LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2018

DECODING WITH FILTERS

SECRET MESSAGES

ULTRASOUND:
RHEUMATOLOGIST'S
STETHOSCOPE

SJÖGREN'S:
NOTORIOUS MIMIC

WHY WE NEED FILTERS

One of my favorite paintings is deceptively simple. If you were to glance at it, you'd see a jungle scene, with some plants and a couple of animals. But if you looked at it through a red filter, you would see the picture teeming with wildlife. Use a green filter, and you see only plants – a tropical rainforest. With a blue filter, the other animals and plants are gone, and instead, you see more than a dozen monkeys.

The idea here is that if you take a confusing kaleidoscope of information and you apply the right filter, what emerges is something amazing. Every story in this issue of *LEAP* involves applying novel filters to help us see clinically relevant subgroups. We use a variety of data and measurement filters – a multidisciplinary approach to patient evaluation in our Sjögren's Center (see page 10), ultrasound to look at the muscles in patients with myositis (page 6), different antibodies to stratify cancer risk (page 17) and even complicated math formulas (page 2) to help us find antibody signatures in scleroderma patients – to define subgroups of patients within diseases who behave similarly.

Why is this important? Because the unique features of disease subgroups – how they manifest and how they progress – often result from distinct biological mechanisms. For too long, doctors treating rheumatic diseases have had to base their management on instinct and experience. The problem is that each physician has a limited experience – which means that many times we basically had to guess at how to treat a specific patient, using trial and error to find out what might work best.

The opposite of that is to use filters, combining our unprecedented ability to measure – using revolutionary modern tools with new data analytics powered by computers, and increasingly sophisticated algorithms – along with the powerful human intuition that comes from listening to our patients and observing how the illness behaves differently in each one. This allows us to treat and even help prevent problems in a precise and accurate way. This is precision medicine; it's revolutionary, but at its heart is the incredible partnership we share with our patients.

Antony Rosen, M.D.
Director, Division of Rheumatology
Vice Dean for Research

WINTER 2018

LEAP

JOHNS HOPKINS MEDICINE

WRITER/EDITOR: JANET FARRAR WORTHINGTON
EDITORIAL CONSULTANT: ALLAN GELBER, M.D., PH.D., M.P.H.
DESIGN: SKELTON DESIGN
MAJOR PHOTOGRAPHY: HOWARD KORN

SECRET MESSAGES

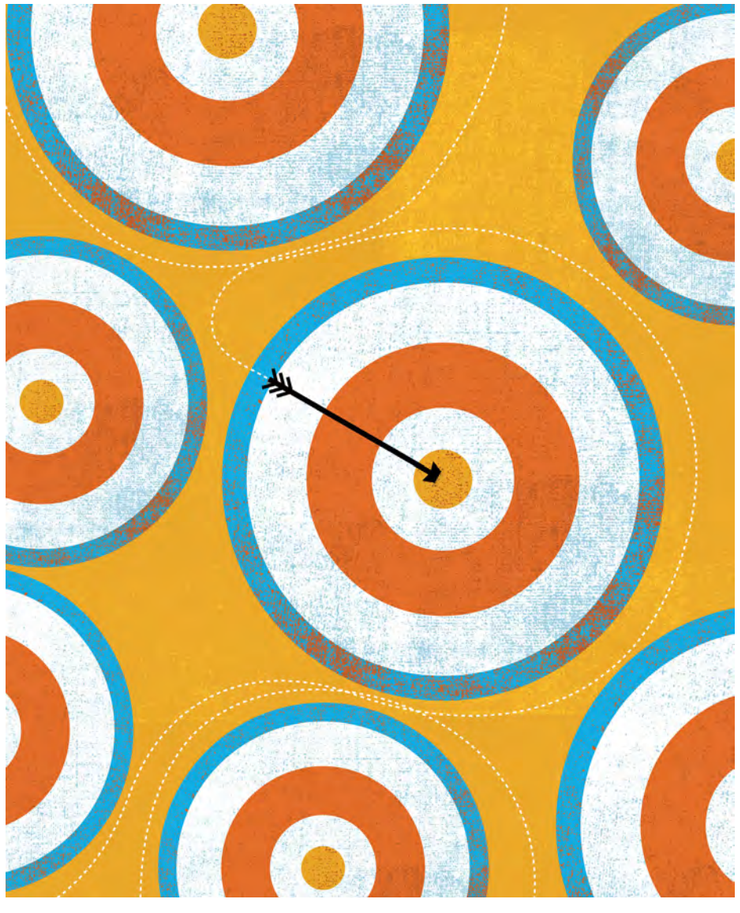
WHEN YOU WERE A KID, DID YOU EVER PLAY WITH INVISIBLE INK?

It's fun: Just write a secret message with something simple, like lemon juice, milk, baking soda, or even a white crayon. The best part: Nobody else can read the message unless you reveal how, because each type of ink needs its own decoders. For lemon juice or milk, you need heat to make the words visible; for baking soda, grape juice can show the message. If your message is written in white crayon, a wash of watercolor will unmask the hidden letters. Whatever the ink, the message is unreadable unless you know what to look for.

Scientist Livia Casciola-Rosen, Ph.D., happens to be the very best in the world at finding a certain type of secret messages: patterns of autoantibodies in the blood samples of patients with rheumatic diseases. She looks for exquisitely subtle differences and similarities to identify patients who might fall into subsets – people who could respond equally well to one particular drug or treatment *that might not help others with the same disease.*

This is individualized medicine, which Johns Hopkins rheumatologists believe is essential with such diseases as scleroderma, Sjögrens, myositis and rheumatoid arthritis that defy one-size-fits-all treatment.

