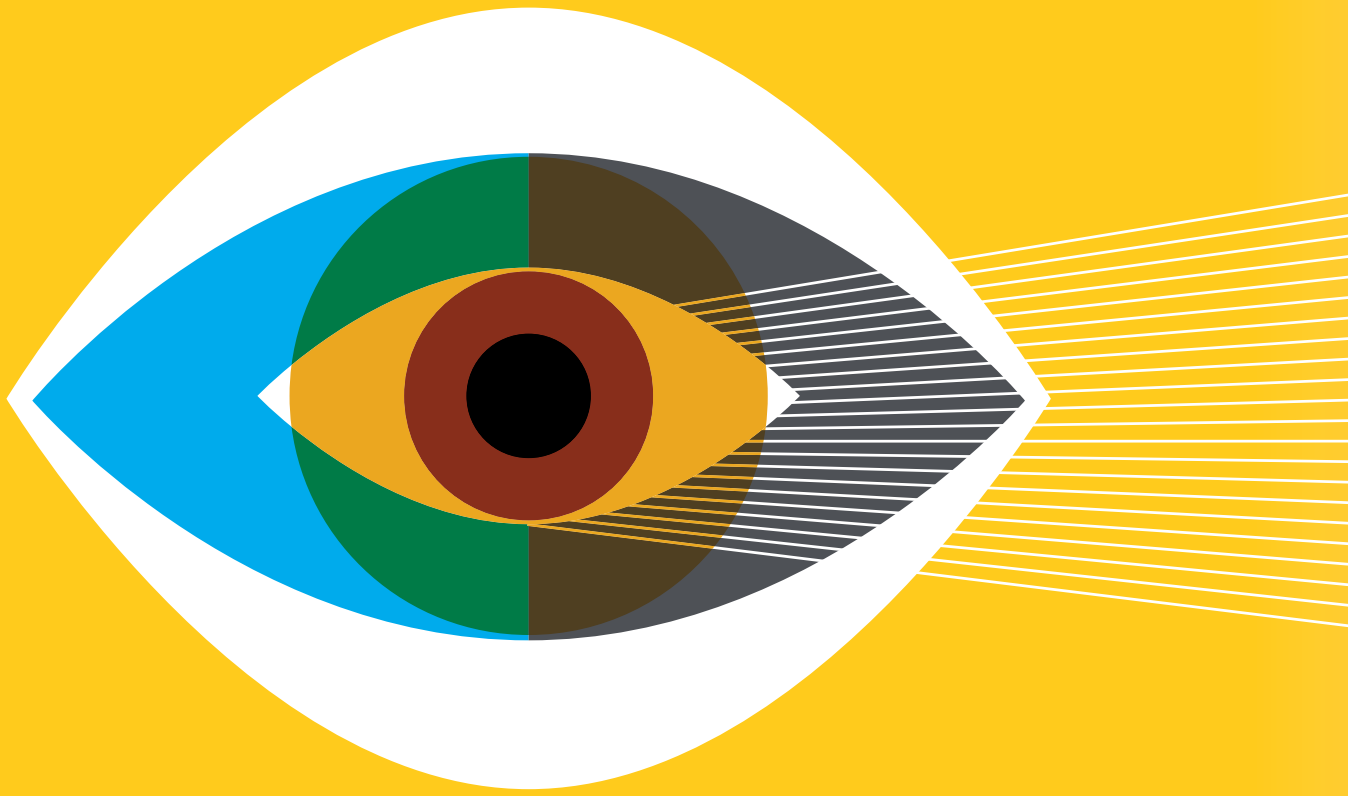


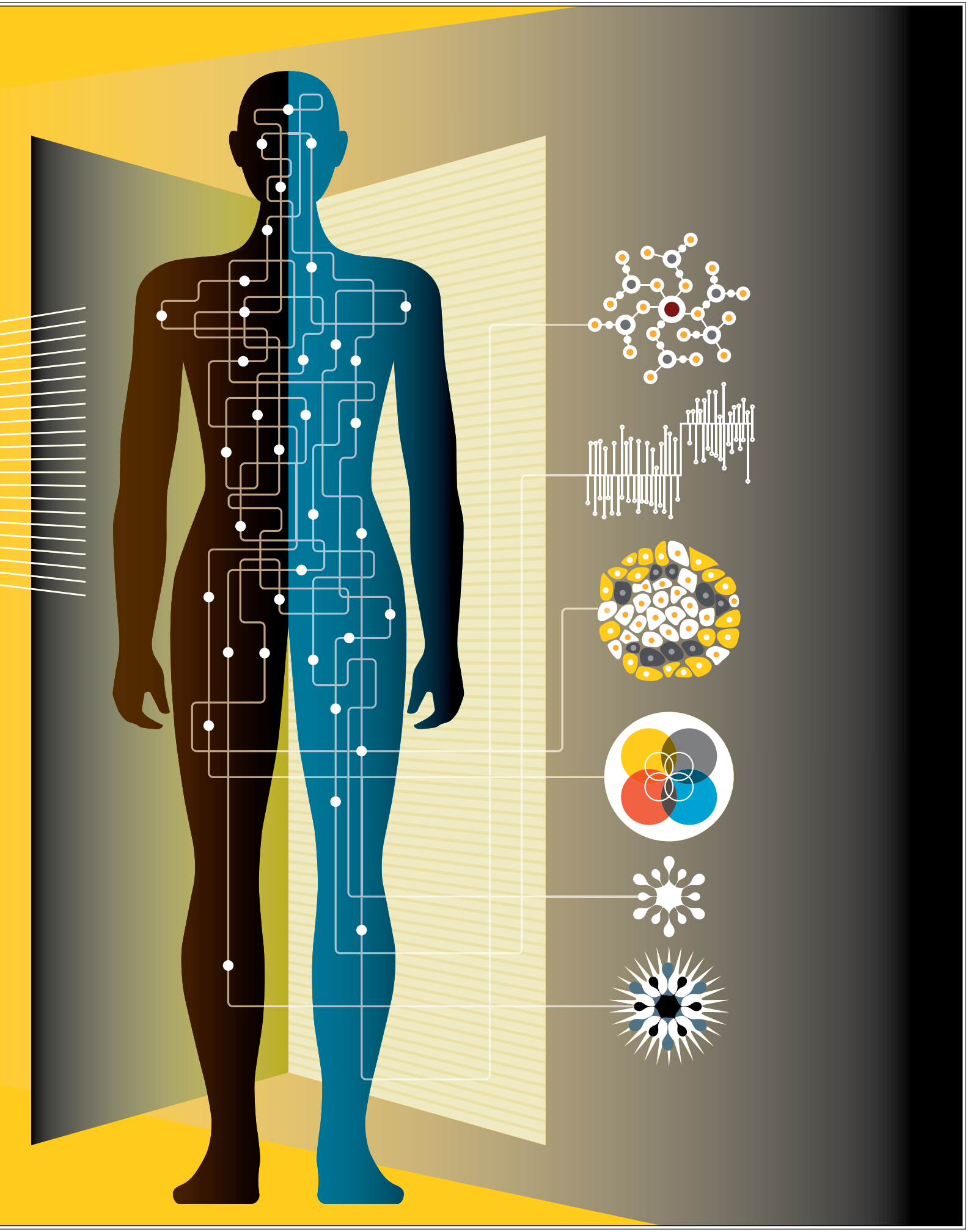
DIAGNOSE THIS

A HEALTH-CARE REVOLUTION IN THE MAKING

Imagine it's the future. Imagine your future self rolling out of bed in the morning and heading for the bathroom. Your smart toilet is an older model and you are thinking of getting a new one. • Sure, the old toilet can do a basic urinalysis, picking up indicators of incipient diabetes or infection. And it can alert you to blood in your stool, a potential sign of colon cancer, just as quickly as you can flush and squint at the readout. Your special test-strip toilet tissue — "*Accurate yet Soft!*" — gives you a green thumbs-up on 30 different daily diagnostics. And the toilet reports that your gut microbiome is up to snuff.

