

LEAP

Johns Hopkins University
School of Medicine
Division of Rheumatology
Winter 2020



DREAM TEAMS

WISDOM OF THE CROWD

PRECISION REVOLUTION

GREENE SCHOLARS

NADIA D. MORGAN

WISDOM OF THE CROWD

Any builder will tell you that strength lies in the crosspieces, where framework or walls intersect. This issue of *LEAP* celebrates intersections: between clinicians and biological scientists, between both of those groups and information scientists, between specialists of different disciplines.

The more we know about rheumatic diseases, the more complex we realize they are. To treat the patients in our clinics and our Precision Medicine Centers of Excellence (see page 6), our rheumatologists bring together Johns Hopkins experts from specialties including cardiology, pulmonology, nephrology, gynecology, ophthalmology, and pathology: people looking at the same problem with different eyes, each contributing wisdom to create a much richer understanding of the disease process. As medicine evolves, multidisciplinary care is becoming a critical component of patient-centered care.

Our patients are also our partners in care: in all of our clinics, we rely on what we call “patient-reported outcomes” – detailed information from our patients about how they are doing and what they hope to be able to do. Our patients are telling us what’s valuable to them in a more focused and personalized way – which they can’t always do during a busy office visit.

This brings us to the theme of our issue: the Wisdom of the Crowd (see page 2). The key to solving the mysteries of rheumatic diseases is seeing patterns – recognizing which patients have similar disease features, learning to see warning signs before they happen, being able to predict and, we hope, improve the course of someone’s illness. Individually, our ability to see some patterns is limited; our experience is limited. The patterns that we are drawn to are very specific; we can’t see the entire, infinite world of potential patterns. No one could. By our nature, we’re each drawn to particular things – just as, if we went to an art museum, some of us would be attracted to certain paintings or sculptures, and others would connect with completely different ones.

But we now have tools – sophisticated computers, and highly complicated, math-driven programs and algorithms devised by data scientists and biostatisticians, including Scott Zeger – that allow us to gather information, analyze it, and find new disease patterns in ways that we never could have before. This is a new moment in medicine, and it requires us to appreciate each member of the team – especially our patients! – for the perspective and wisdom they bring to the picture.

Also in this issue, we’re pleased to highlight four young clinician-scientists (see page 11) who have seamlessly bridged the gap from fellowship to junior faculty, through innovative research, the mentorship of our faculty, and also through private funding. And finally (page 16), we remember Nadia Morgan, a young faculty member whose life and promising career were cut short. She is very greatly missed.

Antony Rosen, M.D.

Director, Division of Rheumatology

Vice Dean for Research

WINTER 2020

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WE'RE GENERATING THIS
VERY PATIENT-CENTERED,
PATIENT-PARTNERING
APPROACH TO UNDERSTANDING
DISEASE MECHANISM AND
UNDERSTANDING WHAT'S
VALUABLE TO OUR PATIENTS
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OUR CREATIVITY.



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WISDOM OF THE CROWD

The autoimmune diseases we treat and study in our Rheumatology Centers are intricate and many-faceted. Our hand-picked “dream teams” of specialists provide meticulous and comprehensive care for our patients. Two great examples of this discipline-spanning collaboration are the Scleroderma Center and the Sjögren’s Center.

The inflammatory process in scleroderma can damage almost every organ – the heart, the lungs, GI tract, kidneys, muscles, skin, and the joints,” says rheumatologist Fredrick Wigley, M.D., world-renowned expert on the disease and founder of the Johns Hopkins Scleroderma Center. “As a consequence, we want people who have expertise in managing each of those body systems to help take care of patients who are in distress.” These experts – because Johns Hopkins is a worldwide referral center for scleroderma patients – are also adding to the knowledge base of the disease. “We’ve been able to take a rare disease – where, for example, the heart may be *uniquely* injured, because the process is different from that of other autoimmune diseases – and have specialists focus on this area and start doing research. It’s not only helped us manage people in their day-to-day care, but we’ve set up novel research programs in scleroderma-related pulmonary hypertension, bowel disease, and heart problems.”

Even though scleroderma is rare, “because of our Center, these specialists

become experts in treating the complexities of the disease. They’re not seeing their first scleroderma patient and wondering what to do,” says Wigley.

One of those specialists is pulmonologist Robert Wise, M.D. “I’ve been working with Fred Wigley since we were both fellows, back in 1978,” says Wise, and when Wigley founded the Center in 1990, Wise was a co-founder. “It started off as basically a one-man band, with Fred, probably the best doctor I’ve ever known, taking care of all the patients. It was a natural fit for me, because my interest was in pulmonary and peripheral vascular disease. We continued our research collaboration over the years, and now there are six rheumatologists who focus almost entirely on scleroderma. We’ve conducted and are participating in a number of seminal multicenter clinical trials of lung involvement in scleroderma.”