Diseases such as scleroderma, Sjögrens, myositis, and rheumatoid arthritis defy one-size-fits-all treatment.



In groundbreaking new research, along with colleagues Ami Shah, M.D., and Antony Rosen, M.D., she has gone "outside the box" of rheumatology – or even of medicine. They have teamed up with Johns Hopkins biostatisticians Zhenke Wu, Ph.D., and Scott Zeger, Ph.D., to discover autoantibody signatures using a whole new type of decoder: complicated math models that have never been used for this purpose. Their work, published in the journal, *Biostatistics,* has the potential to be applied to many diseases.

What kind of math are we talking about? The kind that makes most of us glaze over, that's like a whole other language; the kind of high-level math problems that, without computers, would cover entire chalkboards.

FROM BLOOD TO X-RAY FILM

The patterns that Casciola-Rosen finds start off as blood samples from patients with a particular disease, such as scleroderma. "We take cells in culture and we radiolabel them," by tagging each protein with a radioactive substance. "We generate a mixture of labeled proteins from cells and add serum from a patient. The antibodies that are present bind to the proteins that they recognize." This is called immunoprecipitation. "After you put this through a lot of washes and electrophoresis," a process that uses an electric current in a gel, "the proteins separate based on size. Then you separate the molecules by weight, and you can visualize them on a piece of X-ray film." The end products are "patterns of bands that represent the autoantibodies in patients" – the way a patient's body responds to the disease. Through sophisticated technology, Casciola-Rosen is able to "look at hundreds of patterns and see what is common and what is different. Then we can focus on a group that have the same pattern."

She has done all this for years simply by eyeball. Until recently, she didn't believe there was any other way to do it. But she, Rosen, and Shah started talking to Wu, now on the faculty at the University of Michigan, and Zeger, biostatistician and Co-Director of Hopkins inHealth (the Hopkins Precision Medicine Initiative), who thought they might be able to take the data – turned into numbers – and make sense of it in a different way.

This collaboration required many meetings of "people who didn't even speak the same scientific language," says Casciola-Rosen. "At first, we weren't sure they could do anything. Then, as they started their analysis, they would say, 'Can you please explain this,' or 'what does this mean?' They got us thinking about a lot of things that we took for granted; we have some bias after years of looking at data, and they came in completely naïve." Writing the paper was challenging, too: The math was "a language we don't understand well. But it had to be anchored in biology, which is a language they don't understand well. Together, our conclusions were way more elaborate than either group could generate individually."

Zeger believes biostatistics is the future of better medicine: "There's a misconception that if we simply record more and more information and we manage that information safely, somehow through the use of computers, what is true will emerge," he says. "Nothing could be further from the truth. Really, the trick for bringing to bear the benefits of this complex information is to learn how to analyze, to use that information intelligently. That's where biostatistics comes in. It is a field about how to infer what is true from noisy information."

The math models used by Zeger and Wu don't replace what Casciola-Rosen does, explains Antony Rosen, Director of Rheumatology and Vice Dean for Research. Instead, they will help her do it better. "There's nobody better in the world at looking at patients' autoantibodies –

What kind of math are we talking about? The kind that makes most of us glaze over, that's like a whole other language; the kind of high-level math problems that, without computers, would cover entire chalkboards.

patterns of bands – and recognizing those patterns. She remembers if she's seen them before." But the human eye is used to discriminating: "We focus on the dominant thing or things. We're very good at that. We're not good if there are two very subtle patterns." Also, "if you see things that are very infrequent, and they occur closely together in time, you remember it. But if they occur far apart in time, you don't remember. And humans are not good at processing huge amounts of data simultaneously. But computers are not challenged by how rare something is. Scott Zeger and Zhenke Wu defined a new series of algorithms that look for patterns that humans may or may not find." It turns out that some of the patterns that Casciola-Rosen sees, the computer also finds. "But then there are patterns that Livia never sees. The computer shows them to her, and she identifies a new pattern. This is matching the judgment of a human with the processing power of the computer. That synthesis is going to underlie major advances in medicine."

Defining the molecular markers of distinct subgroups of patients can lead to new tests for diagnosis and monitoring, and new potential targets for treatment. For example, says Casciola-Rosen: "An immune response to RNA polymerase III in scleroderma is associated with cancer" (see story on Page 13). "This immune response arises in response to a mutation in RNA polymerase III in that patient's particular cancer." Finding patients who share the same autoantibody profiles gives new "red flags" that might tell investigators, "you need to screen this patient very carefully, to see if a small cancer is emerging." Imagine the possibilities to help patients who develop scleroderma as a response to cancer: It could be, Casciola-Rosen says, "that if you hit that window and treat the cancer very early, perhaps you could arrest the course of the disease. Down the line, we hope to be doing those clinical studies, as well."

This collaboration, she adds, has shown that "significant progress is made by reaching out, going beyond one's comfort zone sometimes and working with people whose skill sets are different than yours. That way, you get these amazing insights." L

This work has been supported by the Donald B. and Dorothy L. Stabler Foundation, the Jerome L. Greene Foundation, and the Scleroderma Research Foundation.

RHEUMATOLOGIST'S STETHOSCOPE

Ultrasound can show what's happening beneath the surface, in real time.

Through the use of ultrasound, rheumatologist **Myma Albayda, M.D.**, is discovering new facets of myositis – subtle, unrecognized changes in the muscles that doctors haven't even known to look for.