BY JENNIE DUSHECK

ILLUSTRATION BY PAUL WEARING



But your model doesn't test for any of the dozen healthful new gut bacteria discovered among African San hunter-gatherers.

You took the San+™ probiotic capsules; have the microbes colonized your gut yet?

What really has you lusting for a new toilet, though, is the lack of data-share options for your old toilet. Honestly, your doctor and one emergency contact? That's it? Who's going to help you make sense of all this information? What about GloMM, the global health record data bank founded in 2021 that stores and shares all your mobile and other health data? What about your two dating sites? A lot of potential partners expect to know how healthy you are. Not to mention SocialWell, which will match the government's $3,000 rebate if you get a new smart toilet before the end of the year.

'THE FUTURE IS ALL ABOUT BEING ABLE TO INTERCEPT DISEASES EARLY AND, IDEALLY, PREVENT THEM. IF WE CAN ACTUALLY DO SOMETHING ABOUT A DISEASE SUCH AS AN AGGRESSIVE CANCER, THEN IT IS WORTH MONITORING FOR IT.'

Back in the present, we are talking with Sanjiv Sam Gambhir, MD, PhD, who's working to translate such a scenario — or one a little like it — into reality. Gambhir, chair of Stanford's Radiology Department and director of the Canary Center at Stanford for Cancer Early Detection, envisions a future where we nearly continuously monitor our health. The resulting data might tell each of us or our health-care team, right away, if something is amiss. Are we developing tiny aggressive tumors? A slight tremor suggestive of the onset of a neurodegenerative disease? Or organ-damaging high blood pressure?

Current diagnostics, says Gambhir, are so intermittent, it's like trying to watch a movie but seeing it only every 20 to 30 minutes for a few seconds each time until near the end of the movie when you get to watch it for a few minutes. Inevitably, we'll miss critical parts of the story.

In general, diagnostics have been underappreciated. According to a 2015 National Academy of Medicine report, "The delivery of health care has proceeded for decades with a blind spot: Diagnostic errors — inaccurate or delayed diagnoses — persist throughout all settings of care and continue to harm an unacceptable number of patients." Gambhir is one of the few who recognize how systemic the problem is, how colossal the challenge, and who want to change things.

The underpinnings of a greater emphasis on diagnostics will be devices that can monitor health at all times. Radiology lecturer Seung-min Park, PhD, who works in the Gambhir lab, is helping to lay the foundation for Gambhir's diagnostic vision. If you want to continuously monitor the body, says Park, you can't do that with anything like surgery, blood draws or X-ray imaging. No one would put up with that.

It is clear, Park says, that the perfect sources of diagnostic information are the molecular contents of sweat, saliva, urine and feces, naturally excreted every day and packed with information. Researchers around the world have realized that these substances can provide clues to our health.

Park is engineering a smart-toilet prototype that can collect urine for testing several times a day. To get the project started, he's using an off-the-shelf commercial test strip that measures 10 factors such as acidity, which can tell you about your risk of kidney stones, and glucose, an indicator of diabetes.

The Gambhir lab is also working on a smart bra designed to continuously image breast tissue. The bra uses a combination of infrared light and sound to image and detect minuscule breast tumors, so they can be removed long before they metastasize. Like the smart toilet, the smart bra is still under development. For now, the lab's engineers are scratching their heads over challenges like how to analyze the nonstop flow of data and where to place the battery.

Cardiologists are already making the vision of continuous monitoring a reality. Information from pacemakers and other devices implanted in the heart can be transmitted automatically through ultralow radio frequencies so that patients can be monitored for signs of crisis.

For example, when an infant was born with a deadly heart arrhythmia, her doctors at Lucile Packard Children's Hospital Stanford implanted a pacemaker and defibrillator in her heart that could report back to her doctors if the defibrillator was activated. At 7 months, the defibrillator began to go off. Although the baby looked fine to her parents, she was in serious trouble. The hospital told the parents to bring the baby in right away, and within a few weeks a heart transplant saved her life.