At regular pulmonary case conferences with the Center’s physicians, “we review the pulmonary function tests, X-rays and case histories, and come up with a plan. I’ve seen literally hundreds of patients with scleroderma lung disease – more than most pulmonologists ever get to see in a lifetime;

some of these patients we've followed for 15 to 20 years. Together, we have seen every possible facet of scleroderma lung disease. Our strategy is not 'one size fits all.' We've always taken a very personalized approach to scleroderma, and the physicians here have basically considered every patient they see as contributing to the knowledge of how scleroderma affects people, and what is the best way to approach the treatment of the disease. I think the Scleroderma Center has really been able to set a standard of how to care for and follow patients with scleroderma lung disease."

Sjögren's Syndrome: Team Diagnosis, Team Treatment

For patients with Sjögren's syndrome (SS), is the exact diagnosis that important? Many rheumatologists don't think so, says Alan Baer, M.D., Director of the Johns Hopkins Jerome L. Greene Sjögren's Syndrome Center, "given the lack of disease-modifying therapies. Many rheumatologists believe that the steps required to secure an accurate diagnosis, including a lip biopsy, would not likely change the treatment, so they forego asking their patients to undergo an extensive evaluation."

Baer disagrees, and he suspects that many patients do, as well: "For patients, the diagnosis of SS can be a scary one, raising concerns about a chronic illness marked by persistent fatigue, pain, progressive dryness of mucosal membranes, sexual dysfunction, internal organ involvement and a heightened risk of lymphoma." Unfortunately, all of these problems are easily attributed to other causes. For example, many people have dry eyes; many women suffer vaginal dryness as they get older; numerous medications can affect salivary gland production; fatigue has myriad possible causes.

Thus, every patient who comes to the Sjögren's Center starts out getting a thorough, one- to two-day, multidisciplinary workup that begins with an evaluation by a



"I've seen literally hundreds of patients with scleroderma lung disease – more than most pulmonologists ever get to see in a lifetime; some of these patients we've followed for 15 to 20 years. Together, we have seen every possible facet of scleroderma lung disease. Our strategy is not one size fits all."

rheumatologist, but often includes evaluations by an ophthalmologist, Esen Akpek, M.D., an otolaryngologist, Jean Kim, M.D., Ph.D., who has expertise in lip biopsy of Sjögren's patients; and a gynecologist, Anne Burke, M.D. Patients undergo a battery of tests, as well, including measures of salivary flow, lab tests, and salivary gland ultrasound.

These tests – and, importantly, accurate interpretation of the biopsy by Lisa Rooper, M.D., a pathologist with expertise in SS – not only help pinpoint the diagnosis, but “if it is Sjögren's, then we can judge the disease severity and provide an estimate of the risk of lymphoma, the development of other manifestations, and the current severity of their disease.”

Once the diagnosis is made, SS often requires “multi-faceted management,” Baer continues. As in many rheumatic diseases, there are distinct subsets, or phenotypes, of patients. One subgroup of patients is at higher risk of developing lymphoma; another subgroup develops neuropathy – nerve damage that can result in numbness or tingling, muscle pain and weakness. Sjögren's patients also may have a second rheumatic disease, such as rheumatoid arthritis, lupus, scleroderma, or polymyositis, Baer notes. “Other non-rheumatic autoimmune diseases occur more commonly in SS, as well” including pernicious anemia, celiac disease, and Hashimoto's thyroiditis. Understanding the different phenotypes helps Baer and colleagues stratify patients' risks and develop individualized plans – and treatment teams – for their care.

Nearly all – 98 percent – of people with SS have dry eyes. But don't a lot of people? Wouldn't the same over-the-counter drops that help people with irritated eyes from allergies help people with Sjögren's? No, says Akpek, and the consequences of improper treatment can be devastating.

“If the dry eyes are not treated correctly, there can be permanent damage. First, the

If the eye dryness in Sjögren's is not treated, it can cause permanent damage. However: “With good, appropriate and early treatment, patients get better. We can actually reverse some of the superficial damage on the eye surface.”