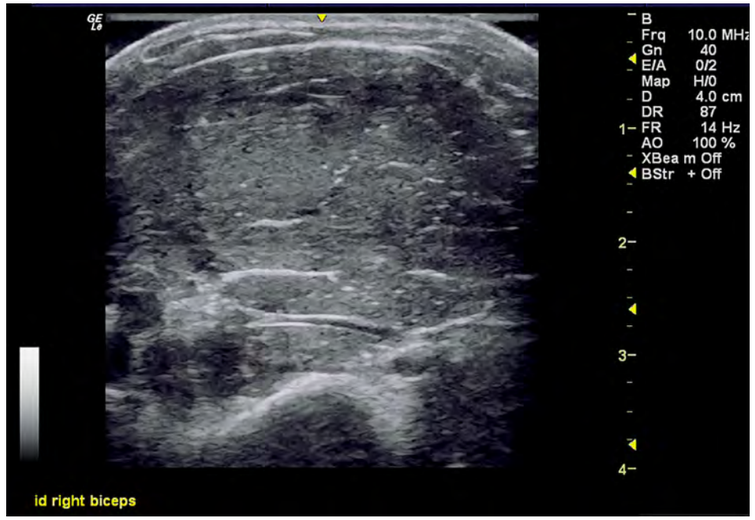
Albayda, who heads the musculoskeletal ultrasound program in rheumatology, is accustomed to using ultrasound to look at the joints in early inflammatory arthritis. But she also takes care of patients with myositis, a rheumatic disease characterized by muscle weakness and inflammation, and one day she asked a simple question: "Why aren't we using ultrasound to look at muscle?"

In myositis, the standard means for evaluation is MRI – but this does not lend itself to frequent use. MRI is expensive, it's time-consuming, and it's not for everyone – those with a pacemaker, for instance, or people who are claustrophobic or who can't lie still for very long. The MRI machine is the opposite of portable; it basically takes up its own room, and patients must come to it, and then wait for a radiologist to read the images. "It takes an hour to set up, and we just choose one muscle group to focus on – the thigh, for example, and not the whole leg."

Ultrasound, in comparison, "is cheap," says Albayda. "We can do it right in the examination room, and image as many muscles as we like, rather than send patients off to radiology. I can figure out what's going on with a patient pretty quickly." Ultrasound gives an immediate look at "what's happening with inflammation in soft tissue. It is also the only modality that can show movement. We can evaluate how the muscle contracts in real time. "

Myositis, like all rheumatic diseases, is heterogeneous: it differs from person to person, and so does the response to treatment. It is challenging to treat. In turn, one drawback to ultrasound is that it is "operator-dependent," says Albayda. In other words, "pretty subjective." In a disease that has many manifestations, is it possible to standardize ultrasound – to establish some guidelines "that could be used across multiple centers?" Moreover, can ultrasound provide another means for rheumatologists to tell which patients have similar disease patterns? Rheumatologist Allan Gelber, M.D., Ph.D., M.P.H., believes it can. "Ultrasound is another technology-based filter (see Page 2) that will help us classify patients with myositis into groups that are clinically relevant, and likely biologically-anchored."

With funding from the Jerome L. Greene Foundation, Albayda has spent many hours taking ultrasound scans of people with

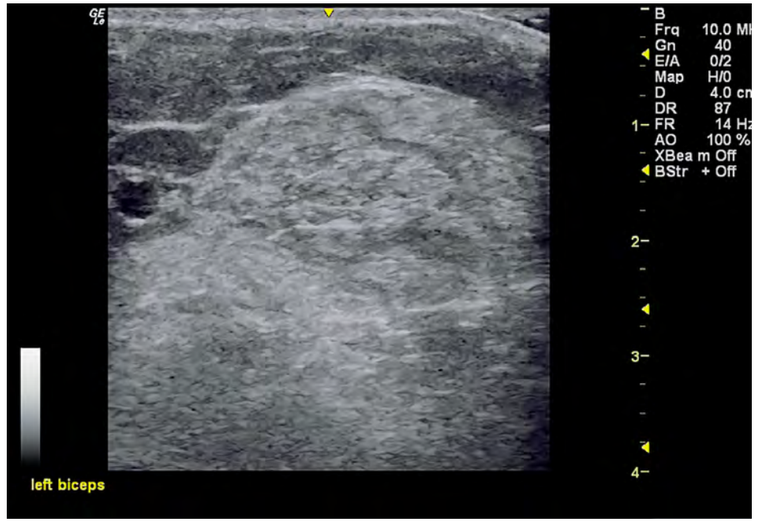


Muscles may not look very different on the outside, but ultrasound can tell the difference inside: at left, normal muscle. At right, inflamed muscle.

One benefit to bedside ultrasound: Patients don't just have to take the doctor's word for it. They can look for themselves, and make more informed decisions about their care.

myositis and people without it (as controls), "making an ultrasound image bank to establish a scoring system." For example, "we draw a region of interest in the muscle and different layers of tissue above it, and obtain a grey scale value based on how white the damaged muscle appears," she explains. "This then becomes a numerical value that can be followed over time."

Can these findings be made more objectively? Working with engineers including Philippe Burlina, Ph.D., at the Johns Hopkins Applied Physics Laboratory, Albayda has taken all these images and tested machine learning, "to see how well computer-aided diagnostics can assist with ultrasound." This research is the first of its kind in the field of muscle imaging. "It's exploratory, leading us to more questions and how to answer those questions even better. Right now, machine learning requires big data, but we don't have that many images yet," because myositis is rare, affecting just a handful out of every 100,000 people. As an offshoot of the APL collaboration, Albayda is working with



In myositis, the standard means for evaluation is MRI – which is expensive and time-consuming, and not an option for everyone. The MRI machine is the opposite of portable; it basically takes up its own room. Patients must come to it, and then wait for a radiologist to read the images.

experts in Applied Math to analyze patterns using smaller data sets.