Gambhir's vision

DIAGNOSTICS HAVE MOVED far beyond old-fashioned X-rays for broken bones. We already live in a world where, if we wanted, we could monitor our health around the clock with a variety of ingenious devices that can potentially help foretell illness.

Wearable and implantable devices can deliver rivers of information that can both help health-care systems

track the health of individuals and help researchers study the effectiveness of treatments or preventive health programs in whole populations. Some people won't want to be monitored all the time, Gambhir acknowledges, but he thinks that for many the desire for the benefits will outweigh their concerns about privacy.

Gambhir compares the future of diagnostic medicine to the approach used to keep the engines of commercial jets spinning smoothly and safely. "Most people have taken a flight on a commercial jet," he says. "You may not know it, but the jet engines on that plane are almost continuously monitored by an engine-health portal that sits at General Electric or Rolls-Royce. Every 30 seconds, each engine on the airplane sends information down to the engine-health portal. Hundreds of sensors built into that jet engine are letting the health portal know if there's a problem with the engine — even in flight. If there's a problem, adjustments to the engine can be made, without the pilots even knowing, still in flight." For more serious problems, a plane can be forced to land. Just as importantly, jet engine engineers have learned when not to intervene and just continue to monitor — to avoid false alarms.

"There is no real equivalent in health care," says Gambhir. "There isn't a continuous monitoring of your health. The future is all about being able to intercept diseases early and, ideally, prevent them. If we can actually do something about a disease such as an aggressive cancer, then it is worth monitoring for it."

Yet when research dollars are doled out, diagnostic tools are often treated as an afterthought, Gambhir says. People don't think of diagnostics as saving lives, but treatment depends heavily on accurate diagnosis — and biomedical research even more so. Expenditures on the field of diagnostics research are not tracked separately, but he estimates that no more than 7 percent of total biomedical research dollars go to diagnostics, with the rest going to discovering ever more treatments.

Gambhir would love to see that ratio reversed, he says, so that the "anticipating and preventing disease" part of Stanford's precision health approach takes priority over endless new treatments.

But he concedes he'd be happy with a 50:50 funding split between diagnostics and therapeutics and anticipates such a transition in the coming years. It makes much more sense, he argues, to put resources into preventing disease or at least diagnosing disease early — when, in many cases, it's easier to treat — than doing nothing until people are quite ill.

But the way biomedical research is funded and the way medicine is practiced are still structured around treatment, not diagnosis. So a diagnostics-first approach would mean major changes.

The structure of medicine

KATHRYN MCDONALD, the executive director of Stanford's Center for Health Policy and the Center for Primary Care and Outcomes Research, concurs with Gambhir that diagnostics are severely understudied, given how important they are. "Our health-care system is organized around what happens once you already know what's wrong, as opposed to figuring out what's wrong," McDonald says.

In 2015, the National Academy of Medicine reported that at least 5 percent of U.S. outpatients experience a diagnostic error, 6 to 17 percent of adverse events in hospitals result from diagnostic errors, and diagnostic errors contribute to 10 percent of all patient deaths.

Yet, despite the importance of diagnostics, they receive minimal funding, says McDonald, who serves on the National Academy of Medicine's Committee on Diagnostic Errors in Health Care. "If you look at the dollars associated with diagnostic testing, it just pales in comparison to dollars spent on pharmaceuticals. And there's a parallel in the research world."

One reason is that diagnostics is primarily a cognitive activity, McDonald says. It's your doctor sitting and thinking, reading, thinking some more, calling a colleague and talking until they figure out what's wrong with you. And there's almost no support for thinking and talking, she says. Physicians and others are compensated for treating patients and, to a lesser extent, for seeing patients, but not for thinking about them.

We need to look for ways to reward that cognitive work and teamwork, says McDonald.

False positives, false negatives and false reassurance

ALTHOUGH DIAGNOSIS may happen through thinking and communicating, diagnostic tests themselves, and how physicians think about them, are susceptible to error. Tests are notorious for generating false positives and false negatives, and the more rare the condition, the easier it is to be misled by such false information.