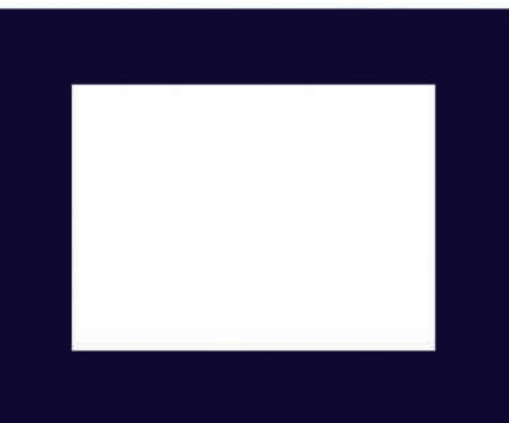
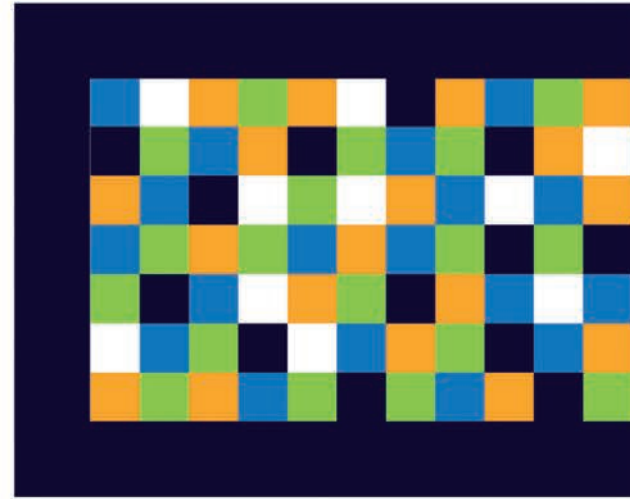
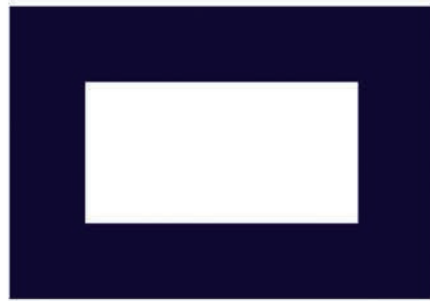
tear film becomes unstable over the cornea, and this causes fluctuating vision. Patients can't sit and read for prolonged periods of time, drive, or use their computer. The tear film overlying the cornea breaks up the picture – so the image that is sent to the brain is blurred; they have to blink, and redistribute the film. That takes a long time and effort, and patients get fatigued.” Akpek's research group recently showed for the first time that reading speed also decreases in Sjögren's. “When there is so much dryness on the corneal surface, patients start having high turnover of epithelial cells; just as the skin sheds its cells, the cornea also sheds cells on a regular basis. But when there's dryness, this is exaggerated, and healing is delayed. Tears are nourishing – like blood flow to your tissue. If you don't have good tears, healing decreases, you get blurring of the vision, glare and light sensitivity.”

It gets worse. “If the dryness is not addressed, this can lead to ulcerations, perforations, even secondary infections in the cornea. However: If SS is identified early, “with good, appropriate and early treatment, patients get better. We can actually reverse some of the superficial damage on the eye surface,” says Akpek. “But once permanent damage happens to the tear-secreting glands, we can't help it with medicine.” Akpek and colleagues at Wilmer are trying to raise awareness of SS among eye doctors, with lectures and a

Continuing Medical Education conference.

Another cause of great discomfort in SS is vaginal dryness – and again, here is another symptom that is so common, because it is experienced by many women during menopause, that many doctors don't consider SS as a possible cause. “Often, I see women who have been experiencing vaginal symptoms for a long time and not really knowing what to do about it,” says gynecologist Burke. “Sometimes it's not very easy to tell that it's Sjögren's,” although the symptoms can be more severe. “It's a very significant problem.”

Because the disease is relatively rare, “many gynecologists don't see a lot of Sjögren's patients, and a lot of non-gynecologists don't ask about the vagina during a regular check-up.” Even though Burke does see many women with SS, “I do not have a perfect treatment; we may end up trying different things. Often, if a component of the dryness is due to menopause, hormonal therapy will help. There are over-the-counter products that provide additional moisture; compounded products (made at specialized pharmacies) can help, and so can different oils or vitamins.” Localized treatment works even better alongside systemic treatment, and Burke coordinates with the patient's rheumatologist at the Center “to find the treatment pathway that works best for each patient.” [L](#)



PRECISION REVOLUTION

Imagine a room full of crates — like the giant warehouse at the end of “Raiders of the Lost Ark.” Your task is to try to make sense of what’s in there. It seems impossible. You take a deep breath and start with the first shelf of Row 1 — knowing, even as you pry the wooden lid off the first crate, that this monumental job is just too big to tackle on your own.

But what if you had some help from a powerful computer? One that could not only analyze the contents of every crate very quickly, but study tens of thousands of artifacts at once? Just think of what you could do!

This is happening right now, except instead of opening up bulky wooden crates, our scientists and clinicians are unlocking countless mysteries found in tiny bits of blood, tissue, cells, DNA, RNA, protein, lipids, and metabolites. They're looking at clinical data, radiology and imaging studies, patient-reported outcome measures, recognizing patterns and making connections at lightning speed – thanks to sophisticated computer programs and

says Antony Rosen, M.D., Director of Rheumatology, who is also Vice Dean for Research at Johns Hopkins. “This enormous web of interconnected information is changing the way we generate, capture, analyze and deploy data. It’s also changing how we make treatment decisions.