"My goal," she explains, "is to get ultrasound to the clinical arena, to use it at the bedside, and have everybody be able to use it in a more standardized fashion so that it becomes an alternative imaging modality to MRI." Critics may say that ultrasound will never be better than MRI, she adds, "but that's not the point. There are certain scenarios where MRI is better, and I will always use that. But sometimes ultrasound may be better. If it turns out that the information gathered from MRI and ultrasound is comparable and ultrasound – which is much cheaper – can provide me information then and there, then it can really help me to understand what's going on at the structural level. And that will always benefit the patient. I call it the rheumatologist's stethoscope. That's what I love about this: I'm learning about the disease itself as I do the ultrasound."

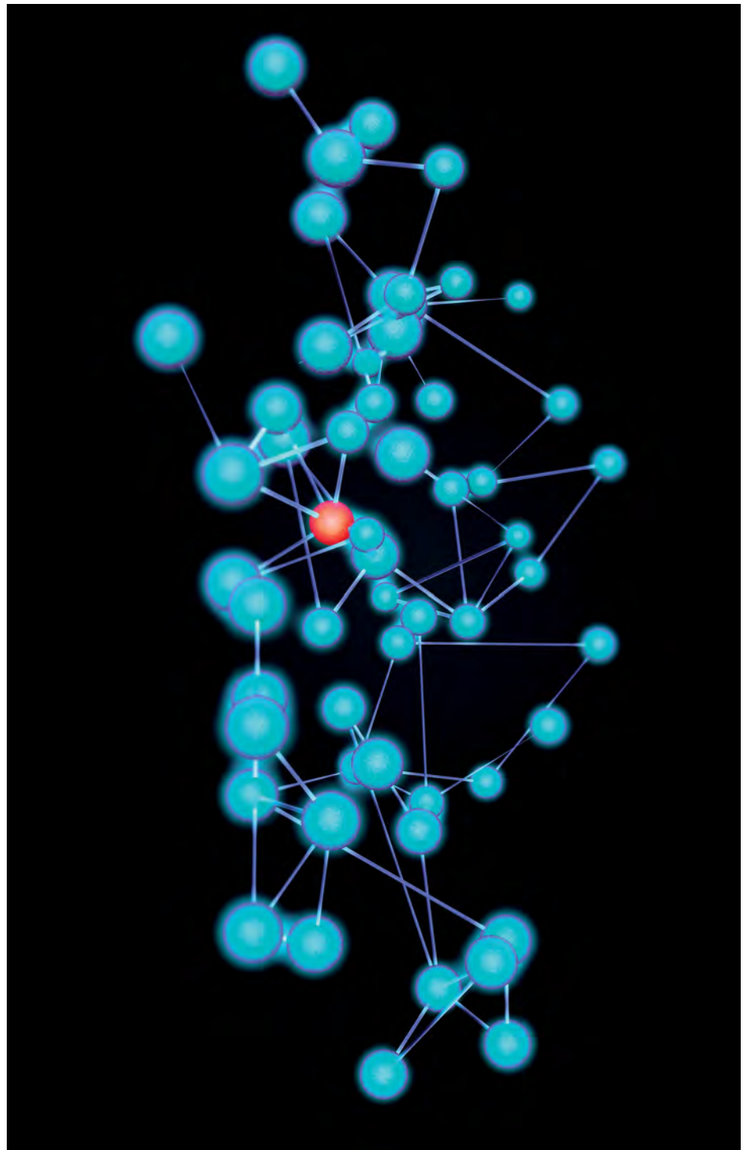
Ultrasound is teaching Albayda about prognosis, as well: "If I see the muscle is so small and all white, it's pretty clear that the patient will not get back a lot of previous muscle strength, because the muscle has already been replaced by fat. We see this is in some diseases like Inclusion Body Myositis and (this finding) can even help clarify an uncertain diagnosis." Another example: One of the most difficult aspects of Dermatomyositis, a form of myositis, is calcinosis, the presence of rock-hard calcium deposits in the skin and lining above the muscle. "I can look at the skin and it looks fine, but my eye can't see the deeper layers." Ultrasound can, and "when the fat layer looks really swollen, those are the patients who are going to get calcinosis later on." Some MRI studies have shown the presence of inflammation in the layer of fat ahead of the calcinosis, but it's not feasible to do screening MRIs. "If ultrasound shows this, then we can say, let's double up on medication, be more aggressive," and go after it in an effort to prevent calcinosis from developing.

Another thing Albayda likes about ultrasound is that patients don't just have to take her word for it: they can look for themselves, and make more informed decisions about their care. "When they can see what's happening in pictures, they understand," she says, "and patients who don't want to take more medicine, when they actually see what's going on with their organs and muscles, they say, 'Give me that next drug. I really want to get better.'" L

This work has been supported by the Jerome L. Greene Foundation and the Dr. Ira T. Fine Discovery Fund.

NOTORIOUS MIMIC

SJÖGREN'S IS TRICKY TO DIAGNOSE, AND REQUIRES EXPERTISE TO TREAT



Sjögren's may be the chameleon of rheumatic diseases: It often fools doctors because its symptoms can easily be mistaken for those of more common conditions.

The great need for answers – starting with an accurate diagnosis – and for comprehensive help is why people come from all over the world to the Jerome L. Greene Sjögren's Syndrome Center at Johns Hopkins. The center, which was begun in 2009 with funding from the Jerome L. Greene Foundation, saw 1,272 patients in 2016, and "interest in our Center keeps growing," says its Director, rheumatologist Alan Baer, M.D.; last year saw a record-breaking 114,426 visitors to the Center's website, with 262,214 page views.

Many of the patients who visit in person or online have been misdiagnosed – sometimes for years. Others know they have Sjögren's but aren't being treated for all of their symptoms, which can be manifested throughout the body.