In the case of a test for blood in the urine, a false positive would indicate there was blood when there wasn't actually blood there. Likewise, a false negative would

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doctor came out of the room and said to Mike with barely veiled hostility, "Is your kid on drugs?" He was implying street drugs like heroin, not the painkillers Macy's doctors were prescribing, although chemically speaking there is almost no difference between the two. Would his reaction have been the same if Macy were white instead of black?

"No," said Mike, without a moment's hesitation. "How do you know?" challenged the doctor.

"I know because I know my daughter, and because we're with her all the time, and because she's not hanging out with other people doing drugs."

"Your daughter is a drug addict," the doctor said. "Don't come back here for pain medicine again."

Mike said nothing. He was without words. He gathered Macy up in his arms and drove her home. When he got her there, she lay on the floor, moaning and crying out.

"Give her some pain pills," he said to his wife and daughter Katherine, who were looking on helplessly.

"They're all gone," said his wife, a pleading look in her eyes. "Dammit," Mike shouted. He wanted to shut his eyes and make it all go away. Then he made a decision.

"That's it," he said, grabbing his car keys. "If those doctors won't help her, I will." Without another word, he left the house and got in his car. He headed back to the old neighborhood, silent tears streaming down his cheeks. He still had some old friends who sold drugs. He would find them and buy some Percocet, or some heroin if he had to. That would stop Macy's pain.

As Mike was driving, a memory from his childhood intruded on his thoughts. He was crouched at the base of the chimney in his childhood home, tracing the outline of the inner brickwork with his chubby fingers, looking for the hole between bricks where the mortar had long ago crumbled away. He felt the divot and shoved his fingers inside, hoping for the crinkle of plastic. He found it. He pinched his fingers to get a hold of the bag and slowly pulled it out.

"Mommy, Mommy," Mike called, "I found one!"

He ran to the kitchen holding the plastic bag in front of him, the little blue and red pills bouncing around inside of it.

His mother was cleaning the kitchen, tired after working one of the many jobs she had over the years — housecleaning, cooking at a local diner, working the line at the Del Monte Cannery, forklift driving. Mike was her fifth child, with a different father than the rest, her child of that no-good drunk she sent away the day Mikey was born, knowing in her heart he wasn't going to be the father her son needed. She dried her hands on her apron and folded the little boy in her arms.

"You found one, so you get a dollar from me," she told him, "just like I promised."

She reached inside her purse and handed him a dollar bill.

"Now you listen to me," she said, kneeling down and looking him in the eye, "I don't want you ever doing those drugs like your brother and sister. It's no good, no good.

"I won't Mama," he said, "I promise. I don't ever want to make you cry."

As if waking from a dream, Mike took the next exit off the freeway, turned the car around, and drove home again. When he got home, he bundled the still crying Macy back into his car and took her to a different hospital emergency room. After hours of waiting, the doctor finally came. Mike turned to him and said, "This is my daughter Macy, and she has terrible pain all over her body which no one can understand. She is also addicted to pain pills, and doctors made her that way, so don't turn your back on her. Don't judge her. Help her."

This new doctor, perhaps humbled by Mike's desperate admission, took Macy in and admitted her to the hospital, using the occasion to get her a treatment plan that included assessment and treatment for addiction, which had never previously been suggested or offered and which is how she eventually ended up with me.

Once in addiction treatment, Macy's problems did not magically disappear, but with time, patience, courage and effort, Macy made her way slowly to a better place, with decreased pain, improved function, a job and plans for the future, which Macy also deserves. **SM**

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FEATURE

Diagnose this

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essentially be a miss; the test result would say there is no blood when in fact there is.

False positives can generate a lot of anxiety for patients and waste healthcare dollars for everyone. But besides the problem of false positives and negatives, McDonald also points out that continuous monitoring could be prone to false reassurance. If you are using a smart toilet or smart bra, she says, you might decide you don't need a regular lab test. But the device could stop working, and you might not know it.