“We’re generating this very patient-centered, patient-partnering approach to understanding disease mechanism and understanding what’s valuable to our patients in a more focused and personalized way, using tools that allow us to augment

the same disease behaves the same way,” says Christopher Mecoli, M.D., M.H.S., Director of Research Operations and Physician Lead for the Myositis PMCOE. This PMCOE is housed within the Myositis Center, led by Lisa Christopher-Stine, M.D., M.P.H. “Patients with the exact same diagnosis, under the same umbrella term of ‘myositis’, can be extremely different from one another.” Thus, he continues, “patients should not all be diagnosed the same way; they probably should not be monitored or treated the same way.”

What defines a subgroup? Is it just the symptoms and signs, the way a disease manifests itself in a particular group of patients? Not always. The recognition of subgroups also comes down to the particular filters used to look at patients. Just as, for example, you might have used colored lenses as a kid to see hidden pictures on a cereal box; a tiger visible with a red lens might be invisible with a green lens – but that lens may reveal a hummingbird in a tree. “We can look at genetics, treatment response, biomarkers in the blood, trajectories of the disease course,” says Mecoli. The number of filters is, seemingly, limitless – expanding all the time, as scientists find new markers of disease.

A Transformation in Collecting Data

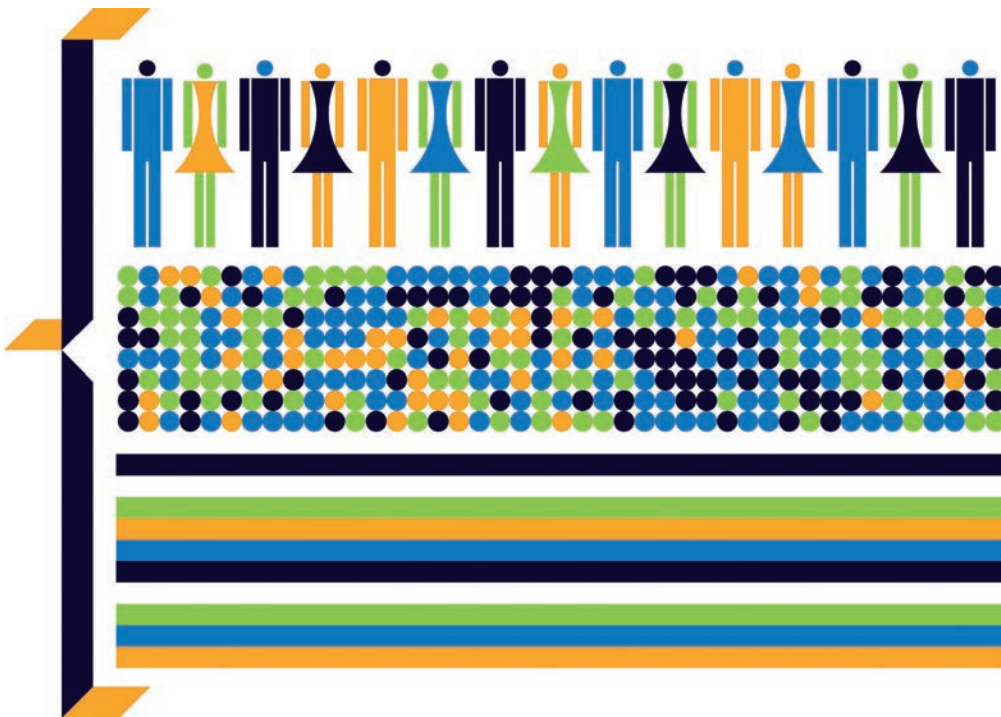
In the year since the Scleroderma Center was designated a PMCOE, “we’ve really undergone a major transformation in how we collect data,” says Ami Shah, M.D., M.H.S., Director of Clinical and Translational Research at the Scleroderma Center. It used to be, “we would do a routine history and exam, write it down on paper, manually enter that into a database, and ask patients to fill out questionnaires about their symptoms that we would also enter into a database.” In collecting data for research and for routine patient visits, “we would duplicate almost all our work. Now we’re collecting data for clinical care and research at the same time. The integration of that data has been very challenging, involving multiple databases, including

extra resources, including top-notch data scientists, at two separate Johns Hopkins Precision Medicine Centers of Excellence (PMCOEs) within Rheumatology: one for Scleroderma, the other for Myositis.

What makes these PMCOEs different from other Johns Hopkins Rheumatology clinics? Not the patient care! That’s the same excellent, personalized care that all of our patients receive. The difference is in what’s happening with the data collected at these PMCOEs. One day, we hope to be able to have this “breadth of interactions across interfaces” in all rheumatic diseases,

both our processing power and our creativity.” For years, Rosen has been a steadfast advocate for precision medicine – for “precision diagnosis and precision treatment. Because even though you can aggregate diseases under one label, many diseases – especially rheumatic diseases – are heterogeneous.” For example, some people who have scleroderma have lung involvement; some do not. Some people with Sjögren’s syndrome develop dry eyes, and some do not.