Why is Sjögren's so tricky to diagnose? Turn on the TV or open a magazine and you're likely to see ads offering help for dry eyes, fatigue, musculoskeletal pain, dry mouth, neuropathy, or, for post-menopausal women, vaginal dryness and discomfort – all very common problems that can be caused by a host of other things, including medications and simply getting older.

How, then, do you know if the persistent eye dryness is Sjögren's – especially if you are also taking medications known to cause such side effects, or if you have another rheumatic disease? How can you tell if peripheral neuropathy, pain in the hands and feet, is happening because Sjögren's has affected the small nerve fibers in the extremities – particularly if you also have diabetes, which can produce similar pain? If you have musculoskeletal pain, is it coming from Sjögren's, or from something else, like fibromyalgia?

Then there's the reverse problem: other conditions such as allergic inflammation can cause swelling of the saliva-producing glands. They look like Sjögren's but aren't – and they need very different treatment. So, to sum up the problems facing someone with any of these symptoms: Some doctors don't look far enough to *include* Sjögren's in the differential diagnosis, and some doctors don't look far enough to *rule it out*. "In fact, a diagnosis of Sjögren's often takes a team approach." That's why the Center's multidisciplinary faculty includes rheumatologists, ophthalmologists, neurologists, gynecologists, otolaryngologists, audiologists, radiologists and pathologists. Not having the proper diagnosis doesn't just mean prolonged discomfort from the Sjögren's symptoms; it can result in permanent damage. For example: "Dryness of the eyes is a very common symptom, but if it is not managed properly, patients can get corneal erosions or ulcerations," notes Baer.

"We also pay particular attention to the loss of saliva, because it can lead to rampant dental decay," and this, in turn, can cause serious infection that can affect the heart, brain, or lungs.

Biopsy Expertise

Sometimes, diagnosis requires a sampling of salivary gland tissue that lies just beneath the lip's inner lining. This delicate procedure has some risks, including persistent numbness of the lip; at many hospitals, it is not commonly performed. Otolaryngologist Jean Kim, M.D., Ph.D., has done more than 800 of these biopsies since the Center opened, and recently published her very low rate of complications and post-operative pain in the journal, *Laryngoscope*. No one wants to get a biopsy – but "Dr. Kim's large cumulative experience and meticulous approach have resulted in excellent outcomes for our patients," says Baer. A striking aspect of her prospective cohort study was that more than 70 percent of the participants reported that they would even consider getting a second biopsy if asked by their physician.

The lip biopsy not only requires surgical expertise but "proper interpretation," Baer adds, by pathologists who are used to looking at these tissue samples.

The "One-Stop" Approach

Because so many of the Center's patients come from far away, Baer reviews their records and does his best to determine what they may need ahead of time. "We can plan for an evaluation that may take one to two days," he says, which may include ultrasound, scintigraphy, or imaging tests, a visit with a rheumatologist and the Center's other specialists, depending on where Sjögren's has manifested itself.

"Crossover" with other autoimmune diseases is another issue that requires expertise. "Sjögren's is the most common rheumatic disease to overlap with other rheumatic disorders," says Baer. "People who have rheumatoid arthritis, lupus, polymyositis or other diseases can also develop Sjögren's." Conversely, people who have Sjögren's can also develop autoimmune thyroid disease, celiac disease, biliary cirrhosis, or other autoimmune illnesses. Hopkins rheumatologists have expertise in managing such complicated diagnoses. "The Center is the glue that holds it together."

Great Promise in Clinical Trials

Baer is delighted that, after years of a "drought" of potential new treatments for Sjögren's, "there are now 13 clinical trials of systemic drugs. This is a remarkable development – a dramatic blossoming of effort and hope for a disease without any existing FDA-approved systemic treatment. It really shows that the pharmaceutical industry recognizes the great need for better treatments and is willing to invest in developing them."

Meanwhile, through the Division of Rheumatology's internationally recognized research program in Sjögren's, Baer and other investigators continue working to personalize care by characterizing pathways and identifying subsets of people with similar molecular underpinnings of the disease. They are also working hard to develop better ways to measure the activity of the disease, and to monitor how it changes with treatment. "A major problem with most clinical trials, which may only last for 12 to 24 weeks, is the lack of a way to determine clear improvement in the disease," says Baer. Ultrasound has promise as a means of tracking changes in the salivary glands with treatment; Baer also seeks to collaborate with Hopkins radiologists – who already have a proven track record of success in the development of radioactive molecular tracers for use in diagnosing and treating prostate cancer – in the development of similar tracers, "whose accumulation in the salivary glands would occur in direct proportion to the amount of healthy or inflamed tissue."

