LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2023

YOUR DISEASE IN CONTEXT

BIG DATA, INDIVIDUALIZED CARE

LITTLE BANG

GREENE SCHOLARS

MEDICINE IN THE DATA ERA

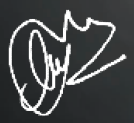
In Rheumatology, we have more bits of information about our patients with chronic diseases than we can manage, without help. Just one visit, for example, generates results of tests and scans, autoantibody profiles, patient-reported symptoms, and findings from the history and physical exam. Multiply that every few months, times many years, and what we get are trajectories. Timelines and graphs of a patient's chronic rheumatic disease over a lifetime. Now – in the case of scleroderma at Johns Hopkins – multiply that by more than 4,000. That's how many patients we have in our Johns Hopkins Scleroderma Center database, some of whom have been treated here for many years. We have similar databases for lupus, Sjögren's, myositis, rheumatoid arthritis, vasculitis, and other rheumatic diseases. Patients each have their own trajectory, but we can learn much more by comparing a single individual's course to the trajectories of many, even thousands, of patients with similar diseases.

We are collaborating with people who are highly expert at making sense of data. We believe this is essential, so that we can truly unleash the power of this data era. And although some people worry that "the machines will take over," that humans have become irrelevant to understanding medicine, disease, managing people, affecting life and death, that AI and machine learning are displacing the human, we believe absolutely that this is not true. In fact, medicine, as the synthesis of biology and spirit, requires the opposite: that both the human as the source of discovery and the human as the target of healing are sacrosanct. That our use of these powerful new data-managing tools augments human capacity, rather than replaces it. That our gifts, our intuition, our values, our empathy, and our dedication to our patients are supported by these tools, but never, ever, replaced.

So that's the background for this data-themed issue. The more information at our disposal, the more precisely we can help our patients. The machines can't tell us what is clinically important; they can't yet take the leaps themselves, though they can enable us to make those connections that involve creativity and intuition. We can use them to harness data, to analyze patterns, so our patients and clinicians can make better decisions together. Our cover story (Page 2) focuses on someone who is not a rheumatologist: Scott Zeger, who is helping our physicians use patterns we can see in the data to provide proactive, personalized care.

If you have a rheumatic disease, you know there are precipitating events: something the body reacts to, which sparks a cycle of autoimmunity. These events are tiny, but dramatic. Brendan Antiochos and J. Sohn, a clinician-scientist and a biophysicist, come from two very different approaches: the macro, the human level, and the micro, the molecular level. Together, they have discovered an event – a "Little Bang" – occurring at the onset of lupus (Page 8).

We are so proud of our young investigators, and are proud to highlight the work of four of them, our Greene Scholars (Page 14). What they are doing, and what our Division of Rheumatology is doing, is truly wonderful, world-class research that continuously improves our knowledge and ability to care for our patients.



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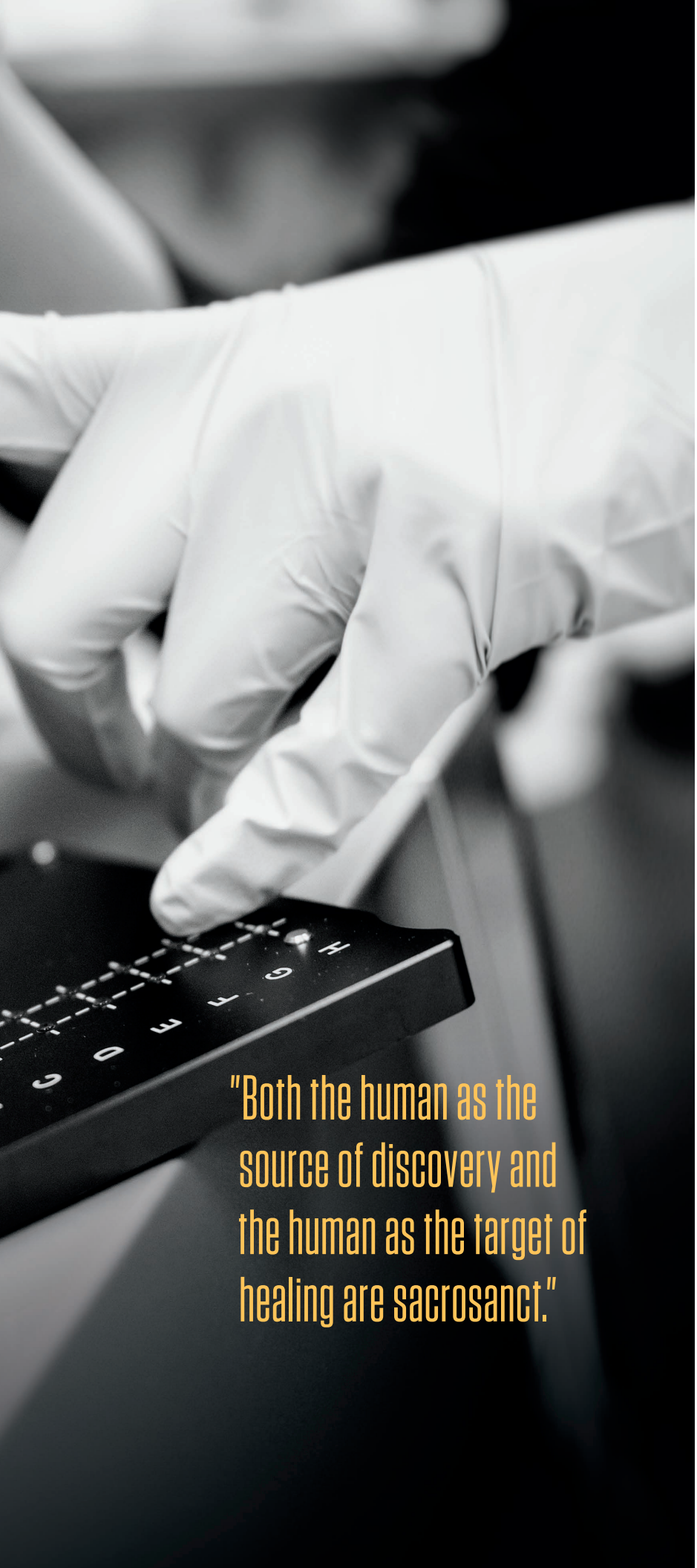