“Because of Dr. Rosen’s vision of subgrouping, we no longer treat these conditions as though everyone who has



information in the electronic medical record (EMR), research databases, and outside test results.” But the groundwork has paid off, she continues. “We have secure data pipelines, where the data goes from the EMR into a REDCap (Research Electronic Data Capture) database, and from there into the Precision Medicine analytics platform. Pulmonary function tests and echocardiogram results used to be manually entered. Now they’re electronically transmitted, and we can get a comprehensive look at the data in a more seamless way. For the physicians and staff, this is really transformative.”

In the Precision Medicine Analytics Platform, lab and test results and information from the visit are also integrated with data produced by the patients themselves – on iPads in the waiting room, patients report in detail how they are doing – their symptoms, their quality of life, their goals for treatment. “We’re getting patients much more involved in their care,” says Mecoli. On the iPads, “patients are telling us what they think is most important,” which doesn’t always happen in traditional office visits. “Often, what patients and physicians feel is important are different things; we may have different goals.” Sometimes in a clinic visit, patients only respond to direct questions from physicians, and don’t volunteer anything; sometimes, physicians don’t ask that one question whose answer might shed unexpected light on what’s really going on with the patient. Sometimes, both physicians and patients are focused on a test result or troubling symptom, and don’t get to cover everything else. That’s where the iPad questionnaires have proven so helpful.

The Importance of Trajectory

Let’s say Mrs. Smith, a patient in the Scleroderma Clinic, is due for her regularly scheduled visit, and Shah will be able to show her much more: “Our vision is that on the EMR, I will be able to pull up graphs of Mrs. Smith’s own data, show her what her skin scores have done over time, how her lung function has been, and where she is now compared to where she’s been. Either things look stable, and we don’t need to make any changes, or there’s a concerning trend and we need to initiate or change therapy. We think this will help patients feel engaged in medical

or whether we need to initiate or change her course of therapy.” With the PMCOE technology, Shah will be able to show her much more: “Our vision is that on the EMR, I will be able to pull up graphs of Mrs. Smith’s own data, show her what her skin scores have done over time, how her lung function has been, and where she is now compared to where she’s been. Either things look stable, and we don’t need to make any changes, or there’s a concerning trend and we need to initiate or change therapy. We think this will help patients feel engaged in medical

form of scleroderma, who are positive for this particular antibody. How do you compare to this subgroup? This is helpful to the physician, not only for immediate care, but it can also give insight into other research questions and may foster additional scientific discovery.”

Looking at the trajectory could help patients understand why a proactive change of medication may be needed: “Patients may think they’re doing pretty well,” says Mecoli, “but if we pull up a graph and show that they have actually

“Traditionally, medicine depended on the knowledge, experience, and intuition of individual physicians to make decisions. But medicine is changing so that now we are bringing the relevant data, in easily accessible forms, right in front of the patient and provider, so that decisions are data-driven.”

decision-making, and also give them a better understanding of their disease.”

Trajectory modeling can also show patients the bigger picture, notes Mecoli. “Soon, we will be able to plot patients’ disease course and compare it to other patients like them. We can say, ‘here are the trajectories of other patients like you – your same disease features, sex, race, and within 10 years of your age – and here’s where you stack up.’”

The comparisons can be made within subgroups, too, Shah adds: “Here are other patients who have the same diffuse

been in a gradual decline over a two-year period, they can see why we think a change is needed: ‘I know you feel well, but I don’t like the direction you’re going.’”

Understanding trajectory is good for physicians, too, Mecoli says. “Sometimes we’re not very good at incorporating time; we see a patient right then and there and things look okay, but sometimes we’re surprised when we look at the data and see a trend – for example, the lung function has been deteriorating slightly, or strength has improved. It helps us look beyond the cross-sectional world of a single point, or a single slice, in time.”

And what about the future? The PMCOE physicians and scientists have access to the skills of Johns Hopkins University data scientists, including Scott Zeger, Ph.D., Professor of Biostatistics and Medicine, and Co-Director of Hopkins inHealth, to help foresee what may lie ahead. “Scott Zeger is the scientist who came up with the series of equations that allow these trajectories to be calculated and used,” says Rosen. “Traditionally, medicine depended on the knowledge, experience,


record more and more information, and we manage that information safely, that somehow, through the use of computers, what is true will emerge.”

In fact, he adds, “Nothing could be further from the truth.” The challenge is to learn how to analyze, to use that information intelligently. That’s where biostatistics comes in: we learn how to infer what is true from noisy information. We want to refine what we think is true for a population, and understand whether that applies to the individual – or

“If we know what somebody looks like at the beginning of their disease,” says Shah, “can we predict what is likely to happen, and with what degree of accuracy can we make that prediction? Can we identify those patients most likely to progress, and can we then intervene early and change outcomes?” New measurement tools available through the PMCOE could improve early detection: for example, Laura Hummers, M.D., Sc.M., Co-Director of the Scleroderma Center, is leading an important study examining the ability of quantitative chest CT imaging to predict those most likely to progress from scleroderma lung disease.