The integration piece

Collecting information about ourselves is only a piece of what gets us to better patient care, says Leslie Saxon,

MD, professor of clinical medicine at the University of Southern California. Saxon heads the USC Center for Body Computing, a major center for the development of diagnostics.

Diagnostics could be information from wearable devices, says Saxon, a member of the small cadre of researchers interested in what diagnostics can contribute to the future of medicine. "But diagnostics is also what patients are telling me, or what their mother or sister are telling me: 'He hasn't gotten out of bed for three days. He's depressed.'" Diagnostics, she says, have to be integrated with everything we know about patients.

For example, information from devices for monitoring heart activity have to be considered in the context of what else we know — whether a patient is taking her prescriptions or how she is using the monitor.

And diagnostics and biomarkers are just a piece of the puzzle, she says. The bigger challenge may be handling that information — processing it, integrating it and sharing it — in a way that helps both patients and researchers.

Not so fast

Peter Schmidt, PhD, senior vice president and chief mission officer at the National Parkinson Foundation, casts a gimlet eye on what he views as overenthusiasm for biomarkers and diagnostics.

It's not that he's against diagnosing people who are ill. But for a variety of reasons, not all diseases are good targets for continuous monitoring, he says. Cancer, for example, is an appropriate target for continuous monitoring because it's typically easy to treat when caught early, difficult or impossible to treat when caught later. But neurodegenerative diseases such as Parkinson's disease are difficult to treat at all, let alone cure, so knowing you have it before you even feel sick could be a negative.

"A human is not a jet engine and we deal with problems in our own way," Schmidt says. He questions the wisdom and ethics of diagnosing people with illnesses when they feel fine and when intervention won't clearly do them any good.

Imagine, he says, that you are 70 years old and have been feeling fine, but a test has just revealed that you have Parkinson's disease. "You aren't actually aware of any symptoms, and then you die a year or two later from a heart attack. Having been told you have Parkinson's disease would have helped you not at all.

"Parkinson's disease can be completely managed for a year or two after diagnosis," Schmidt adds. "During that two-year period, Parkinson's disease is mostly a disease of fear, where people will think, 'Eventually this disease is going to overcome the effects of the medications, and it is already doing something bad to my brain.' That's a scary thing."

Manifold challenges

Diagnostics encompass far more than just figuring out what is wrong with one patient. If medicine moves toward a more preventive model, that will require better diagnostics. Such a future requires support for research on diagnosis and structural support for timely and accurate diagnosis, says McDonald.

"And," she says, "the research is not just about training physicians to do a better job. It's about how the delivery system is supporting them in doing that, how the payment system is supporting them in doing that, how the legal system is supporting them in doing that."

The number of people looking at how the entire health-care system can support diagnostics is, for now, a "small tribe" of people, says McDonald. "This problem matters. It needs attention, and no one is funding the research to build a knowledge base to help you write your article," she says with a smile.

As Gambhir emphasizes, the changes, if they come, could take decades, and the challenges are manifold. At one level, he says, the challenge is in understanding both our biology and the output from all these new devices well enough to know what to do with the information. The biology of early disease is not necessarily the same as that of late disease. Another major challenge, says Saxon, is handling and processing and sharing that information in a way that helps patients. And, as McDonald says, "The current health-care system is shaped more for treatment than for diagnosis, more for action than for thinking."

The smart toilet of the future won't be a stand-alone device, but part of an integrated network of information about you and billions of other people, in a system — of devices, servers, institutions and individuals — that actively prioritizes diagnosis, communication and prevention. Instead of flushing millions of petabytes of data into the sewers each day, we'll wrest from it the seeds of a healthier future. **SM**

— Contact Jennie Dusheck at dusheck@stanford.edu

FEATURE

Hearing things

CONTINUED FROM PAGE 13

world. It works with our senses to give the brain information about where we are in space, whether we are moving, and the direction and rate of our movements. It keeps us from stumbling when we get out of bed in the middle of the night; it maintains balance and spatial orientation and keeps us from falling.

The sensory information about motion, equilibrium and spatial orientation is provided by the vestibular