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JOHNS HOPKINS MEDICINE

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BIG

DATA

Individualized Care

YOUR DISEASE IN CONTEXT

What can we learn from other patients about your rheumatic disease? Can their experience forewarn us about a flare or event that could soon happen to you?

These are fundamental questions

being asked throughout Johns Hopkins Rheumatology. They're not new; for centuries, doctors have observed patients, noticed patterns, remembered what has worked in similar circumstances and consulted medical literature to fine-tune treatment. They have recognized that – although many patients can have the same disease – there is rarely a "one-size-fits-all" approach. Back in 1914, Sir William Osler, the great Hopkins physician, wrote:

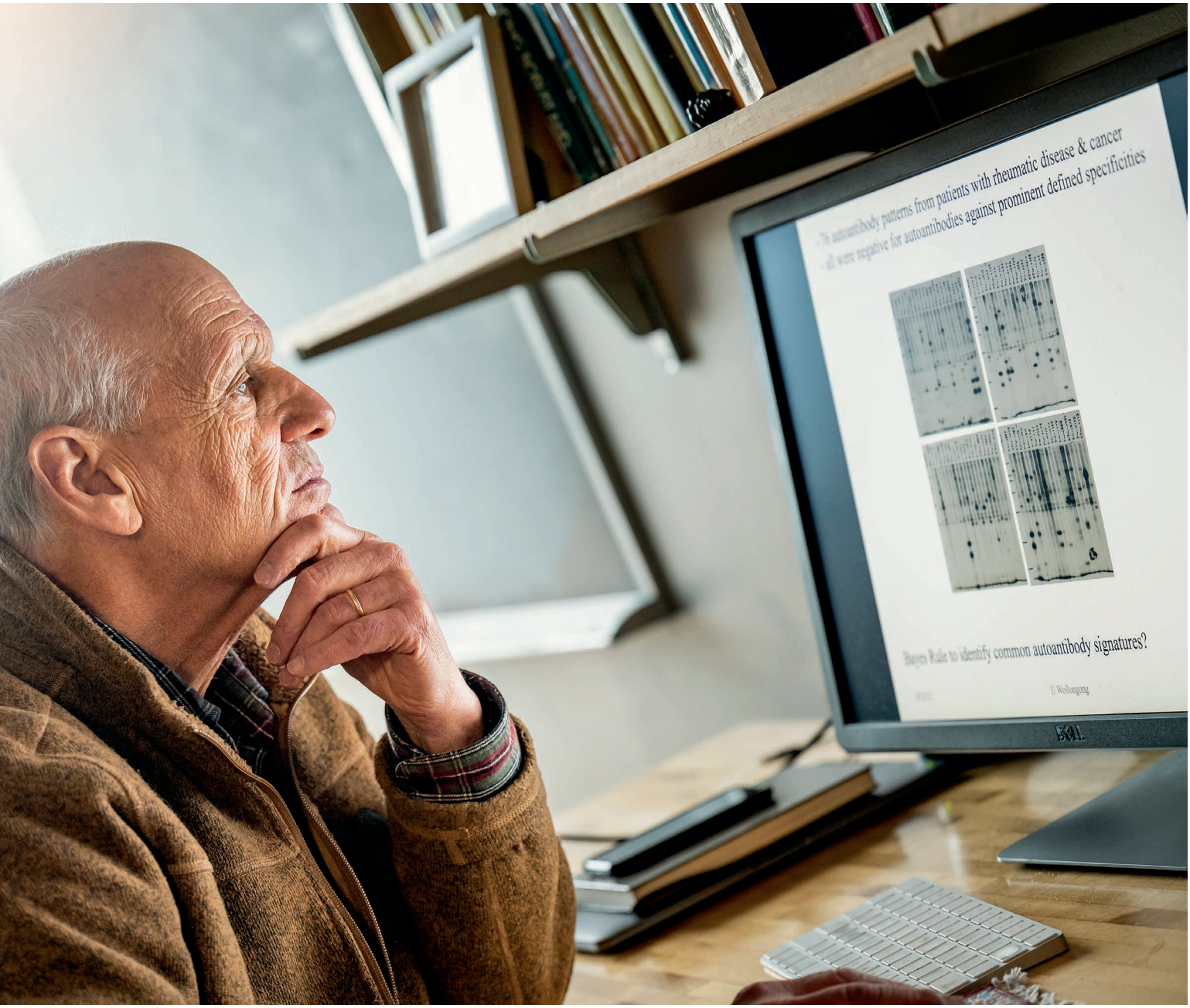
"Our study is man, as the subject of accidents or disease. Were he always, inside and outside, cast in the same mold, instead of differing from his fellow man as much in constitution and in his reaction to stimulus as in feature, we should ere this have reached some settled principles in our art."