WORKING TOGETHER

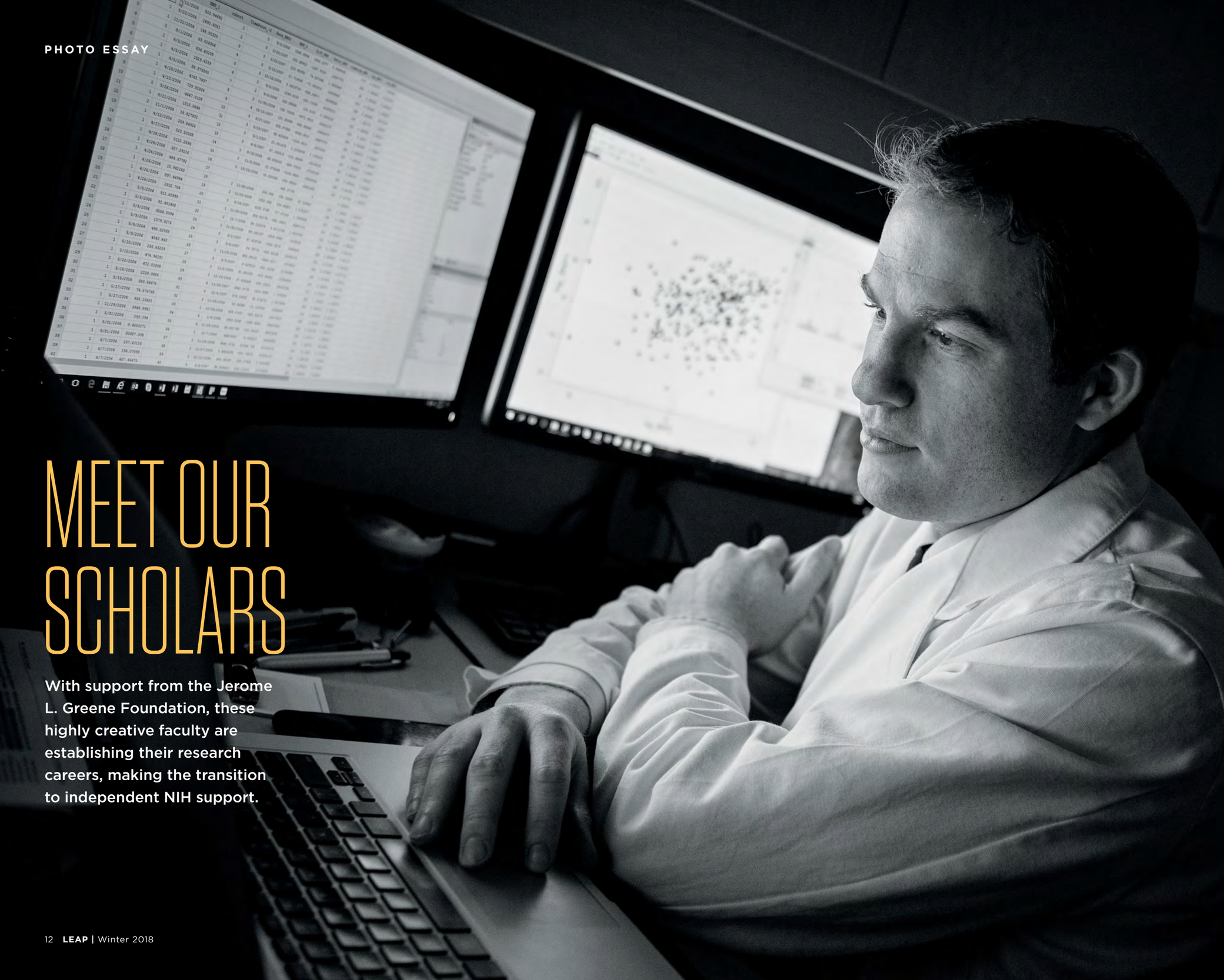
The Jerome L. Greene Sjögren's Syndrome Center has some one-of-a-kind features. First and foremost, says Antony Rosen, M.D., Director of Rheumatology and Vice Dean for Research, "our patients are partners in discovery. Many patients consent to providing their data and samples for research studies, and knowing that they may be helping us to find better treatment is empowering."

Because the Center follows a diverse group of patients over time, this gives rheumatologists and scientists an important opportunity to observe the trajectory of disease. It also helps them discern subgroups of patients who may need different approaches to diagnosis and management.

This collaboration – doctors, scientists, and patients – "is bringing us new filters (see Page 2) and innovative ways to measure and understand the pathways driving this disease," says Rosen.

MEET OUR SCHOLARS

With support from the Jerome L. Greene Foundation, these highly creative faculty are establishing their research careers, making the transition to independent NIH support.



CHRISTOPHER MECOLI, M.D., M.H.S.
INSTRUCTOR, DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR

I'm part of both the Scleroderma Center and the Myositis Center. With the mentorship of Drs. Fred Wigley, Laura Hummers, and Lisa Christopher-Stine, I am seeing patients and also engaged in research projects. One of our overarching projects in both centers is an effort to incorporate precision medicine – to determine which patients will respond best to which therapies. We're trying to phenotype patients, to place them into more homogenous groups, which allows you to better study the mechanisms at play within the disease process.

For example, we are looking at different types of biomarkers in patients with scleroderma that may help us predict who will have vascular complications such as pulmonary hypertension and ischemic digital ulcerations. We currently don't have great ways of predicting who will experience these complications. We have assembled a cohort of 300 patients who have been followed for five years, and we have good data on which patients develop these complications. We are working very hard to find new ways to help predict and potentially avoid some of these potentially devastating problems.

To help patients with myositis, we're developing a patient-reported outcome measure that will take the patient's perspective into account. It's important to acknowledge that monitoring a patient's disease is not just watching whether some biomarker increased or decreased, but how the disease is affecting quality of life – symptoms like fatigue, pain, and depression. Given that all our diseases are rare, this is not the easiest thing to do. We're starting basically from scratch to develop this measure and are working with other centers around the world.

I became interested in rheumatology for many reasons. I enjoy longitudinal relationships with my patients, to form a bond and work with them to manage their condition over decades. Many of the diseases we see are uncommon, and there is a big opportunity to increase awareness so patients don't have to struggle as much waiting for a diagnosis. To be part of this research community is an extremely enjoyable and satisfying experience. I love it very much, and I feel very privileged to go to work on a Monday morning. Most people dread Sunday nights, but there are no complaints from my end!