And finally: Can we help rheumatologists and patients beyond Hopkins? “In many forms of myositis, there’s currently no agreed-upon way of treating patients. You’d think there would be, since we’ve known about these diseases for several decades. But when you ask, what is the first-line therapy, what do you start out with – you hear different responses from experts. While treatment guidelines based on expert opinion exist, there are no strategies based on robust data.” The PMCOE research “will give us the ability to predict who will respond to a certain therapy, who will have an adverse effect. Can we predict who will have refractory disease, who will need combined therapy? Who will be able to taper off medication and go into remission? There’s currently no way to identify these people ahead of time.”

The PMCOEs mark an exciting moment in medicine and science, says Shah. “There’s been a revolution in computing, and in measurement, and in connectivity. All these revolutions are coming together. I wouldn’t say we’ve been taking baby steps, but I do think we can accelerate the research in a way we simply couldn’t before, because we now have these resources – institutional resources, data science resources, measurement resources – that didn’t exist before. Maybe we’re at a point where we can make leaps, instead of incremental steps in discovery.”



“If we know what somebody looks like at the beginning of their disease, can we predict what is likely to happen, and with what degree of accuracy can we make that prediction? Can we identify those patients most likely to progress, and can we then intervene early and change outcomes?”

and intuition of individual physicians to make decisions. But medicine is changing so that now we are bringing the relevant data, in easily accessible forms, right in front of the patient and provider, so that decisions are data-driven. We’re bringing science and data to the practice of medicine in highly convenient and rapid ways, and making better decisions based on evidence.”

In a sense, says Zeger, medicine is “becoming an information science as much as it is a biological science. But there’s a misconception that if we simply

how it ought to be changed for a particular individual. That involves probability models, to identify how best to treat the individual patient.” At Johns Hopkins, Zeger says, “it’s the integration of our basic biological scientists, clinical scientists, and our information scientists that allows us to develop hypotheses about what might be true, and we use the data to test those specific hypotheses.” No other place can do this sort of focused research as well as Hopkins, he continues, “because of how closely integrated our scientists are with our clinicians.”

BRIDGING THE GAP

How does a fledgling academic physician-scientist bridge the gap between fellowship and a faculty position? Funding is the scaffolding: without sufficient research funding, this gap can seem more like a chasm. Mentorship, support and nurturing are the planks: “One of the most important and rewarding aspects of a faculty member’s job is to help train and encourage the next clinician-scientists,” says Antony Rosen, M.D., Director of Rheumatology and Vice Dean for Research. “We start with unique and very bright individuals, and create the environment that allows them to ask questions no one has ever asked before. We cultivate their desire to help patients and their scientific inquiry, giving them the tools they need, and with this supportive environment, they are on their way!”

Meet four promising young investigators who have recently crossed this gap, with the support of our faculty and the underpinning of “bridge” funding from organizations including the Jerome L. Greene Foundation, the Staurulakis Family Discovery Fund, the Ira T. Fine Discovery Fund, and the Rheumatology Research Foundation. Private grants gave these junior faculty members time and the means to navigate uncharted waters: original, creative, highly novel projects involving unexplored or newly identified aspects of disease. The gift of protected time also allowed them to gather preliminary data and write the scientific publications that will enhance the field and build their reputations as serious clinician-scholars and thought leaders who will make life better for patients with rheumatic diseases, at Hopkins and everywhere.



CHRISTOPHER MECOLI, M.D., M.H.S.
ASSISTANT PROFESSOR OF MEDICINE,
DIVISION OF RHEUMATOLOGY

In September 2019, I received a National Institutes of Health K23 award to optimize how we identify cancer that is associated with myositis. There's so much we don't know, and because we have the Myositis Center, which draws patients from around the world, we have the opportunity to shed light on which patients with idiopathic inflammatory myopathies are at risk for cancer, and how best to evaluate them.

We know that some patients with myositis develop cancer at the time of the onset of myositis; this is called cancer-associated myositis. But not only does the risk vary; so does the type of cancer. Fortunately, we have expertise in the Division of Rheumatology on cancer and scleroderma, thanks to the work

of Ami Shah, Livia Casciola-Rosen, and Antony Rosen. Expanding their insights to myositis, we can systematically investigate several myositis-specific autoantibodies and use them to help define clinical subgroups of patients. We know these autoantibodies have associations with cancer, but we don't know which patients are at the highest risk for developing cancer, what's the magnitude of their risk, and what type of cancer they're at greatest risk for. Our preliminary data show that these autoantibodies can not only help us better define subgroups of patients who are at higher risk of getting cancer, but they can even tell us which type of cancer those patients are most likely to develop.