Today, with our many diagnostic and follow-up tests and scans in addition to findings from the medical history and physical exam, the amount of clinical information for each patient has ballooned considerably: it's the equivalent of Osler's diagnostic world on steroids.

At the same time, use of the federally mandated electronic medical records (EMR) has inadvertently limited the information available for doctors to see at each patient visit. "Somehow, the practice of medicine has devolved to providing a doctor only with the information about the one patient at hand, and asking the doctor to figure out what best to do," says Scott Zeger, Ph.D., Professor of Medicine at the Johns Hopkins School of Medicine and the John C. Malone Professor of Biostatistics at the Bloomberg School of Public Health. "That's how it works with the EMR. Back in the day, the patient's whole file would be on the doctor's desk," and there, going back through the patient's history, were the notes from every visit, the results of every test and scan, prescribed medicines that worked well and maybe some that didn't; in that same file cabinet were records of other patients with similar disease manifestations. "Then the EMR replaced those files. The doctor doesn't open those files. Many wish they could; it was a lot easier. The doctor still has to remember what worked for other people, what worked better for some patients than others in clinical trials, and any other relevant information, and then make a qualitative judgment."

Zeger was the original director of inHealth, the Precision Medicine program at Hopkins. He began working with rheumatologist Antony Rosen, M.D., Vice Dean for Research, eight years ago to help Hopkins rheumatologists provide better care for each patient, by tapping into the vast storehouse of knowledge gleaned from other Hopkins rheumatology patients over the years. Today, Zeger and Rosen are Co-Directors of inHealth. "If you want to know something about one individual," says Zeger, instead of starting from scratch with that patient, "you try to study how disease in this person is behaving *in the context* of many patients with the same disease."

Until recently, that wasn't happening effectively with the EMR. But with the help of Zeger and his team – particularly, Ji Soo Kim (then a graduate student



in Biostatistics; see Page 16) and her co-mentor, Ami Shah, M.D., M.H.S. – and a new computer program they have developed, called InSight, this kind of contextual information is now enriching the EMR of patients in Hopkins Rheumatology clinics. Kim and Shah "worked endlessly together to create the design and to implement it in statistical software, outside of EPIC (the electronic medical records system Hopkins uses)," says Zeger. Then John Scott, in the Johns Hopkins Medicine Technology Innovation Center, and Zeger worked to implement a version of InSight within EPIC.

HOW IT WORKS

Among other things it does, Zeger's InSight program allows rheumatologists to use "sliders" to highlight relevant data from similar patients and explore questions. Some examples: How does this patient's clinical course compare with those of other patients who share a similar autoantibody signature? Where is this patient on the spectrum of pulmonary function test parameters in diffuse scleroderma? What do this patient's forced vital capacity and diffusing capacity of the lungs (FVC and DLCO; lung function tests) measurements suggest about the risk of future events? Can the echocardiogram-derived right ventricular systolic pressure (RVSP) trajectories of similar patients predict the risk of pulmonary hypertension developing in this patient? How does the skin score trend compared to other patients of this race, sex, and age? Whatever the question, if the answers lie somewhere in the data, Zeger and his team can help rheumatologists find them.

A Natural Fit

Rheumatology is a natural fit for this kind of small-picture/big-picture approach, says Zeger, for several reasons: First, "Rheumatology is a Johns Hopkins Medicine leader in thinking creatively about how to use patient data. Because of Fred Wigley (founding Director of the Johns Hopkins Scleroderma Center), *they have the clinical data* from more than 4,000 patients, whom they've followed from the onset of scleroderma. Very few other clinics had the foresight to create a database going back more than 30 years." Next, rheumatic diseases are *"inherently dynamic, with flares and critical moments," as patients are cared for over many years*. And then there is the nature of Hopkins rheumatologic research itself: It is "very mechanistic; there's a real effort to get under the basic measures of the patients' physical state and their function, to the mechanisms – what's actually happening, and why it's happening." *Because rheumatic diseases tend to involve multiple organs, there are many variables*. "For example, scleroderma affects the skin, kidney, muscles, lungs, heart, and gastrointestinal tract." Rheumatologists measure function and look for changes in many organs in each patient, multiple times over years, creating many points of data.

"If you want to know something about one individual, you try to study how disease in this person is behaving in the context of many patients with the same disease."

What Zeger did, working with Rosen, Shah, Laura Hummers, Wigley, and other Rheumatology clinicians and scientists, was to add new dimension to the EMR through the InSight tool (used like an app on a computer). "We said, the data that the physicians should be able to see is not about just that one patient," but includes the frame of reference of similar patients. Zeger designed a "slider" – something the physician can click on and move around on the screen – to "put this person in relief, to look at many people's data, to see how this patient's trajectory compares to the trajectories of other patients who are like this patient in a number of specific ways." For example, the physician may want to look at patients who had the same autoantibodies, "the same signature of the original cause of the disease." Or the physician may want to look ahead to anticipate likely medical events. "The slider also shows the distribution of the trajectories," showing patients who did better, and those who did worse. "You quickly put the patient in the context of what's come before. It is unique."