ELENI TINIAKOU, M.D.
INSTRUCTOR, DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR

I see patients in the Myositis Center and one part of my research is myositis. I'm working to find specific T cells called CD4+ T cells (studying blood samples from Hopkins myositis patients and also looking at control samples). We think these cells start the disease process in myositis. If we can find these T cells, we could develop more targeted medicines to treat the disease, or new tests to monitor disease activity and predict the course of disease. We are developing similar techniques that we can use to find specific T cells in Sjögren's, in patients who have specific antibodies; we are also doing it in scleroderma.

As a medical student in Athens, I had a professor who was a rheumatologist. After seeing those patients in the clinic, I started getting interested in autoimmunity. In 2013, when I interviewed for my fellowship here with Antony Rosen, I discovered that Hopkins has a very different approach to rheumatic disease than anywhere else, a scientific approach – trying to find out why, and not just treating the symptoms.

Over time, I have come to realize that patients have more insight into their disease than they are often given credit for. They can tell; as an example, not everyone who takes statins develops muscle weakness, but some people do, and at first they were not taken seriously. Now we know that they have developed autoantibodies against the enzyme target of these drugs. Just because we don't have the tools to verify doesn't mean it's wrong. Listening to the patient is just as important as what the tests can tell us.

NADIA MORGAN, M.D., M.H.S
INSTRUCTOR, DIVISION OF RHEUMATOLOGY
STAURULAKIS SCHOLAR

I see patients in the Scleroderma Center, and in my research I'm particularly interested in the fibrosis part of the disease, which is so much more than skin-deep. Patients may experience thickening of the lungs, and this often poses a big issue. I'm collaborating with my mentor, Fred Wigley, and others in the lab looking at biological factors that contribute to fibrosis; genes as well as particular proteins in the blood. We are also part of a larger project begun by Fred Wigley, Genome Research on African American Scleroderma Patients. We have assembled a cohort of over 1,000 patients, and we are working closely with the NIH to do genome-wide sequencing to see if we can find inherited factors that increase the risk for fibrosis and other complications.

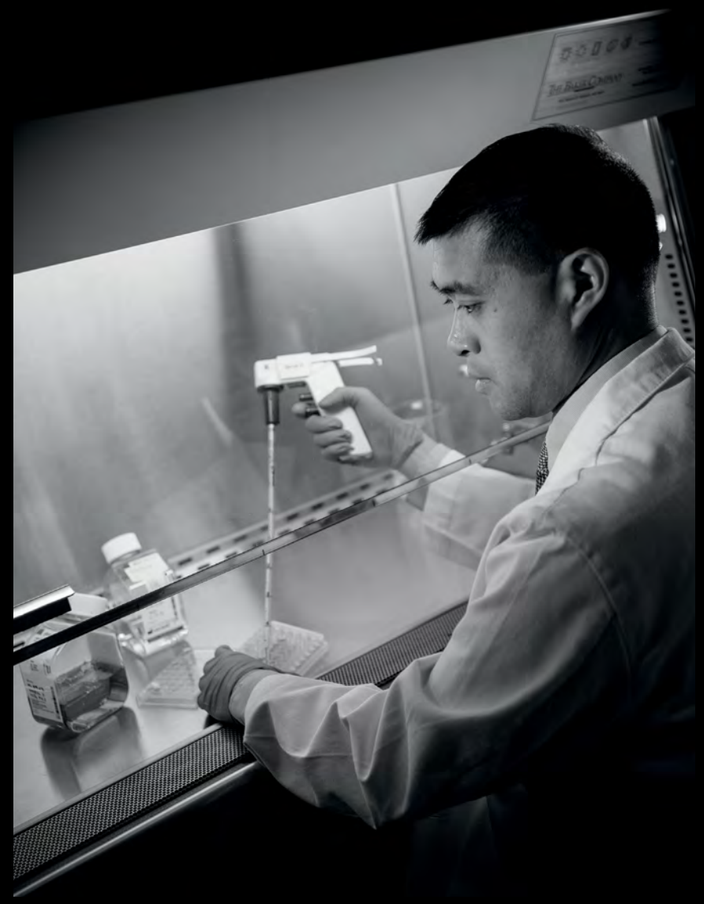
With the group in the lab, I am looking at levels of proteins in the blood to see how that may influence clinical manifestations like lung fibrosis and the extent of skin fibrosis. My hope is that if we identify any proteins or cytokines of significance, these may be potential targets for therapy.

I'm originally from Kingston, Jamaica. For over 20 years, there was only one local rheumatologist. As I did my medical training, I encountered a number of patients, even some family members, with autoimmune diseases. I realized the knowledge and expertise to treat these conditions was very scarce, but the need is great.

I chose Rheumatology because I really love continuative care – not a "one and done" situation where you interact with a patient and that's it. In Rheumatology, you get to establish a rapport that lasts a long time. Another key reason, which has a lot to do with my research, is that in Rheumatology there are still a number of unanswered questions. There is a lot of opportunity to make some meaningful discoveries. Somebody needs to do it. Why shouldn't that somebody be me?

It's great to be part of a collaborative effort, both with the patients, and with us the physicians and researchers and donors all working together toward the same goal. As a clinical investigator, I'm able to do what I do because of support from the Staurulakis Discovery Fund, which helps protect my time to do this research. More importantly, it's an investment in the patients themselves. We want to help them get better, to find out what's driving the process behind their disease. It's great to be part of that.

ERIC J. GAPUD, M.D., Ph.D.
INSTRUCTOR, DIVISION OF RHEUMATOLOGY
JEROME L. GREENE SCHOLAR



I see patients in the Vasculitis Center and also do research. With the mentorship of Livia Casciola-Rosen and Antony Rosen, I am working to understand the role of an immune mediator that is found in the tissue of patients with Sjögren's, rheumatoid arthritis (RA), lupus, and other rheumatic diseases. This particular mediator, a molecular "scissors" called granzyme B, has been thought to play a role in disease, but how it influences tissue function, and which molecules must be snipped to achieve that effect, remain unknown.