Also, we have demonstrated that despite the widespread use of a variety of cancer-screening tests used by clinicians throughout the U.S., not all these tests have equal value in people with myositis. We do a lot of tests, but

we don't know how helpful they are. So: what's the best way to go about screening these patients? What tests lead to good results, what tests lead to false positives? This is important, because the answers we receive will lay the foundation for us to develop evidence-based guidelines that will improve the field. To find out, we are using one of the largest cohorts of myositis patients in the world to define and validate autoantibodies associated with a higher cancer risk, and to see just how useful they are in showing the risk of cancer-associated myositis - in all patients with myositis, as well as in these distinct autoantibody subgroups. We hope not only to improve the current standard of cancer assessment in myositis patients, but to come up with a smarter, less harmful strategy - requiring fewer imaging and invasive studies - for cancer detection. These more specific approaches are often cheaper!



ZSUZSANNA McMAHAN, M.D., M.H.S.
ASSISTANT PROFESSOR OF MEDICINE,
DIVISION OF RHEUMATOLOGY

My project, on gastrointestinal (GI) disease and scleroderma – specifically, complications in GI transit (the movement of food through the digestive system) – was inspired by a very challenging and interesting patient. When I looked for answers, I realized there weren't any! No one was working in this area. I feel very fortunate, not only for this opportunity to contribute to the field, particularly in the specific niche of neurogastroenterology in scleroderma, but also for my amazing mentors: Fred Wigley, who has unrivaled clinical expertise in scleroderma; Livia Casciola-Rosen, a pioneer in identifying novel antibodies, and Antony Rosen, renowned for his expertise in translational investigation. I also have an outstanding, interdisciplinary group of advisors, including Jay Pasricha in Gastroenterology.

Scleroderma can affect the GI tract anywhere from the esophagus to the anorectum, but while 90 percent of patients are affected by GI problems, there is big variability. Some people have *upper* GI involvement – reflux, gastroparesis (impaired functioning of the stomach), nausea – but have completely normal lower GI function; for example, they have no trouble with bowel movements or with fecal incontinence. Other patients have bacterial overgrowth, severe constipation, and *lower* GI problems, but have a normal upper gut. Our goal is to understand the differences, to learn how they affect disease mechanism, and to develop strategies for more targeted therapy.

With the K23 award, I am focused on clinically characterizing these subsets of GI dysmotility using a radionucleotide-based whole gut transit study, and then developing autoantibody correlations for potential biomarkers: (for example, is there an autoantibody particularly associated with upper GI symptoms in scleroderma?). With the Rosen Lab, we're looking at traditional autoantibodies associated with scleroderma, at antibodies that target neuromuscular transmission



pathways, and also screening for novel autoantigens that target the GI tract in scleroderma. Further, we hope to understand how these autoantibodies affect transit in specific layers of the gut, by applying the patient's serum to layers of muscle and nerve in the mouse gut that are important for controlling transit – trying to see where these autoantibodies bind and what cell types might be relevant in abnormal transit.

Currently, we know very little about autoantibody-based clinical subgroups in scleroderma GI disease. But we are changing that, and identifying GI subgroups will give us a platform to study disease mechanisms and, in the

future, to explore novel therapies. We already have strong evidence from our preliminary data that specific patterns of GI dysmotility exist in scleroderma, that autoantibodies to neuromuscular transmission pathways are present in patients with scleroderma, and that these may be linked to specific GI outcomes. We also have evidence, using the serum of patients with scleroderma GI dysmotility, of distinct target cells in the gut, which we hope will provide insight into the biology of scleroderma GI problems, and help us focus on novel treatments.

GREENE SCHOLARS

LAURA CAPPELLI, M.D., M.H.S., M.S.
ASSISTANT PROFESSOR OF MEDICINE,
DIVISION OF RHEUMATOLOGY

One of my main areas of research is understanding adverse events from cancer immunotherapy drugs, called checkpoint inhibitors. These drugs are designed to help the immune system fight cancer, and they are revolutionizing cancer treatment. However, they can cause too much inflammation in the body, leading to syndromes that look similar to a lot of our rheumatic diseases. For example, patients can get immune-mediated arthritis that looks like rheumatoid arthritis, or dry mouth and dry eyes, symptoms found in Sjögren's disease. My focus with this grant is to enhance understanding of a

new rheumatic disease, inflammatory arthritis due to immune checkpoint inhibitors. It can persist even after the immunotherapy drugs are stopped.

This is a new area, and any time you're doing research in a new area, it can be difficult to find funding. The Greene Scholar Award allowed me to start my research program in cancer immunotherapy-related adverse events, under the guidance of Drs. Bing Bingham and Ami Shah. This funding allowed me to gather the preliminary data and publish papers that made me competitive for governmental funding. In August, my K23 grant from the NIH started. So it's really a direct line for me: the Greene Foundation allowed me to join the faculty and to do something new and different, to establish a program so I could be

competitive for additional funding.

With the award, I hope to accomplish several projects: first, to better understand the epidemiology of inflammatory arthritis due to cancer immunotherapy. I'm working with oncology to do a screening study, looking at everybody who's starting immunotherapy and then following them over time to see who develops arthritis and who doesn't. We'll also look at clinical features and some radiographic features, to see whether patients have osteoarthritis or other pre-existing joint disease that might predispose them to arthritis.