This is a breakthrough idea. And yet: "It still doesn't work in most of medicine because the systems prevent it from working, out of the effort to separate clinical care from clinical research," says Zeger. The idea behind locking up data is to safeguard patients' health information, which is very important. "But imagine, if Google was going to try to sell you a watch and never looked at any of the data, they wouldn't know which watches people were more likely to buy. Every company knows that to do best by a particular customer, to make a good decision, you have to look at all the previous decisions and see how they turned out. This is the way to bring precision medicine to life: to see this patient's data and trajectory, but also to see this patient in the context of other patients."

Let's say a doctor is considering prescribing an expensive medicine such as a biologic. "You want to know, will this patient benefit from this therapeutic intervention? Can we avoid potential side effects?" Wouldn't it be helpful, then, to "look at the subset of patients like this patient, some of whom got the biologic, and some who didn't." To get the broader picture, the doctor can also look at relevant clinical trials, whose published data is downloaded onto the InSight tool. "So the rheumatologist is able not only to look at the average treatment effect, but see the treatment effect among many other patients who resemble this person."

At every step in the development of this tool, rheumatologists have validated how it works and what is available, to confirm whether it truly helps them make better decisions. Patients, too, are involved. Results of their self-reported outcomes questionnaires (which they fill out before a clinic visit) are also valuable parts of the chart. "It's not just the results of the lung function test, but how the patient feels," says Zeger. "If the patient's lung function doesn't seem to be any better as reported by the patient, no matter what the test says, the physician has work to do!"

A "Data-Agnostic" Approach

"Antony Rosen's approach from the very beginning was that we're data-agnostic. A lot of people talk about precision medicine, but what they really mean is genomic medicine: we can not only sequence the genome, we can now sequence the genome in individual cells. It's a totally amazing, revolutionary measure, and if that's the data we need to better manage the patient, then so be it. But we also need to know: what's the pain level and functional capacity, the patient's satisfaction in day-to-day life? If those are the most important variables, then that's what we need. We're agnostic about whether it's immunologic, genomic, or patient-reported. What are the key variables for monitoring the trajectories of this particular disease? That's the data we want in our system."

LEARNING FROM COVID

Zeger has found that the statistical methods he has used in rheumatology can be applied to other diseases – even brand-new ones. "When Covid first appeared in March 2020, we started to care for these patients at Johns Hopkins with this unknown disease. Whereas Fred Wigley had organized a database of 4,000 patients, we had zero patients and no data. Antony Rosen said, 'Let's use Covid as an example of all the things we're trying to do in scleroderma and other rheumatologic disorders.' We started capturing all the patient data, and we assembled a 30-person team to analyze it. We watched patients through hospitalization: some were getting well and going home, some were getting intubated, and some were dying. Of the ones who got intubated and placed on mechanical ventilation, some of them went home, and some of them died." The hospitalization trajectories were much shorter than Zeger had been used to working with; days instead of years. "Then we said, let's go to the end and look backwards. Let's stratify the four groups: ones who got better, those who were intubated and died, those who were intubated and went home safe, and those who died before they were intubated. What did their respective hospitalizations look like? What was different about the people who went home, from those who were intubated or died? We published a lot of science using this method."

Zitong Wang, a graduate student, is still working through this data. "If we have a patient who is hospitalized with Covid, what we want the clinician to know is, where is this person headed? What is likely to happen every six hours, every 12 hours? We figured out how to calculate those answers by doing retrospective analysis; looking backwards, and turning that around for a new patient." The calculations suggested intervention points, and also helped the doctor determine the risks of potential steps. "You've got to know the risks before you can manage them. What's the likely benefit for a patient with this risk of getting intubated now or not? Here are the risks if you go this way versus that way."

But then, Zeger says, it all goes back to the doctor's judgment. "We give them the facts as we glean them, but in the end, their judgments are most important, because they see many other things – pallor in the face, strength of the voice – things that we don't measure. They take all of that into account."

Little BANG

Straggly protein strings, self-sacrificing Pac-Men, a DNA goo that acts as a beacon. A rheumatologist and biophysicist have identified very tiny but dramatic events at the onset of lupus in some patients.

In 2019, LEAP reported on groundbreaking work that uncovered something very unexpected in Sjögren's syndrome, and we even had pictures: snapshots of *straggly protein strings* forming in the salivary glands, made by an *everyday immune system protein called IFI-16* – which, in turn, had been called into action by *interferons*, immune system proteins that answer the body's call for help when a virus or infection is detected.

Unfortunately, these weird-looking ropes, or filaments, caused their own problems: they were irritants, prompting the body to ramp up the damage control. If the IFI proteins (which belong to a family of DNA-binding proteins called ALRs) were the equivalent of a local police squad car, what came next was like the black SUV containing a highly armed SWAT team: *powerful white blood cells called lymphocytes*, which swooped in and punctured the membrane of the salivary cells containing the filaments. This, in turn, caused more IFI-16 filaments to be made, contributing to a cycle of autoimmunity.