Granzyme B has been of interest to the Rosens for 20 years. It's in a lot of autoimmune diseases, and has always been thought to cause its effects by inducing cell death. Recently, using incredibly sensitive and precise measurements called RNA-seq and proteomics, we have found that granzyme B has other effects on cells that do not proceed all the way to cell death. These have never been observed previously, and may provide important clues into the molecular pathways that may cause tissue dysfunction over time.

Once we have identified those pathways, we will relate and validate them against what we actually see in tissue specimens from many different rheumatic disease patients. Finding new pathways and mechanisms is the foundation for prevention, monitoring, prediction and rational therapy, and we hope our studies will proceed down those paths.

For me, Rheumatology has always been at the cutting edge of our understanding of medicine; that's one of the first things that drew me to it. It is a great opportunity to work at a place like Johns Hopkins with all the great minds here, where they have created a culture that is really, truly rooted in the understanding that the research and the clinical observations – just plain old doctoring and medicine – really are all facets of one great thing.

THE CANCER-SCLERODERMA CONTINUUM

THE BODY'S INITIAL FIGHT AGAINST CANCER MORPHS INTO A FIGHT AGAINST ITSELF.

There's a backstory in people who develop scleroderma: an unseen struggle between the immune system and cancer. Just as in tug of war, one side – the immune system – pulls so successfully that it keeps on going after it wins.

The evidence for this is in the antibodies. Like fingerprints left behind at the scene of a crime, antibodies – made by the body to fight specific enemies – disclose identities of perpetrators that may be long gone. It was landmark Johns Hopkins research that broke this story, reported previously in *LEAP* (Holiday/Winter 2015). Division of Rheumatology scientists discovered that some people develop cancer and scleroderma at about the same time. These people have a very specific immune response (an antibody known as anti-pol) to a molecule called RNA polymerase 3. They also happen to develop a very aggressive form of scleroderma.

But that was just the beginning. The scientists later found that the gene that makes RNA polymerase 3 is mutated in these patients' cancers; the resulting altered protein is attacked by the antibodies, but in a misfire, the original form is attacked, as well – so the body's initial fight against cancer morphs into a fight against itself.

In new research, a team of investigators – Ami Shah, M.D., Takeru Igusa, Ph.D., Laura Hummers, M.D., Kala Visvanathan, M.B.B.S., Carrie Richardson, M.D., Fred Wigley, M.D., Livia Casciola-Rosen, Ph.D., and Antony Rosen, M.D. – looked at other antibodies and disease subtypes that they have identified in 2,383 Hopkins scleroderma patients and found something amazing: "We discovered that there are other groups of patients who also have cancer and scleroderma that we hadn't seen before," says Shah, the study's senior author. "Some have a higher incidence of cancer that we hadn't seen. But others – even more striking – have a way *lower* incidence of cancer, suggesting that this relationship between cancer and scleroderma is a continuum – that some immune responses in scleroderma are so good at getting rid of cancer that it doesn't emerge at all."

Of particular significance are the filters the researchers applied in this study. They looked at people with diffuse and limited scleroderma, and screened for four different autoantibody groups: anti-centromere, anti-topoisomerase-1, anti-RNA polymerase 3 (anti-pol), and those who are negative centromere, topoisomerase I, and pol (CTP-negative). They also looked at the *timing* of cancer and scleroderma: three years before scleroderma onset until the date of cancer diagnosis, and three years before and after scleroderma onset, and compared the incidence of cancer in the scleroderma patients to that of the general population.

One thing they found was that the presence – or the lack – of certain antibodies – matters. "We were able to identify subgroups with distinct risks of overall cancer, and of specific types of cancer," says Shah.

"CTP-negative and anti-pol patients are at increased risk for cancer at scleroderma onset, and those with anti-pol antibodies may have a higher risk of different types of cancer, depending on whether they have limited or diffuse disease." They also found that patients with anti-centromere antibodies seem to have a lower risk of cancer.

But it wasn't just the antibodies; it was the subtype of scleroderma – diffuse or limited. Among the anti-pol patients, as just one example, those who had diffuse scleroderma had a higher risk of breast cancer, while those with limited scleroderma may have a higher risk of lung cancer; larger studies are needed to confirm these findings and come up with approaches for cancer screening in people with scleroderma.

What about those patients with anti-centromere antibodies who had a lower risk of cancer: If these findings hold up in larger studies, "could their naturally occurring anti-cancer responses be harnessed as a cancer treatment?"

And what about the 80 percent of patients with anti-pol antibodies who don't have a history of cancer? "Did they have a cancer that triggered the whole process, but their immune response eradicated it?" The answers to these questions will involve collaboration with oncologists – who already are looking for ways to tap into the body's immune response to fight cancer.

> Some immune responses in scleroderma are so good at getting rid of cancer that it doesn't emerge at all.

Perhaps the greatest of many questions prompted by these findings is this: Could treating the cancer early make someone's course of scleroderma better? "Is there a window of opportunity where you can treat the cancer and shut off the immune response, and shut down scleroderma? Before the autoimmune response becomes its own feedback loop that just keeps going?" Stay tuned. Meanwhile, Shah and colleagues will be out there on the frontier of this disease, "at this interface between cancer and the immune system and autoimmunity."

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Division of Rheumatology
5200 Eastern Avenue
Mason F. Lord Building
Center Tower, Suite 4100
Baltimore, MD 21224
410-550-2017

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"...when we know more than we knew before, when we feel we have – by some manner of a leap – encountered the truth."

— T.S. Eliot