This work was remarkable because a multidisciplinary Hopkins team – rheumatologist Brendan Antiochos, M.D., biophysicist Jungsan "J." Sohn, Ph.D., biophysicist Mariusz Matyszewski, Ph.D., cell biologist Livia Casciola-Rosen, Ph.D., and rheumatologist Antony Rosen, M.D. – basically captured crime scene photos in an autoimmune disease and put those straggly protein strings on a "Wanted" poster. A key feature of these strange structures is that they are *combinations* of the protein, wrapped around DNA like cotton candy.

Now, in another autoimmune disease, Antiochos and Sohn have gone on to look for other members of this molecular crime family, and they have discovered another event – a "little bang," if you will, at the onset of lupus in a subset of patients. In systemic lupus erythematosus (SLE), they have identified the actual target autoantigen, and how and where it is formed.

To explain it, let us consider, for a moment, Pac-Man. The immune system has many different types of soldiers, and among them are white blood cells called *neutrophils*. Instead of poking holes like lymphocytes, they gobble up bacteria or debris like Pac-Man eats dots in the video game. But these Pac-Men are noble warriors who make the ultimate sacrifice: they give their lives fighting the infection, and when they die, they explode their DNA into a kind of goo that is a beacon, calling other immune cells to come join the battle.

A KEY FEATURE OF these strange structures is that they are combinations of the protein, wrapped around DNA like cotton candy.

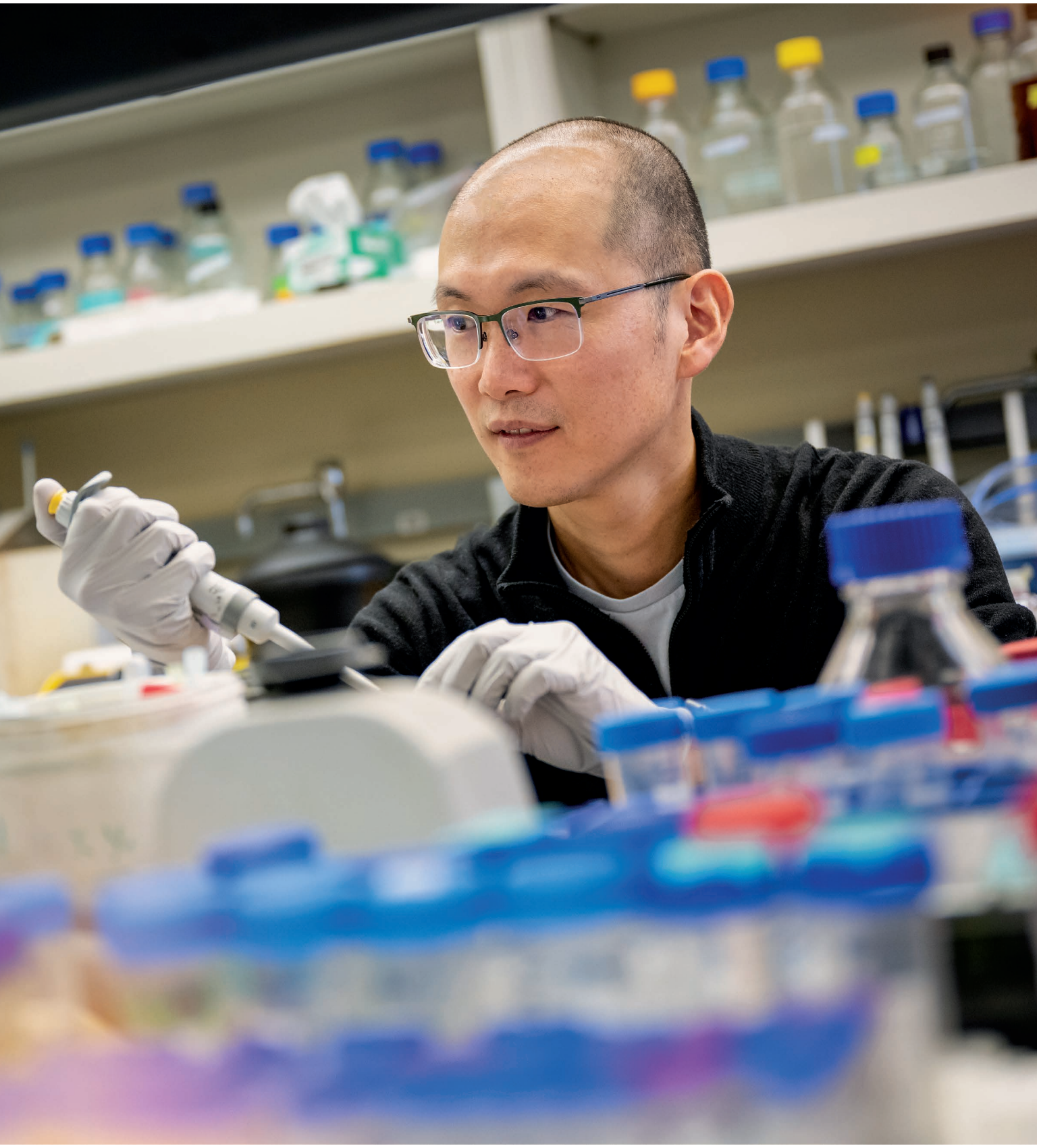
What happens next involves an alphabet soup of initials: The goo, like a spiderweb, covers and stops the enemy. These exploded messes are called neutrophil extracellular traps (NETs). They are rapidly degraded by DNA-digesting enzymes called DNAses. Antiochos and Sohn asked what would happen when another ALR autoantigen (called AIM2) came into contact with these NETs. The answer, they discovered, is that the NETs bind to the DNA and form a similar straggly protein string! "Strikingly," says Antiochos, "when AIM2 binds to NETs, it stops the DNA from being degraded, and generates this long-lived DNA-protein autoantigen complex (string) that drives the lupus immune response in some patients."

The ALR proteins are tenacious. "These DNA sensors recognize pathogenic DNA, or our own DNA from cell death, as something bad," Sohn says. "The AIM2 or maybe ALR binds to any DNA, and what happens during this NET formation to get inflammation going, or to clear out the pathogenic infection, is that it sticks to them really tightly. The body doesn't know how to get rid of them, and as a last resort, raises antibodies against them. Because these guys are so persistent, the immune system thinks they are pathogens."

Antiochos and Sohn found the structures in the lab, and importantly, also in kidney tissue samples taken from Hopkins patients with SLE glomerulonephritis (kidney disease). The studies were published in 2022 in the prestigious journal, *eLife*.

This work has shed major light on the "how" of lupus – and prompted many more

Sohn: *"I'm a basic scientist. I study how molecules interact – geeky fundamental chemistry-physics stuff. Brendan is at the completely different end of the spectrum. He does basic research but is more focused on the clinical side, at the human level. I don't think this sort of collaboration is common."*



"THE NEUTROPHIL

shoots out its own DNA to trap the bacteria," which brings in other immune cells.

questions as to the "why." Among them:

- Are strings of proteins and DNA that don't get degraded more likely to turn on the autoimmune response?
- How do the ALR proteins and the DNA meet? Do the criminals meet up in particular neighborhoods? Do they use particular weapons?
- Could their properties and the places where they hang out be new avenues for therapy?

No one thinks it's possible to undo the damage already caused by this cycle of autoimmunity – but Antiochos believes this research may lead to new targets for treatment that could stop or minimize further damage.

Unlikely Collaboration

Antony Rosen, Vice Dean for Research, believes the creativity of this research is a direct result of the fact that Sohn and Antiochos are approaching rheumatic disease from very different perspectives. "Here are two people with completely different skills, one trying to understand the mechanism of autoimmunity in disease; the other, why molecules signal the way they do, and assemble the way they do," Rosen says. "They should have nothing in common." In addition to his lab research, Antiochos, a rheumatologist, cares for patients with lupus, Sjögren's, vasculitis, and other rheumatic diseases. Sohn, a biophysicist, works with proteins and amino acids, and even gets to use the very expensive, 10-foot-tall cryo-electron microscope that Johns Hopkins University owns to study structures such as the ALR filaments at the atomic level. "Yet they have this resonance between them: one gives insights into how the other one works, and vice versa. They are combining their very diverse approaches for the ultimate understanding and therapy of human disease."

As Sohn puts it: "I'm a basic scientist. I study how molecules interact – geeky fundamental chemistry-physics stuff. Brendan is at the completely different end of the spectrum. He does basic research but is more focused on the clinical side, at the human level. I don't think this sort of collaboration is common. We go from tissue samples and patient phenotypes to target molecules we generate in the lab, to studying how those work at the molecular level and trying to understand why and how these things happen to patients – how they relate back to human lives."

"One of the benefits of being in a place like Johns Hopkins is having collaborations involving people from very different fields," says Antiochos. "My formal training is clinical; to get to think about these diseases with a biophysicist, and trying to unravel what's underlying these diseases that have been described for such a long time, is a privilege."

And, notes Sohn, "we have become good friends. We talk about this all the time. I think that's kind of cool."

NORMAL CELLS, ABNORMAL RESPONSE

All of the players in this molecular drama are what Antiochos has described as "regular old housekeeping proteins." But "for whatever reason in these patients, there's inflammation, which involves cell death, and the NETs occur when neutrophils try to engulf pathogenic bacteria," says Sohn. "The neutrophil shoots out its own DNA to trap the bacteria," which brings in other immune cells. "This is part of the normal immune response against a pathogen (bacterial infection or a virus), but for some reason in lupus patients, this occurs without infection, and the presence of IFI-16 or AIM2 on the NETs seems to impair their clearance. The body doesn't know what to do with them; it raises antibodies, and that whole process starts a vicious cycle of local or systemic inflammation."

Antiochos: *"My formal training is clinical; to get to think about these diseases with a biophysicist, and trying to unravel what's underlying these diseases that have been described for such a long time, is a privilege."*

THE GREENE SCHOLARS

Meet four young physician-scientists who are working to transform the standard of care for rheumatic diseases with support from the Jerome L. Greene Foundation.

EDUARDO GÓMEZ-BAÑUELOS, M.D.

Instructor of Medicine,
Division of Rheumatology

When Eduardo Gómez-Bañuelos was a medical student in Guadalajara (Mexico), he became very interested in patients with systemic lupus erythematosus (SLE) a complicated disease that can manifest itself clinically in multiple organs. This dovetailed with his scientific interest in immunology. He decided to become a rheumatologist, where "you're a detective and a scientist at the same time." There was something else he really liked about Rheumatology: "the opportunity to follow your patients for many years. We get to know them very well as a person, and they get to know us. We get to see how the disease impacts someone's life, and do our best to help them, over the long term."

Gómez-Bañuelos has recently completed a study of a novel autoantibody in lupus targeting DNase1L3 (Anti-DNase1L3), a key enzyme in lupus pathogenesis. This novel autoantibody is useful to identify patients with higher chances of developing lupus nephritis, and more active SLE. Another major finding of this study is that DNase1L3 is the antigen that leads to the generation of antibodies against double stranded DNA which is a major target of the autoimmune response in SLE.

With funding from the Greene Foundation, he is also working to characterize the roles of interferons in SLE and other rheumatic diseases. Interferons are cytokines, key proteins in the body's immune response to enemy invaders such as infection, a virus, or cancer. Once they are activated, they trigger a cascade of responses in cells, including inflammation and prevention of viral replication.

There are different types of interferon in SLE: "Very few patients have only one type; most patients have different combinations of interferon in their blood, and these are associated with different manifestations of the disease. We don't know exactly how they act in the disease yet; there's still a lot of room to try to understand the role of different types of interferons in lupus, and the clinical manifestations that correlate with them."

> "You're a detective and a scientist at the same time."

For example: Type 1 interferon is associated with skin lupus. Patients with elevated Type 2 interferon are more likely to have lupus arthritis. Nephritis, one of the more severe complications of SLE, is more closely associated with the elevation of Type 3. In genetic studies, Gómez-Bañuelos is looking at how these types of interferon modify the immune responses of patients in specific ways. He hopes a better understanding of the interferon types, specific immune responses and their clinical manifestations can be used to personalize care for patients with SLE, and better predict an individual's course of disease. He also believes this work can be applied to other rheumatic diseases, including scleroderma, myositis, and Sjögren's.

RACHEL WALLWORK, M.D.
Jerome L. Greene Scholar,
Division of Rheumatology

Here's a dilemma: "~90 percent of patients with scleroderma can have scarring in the lungs," says Jerome L. Greene Scholar Rachel Wallwork, M.D. "But only 10 to 20 percent of those patients develop progressive disease." So how do you know who needs treatment?

Immunosuppressive medicines can help prevent lung damage, "and the earlier you use them, the better. Once there's a lot of scar tissue, it's hard to reverse." Ideally, lung disease should be treated at the point of inflammation, before scarring occurs. Why not simply treat everyone, just to be on the safe side? Because the medicine can cause its own complications, particularly in the gastrointestinal tract – which can already be affected by scleroderma itself. "We don't want to treat people who don't need it," says Wallwork. "Nor do we want to start treatment after the disease progresses," because drug-induced damage might occur. Instead, the goal is "to try to predict better which patients are at greatest risk, and treat those patients earlier, while sparing those at low risk of progression."

With funding from the Greene Foundation, Wallwork is working with Ji Soo Kim, Ph.D., (see story on Page 16), studying the records of more than 4,000 patients in the Johns Hopkins Scleroderma Center registry. These patients have multiple lung function evaluations over the years, says Wallwork. In particular, she is interested in the trajectories of patients diagnosed with lung disease early in the course of scleroderma and followed for at least 10 years – some of whom remained stable, and some developed more severe symptoms. "There are some known risk factors for progression," including having certain antibodies, being male, and having diffuse rather than limited disease, but Wallwork hopes to develop more definitive thresholds. "Can we use these known risk factors – and are those enough – to try to predict the trajectory of the patient? Or can we add in novel risk factors, like specific serum biomarkers, information from their imaging, and other baseline clinical criteria?"

Immunosuppressive medicines can help prevent lung damage, "and the earlier you use them, the better."

The accepted wisdom, she adds, is that scleroderma patients are at highest risk for lung damage within the first five to seven years after diagnosis; however, some patients progress very slowly, and are considered "late progressors." Do these patients have unique clinical signposts? "Historically, we have looked at lung volume; how much a patient can breathe out in one breath. We also want to look at oxygen exchange." With every breath, inhaled oxygen moves through the alveoli (tiny air sacs in the lungs) to the blood in the capillaries, and carbon dioxide moves from the blood in the capillaries to the alveoli. In pulmonary hypertension, blood pressure is increased between the heart and lungs, and there is a low oxygen exchange, but "the breathing amount is normal. In someone with scarring, both of these measures usually go down together. Mapping those together, and seeing the trajectories of both, might give us a bit more nuance and understanding of what is happening in the lungs."

In other Greene-funded work, Wallwork is looking for better ways to monitor lung changes in patients. "There are no guidelines from the American College of Rheumatology, but in general, patients tend to get breathing tests every six months or so. But that leaves six months where someone could progress without treatment. If patients look like they might have progressed but we can't be certain, we might get a repeat test in three to six months. We've now lost nine to 12 months of time where we could have been treating someone who has progression." In a pilot trial using Fitbits and a home breathing device, Wallwork is hoping to detect changes in patients' breathing, and begin treatment, much sooner.

JI SOO KIM, PH.D.
Biostatistician, Division of Rheumatology, Scleroderma Precision Medicine Center of Excellence

How do you craft precision treatment for someone with scleroderma? There are so many variables, puzzle pieces of information that build a highly specific picture for each patient. The picture calibrates and refocuses continually, as results of lab tests and physical exams, imaging scans, and the patient's own reported assessments, come in every few months – and then those results, in turn, are compared to the findings of other Hopkins patients with similar characteristics.

The amount of meaningful data available to Hopkins rheumatologists is colossal; thankfully, here to help make sense of it are biostatistician Ji Soo Kim, Ph.D., and colleagues at the Johns Hopkins Scleroderma Precision Medicine Center of Excellence.

"The most important role of our research is to *neutralize the heterogeneity* in this very complex disease," says Kim. "Patients can have widely different clinical manifestations, responses to treatment, and trajectories of illness." For the last four years, beginning "as a side project" when she was a Ph.D. student under the mentorship of renowned biostatistician Scott Zeger, Ph.D. (see Page 2), Kim has been helping Hopkins rheumatologists treat scleroderma better. The catalyst was a conversation with rheumatologist Ami Shah, M.D., who said that before she saw each of her patients with scleroderma, she would take two hours to review all of her clinic patients' data. "Scott Zeger, said, 'There's got to be a better way of doing this.'" Shah and rheumatologist Laura Hummers, M.D., gave them parameters that would be helpful, including a longitudinal trajectory charting disease activity in various organs, and another trajectory to show how patients with similar points of illness have done over time.

The amount of meaningful data available to Hopkins rheumatologists is colossal.

In work supported by the Greene Foundation, Kim, Zeger and colleagues began developing a tool called Patient InSight. "We made lots and lots of iterations of it," and sought advice from rheumatologists and patients. Their model, like the disease itself, is complex. It generates the real-time personalized risk estimate of complications including interstitial lung disease, cardiomyopathy, and pulmonary hypertension. It also shows autoantibody status, the patient's own prior trajectories in multiple organ systems, and "includes knowledge from the population of the Johns Hopkins Scleroderma Center's research registry of more than 4,000 patients, to give the best estimate possible of the patient's disease state and risk of having critical events in the near future." The storehouse of available data is continuously growing.

Rheumatologists Shah, Fred Wigley, M.D., and colleagues monitor many markers and clinical features in their patients, ranging from the presence of certain autoantibodies in the blood to subtle but significant changes in lung function. "Scleroderma influences multiple systems, including skin, the heart, lungs, kidneys, and muscles. Aggregating these data is a huge challenge," says Kim. The Patient InSight tool "not only illustrates a patient's measurements over time, but also gives the best estimate of their true health trajectory, given all the noise in the data." Although the program is still being built, much of it is up and running, and helping Hopkins rheumatologists and patients make better-informed decisions about care.

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For some people, a tick bite is the unwanted gift that keeps on giving – particularly if, after treatment with antibiotics, Lyme disease persists in the form of post-infectious Lyme arthritis (PILA). Rheumatologist John Miller, M.D., and John Aucott, M.D., Director of the Lyme Disease Clinical Research Center, are among very few physicians in the country who are studying this unique form of inflammatory arthritis – which usually manifests itself in the form of a swollen and painful knee.

"We used to think that 90 percent of patients had complete resolution of their symptoms with antibiotics, and that 10 percent had PILA in the affected joint," says Miller. "But what we're finding is that even though people may have their symptoms get better after the antibiotics," up to one-third of the patients referred to Hopkins "still have persistent pain, physical dysfunction, and stiffness."

How do you know whose knee is harboring secret inflammation? It's not always evident on a physical exam – but it can't hide from ultrasound.

With funding from the Greene Foundation, Miller, Aucott and Jemima Albayda, M.D., Director of the Musculoskeletal Ultrasound and Injection Clinic, are conducting research that Miller hopes will change the standard of care for patients with PILA. "We are comparing the gold standard – physical exam – to the ultrasound," he says. "We're also collecting patient-reported outcomes, and comparing all the data from the onset of Lyme arthritis, after treatment with antibiotics, and then at follow-up appointments." While ultrasound of the joints and patient-reported outcomes are more commonly used in other rheumatic diseases, "this is pretty novel from a Lyme arthritis perspective."

In a small study published in the *Journal of Clinical Rheumatology* in 2022, Miller, Albayda and Aucott found that even in patients with PILA who seemed to be getting better, musculoskeletal ultrasound showed otherwise: inflammation and damage to the joint were still happening. "The study didn't just show the usefulness of ultrasound to confirm the presence of inflammatory arthritis and guide management; it also highlighted areas of unmet need." In many patients who are treated for Lyme arthritis with antibiotics, ongoing pain, swelling or stiffness are thought to be the result of damage to the joint, which has turned into secondary osteoarthritis (the kind of wear-and-tear arthritis many people develop over time).

But in some of these patients, the ultrasound showed spots of tenacious but very subtle inflammation. And when these patients were treated with hydroxychloroquine or methotrexate, an immune-suppressing medication – instead of further antibiotics or intraarticular corticosteroids (used to treat osteoarthritis) – they got better! "Our goal is to identify people who could potentially be helped by immune suppression, and intervene earlier to minimize joint damage," says Miller, who notes that this work is in its early days yet. He has applied for funding to study this on a larger scale. The good news about PILA is that "if you treat it, it can get better."

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"We are very near to greatness: one step and we are safe; can we not take the LEAP?"

— Ralph Waldo Emerson (1803-1882), American lecturer, poet, and essayist.