I'm also hoping to better characterize the clinical features of inflammatory arthritis caused by immunotherapy, to see if we can divide patients into subgroups; we will look at serum cytokine profiles and autoantibodies before and after immunotherapy treatment, and comparing this in patients who develop inflammatory arthritis and in patients who do not develop it. We have noticed that there are some different patterns to the arthritis and how severe it is. But there's limited data in terms of understanding how much arthritis is really happening, and whether it's more likely to develop with certain drugs rather than with others. It's an exciting opportunity to help understand the underlying biology, to address key knowledge gaps for this emerging disease, and to provide better care to patients. It is also an example of the new type of science, which is highly interactive and collaborative across different disciplines. To understand this type of arthritis, you need a rheumatologist, somebody who knows how to examine joints and take a proper history. To aid the oncologists, we've designed some very simple screening questions for each visit. Then patients are referred to me, so I can confirm the diagnosis or say they don't actually have it. This is a pretty big effort that requires a lot of good collaboration with oncology.



JULIE PAIK, M.D., M.H.S.

**ASSISTANT PROFESSOR OF MEDICINE,
DIVISION OF RHEUMATOLOGY**

My research focus is understanding skeletal myopathy (weakness of the skeletal muscles) in scleroderma, an area of scleroderma that has been poorly defined. Previously, we evaluated the muscle histopathology of scleroderma patients with skeletal myopathy and found a unique subtype, called fibrosing myopathy. We found that these patients are significantly more likely to develop lethal disease due to heart complications, compared to patients with inflammation or necrosis on muscle biopsy. Diagnosing this subtype of patients as early as possible is critical. But it can be challenging, because these patients typically do not have high markers of muscle inflammation in the blood (which would suggest the need for a muscle biopsy).

An alternative and exciting method is to use advanced muscle MRI techniques, because we can not only avoid muscle biopsies — which can be painful and take time to heal — but also identify patients at an earlier stage. With Michael Jacobs, Ph.D., we established new imaging techniques to detect early, disease-related changes in the muscle. We hope to use these techniques to predict outcomes, such as disability or cardiac-related death, and also to measure outcomes in clinical trials.

It takes a village to prepare and get this type of NIH award. My primary mentors, Laura Hummers and Fred Wigley, were instrumental in helping me secure this funding. I truly would not be where I am without their mentorship. Another mentor is Scott Zeger, Professor of Biostatistics at Johns Hopkins, and I'm collaborating with him as part of the Precision Medicine Center of Excellence in Scleroderma (see page 6), funneling a lot of data — specific muscle and scleroderma characteristics and muscle MRI characteristics — into a classification schema that may help us stratify risk and predict the course of disease for our patients. This will help us provide even better care. Andrew



Mammen, Professor of Neurology and Muscle Unit Director at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, also provided his expertise to help me develop my niche of muscle disease in scleroderma.

The bridge funding I received has been a great gift, but for me, the greatest gift has been the time and dedication of my mentors. The support of my mentoring team was crucial at this stage of my career, and I believe that it has molded me into a more successful physician-scientist.

IN MEMORIAM

ONE OF OUR BRIGHTEST

Nadia D. Morgan, M.B.B.S., M.H.S.



Our entire focus of *LEAP*, starting with the name of this magazine, is hope: the joy of discovery, the great optimism that comes from progress and momentum in helping our patients. You can feel it in our clinics, and in talking with every faculty and staff member of the Division of Rheumatology.

One of the brightest examples of hope we can think of is the life of Nadia Dominique Morgan, M.B.B.S., M.H.S., who had just started her career as a young faculty member at the Scleroderma Center.

We, her colleagues and friends, her patients, and the many people whose lives she touched, were devastated on December 15, 2018, when Nadia was involved in a fatal motor vehicle accident.

It is impossible to look at Nadia's life and not see the hope and optimism that she embodied, and that continue to inspire us.

A native of Jamaica, she earned her bachelor of medicine, bachelor of surgery degree at the University of the West Indies, Jamaica, where she received both medical and surgical honors. She completed her internship and residency training in internal medicine at the State University of New York Downstate Medical Center, and served an additional year as Chief Resident. She was recruited to Johns Hopkins to complete her fellowship training in Rheumatology, and she also earned a Master of Health Science degree in clinical investigation from the Johns Hopkins Bloomberg School of Public Health.

During her fellowship, Nadia developed a strong interest in the impact of race on rheumatic diseases. She was an investigator on the largest study ever conducted on patients of African ancestry with scleroderma, and in 2016, she received the Distinguished Fellow Award, the highest honor offered to a trainee from the American College of Rheumatology (ACR). Morgan was the first Afro-Caribbean woman to serve as a member of the ACR's Standing

"She remained tremendously proud of her Jamaican heritage, and often quoted the Jamaican motto, 'Out of Many, One People.' She used this as a way of reminding us that the aspects of life that drew us together were far more important than the quirks that drew us apart."

Committee on Patient Registries. She also served on the ACR's Fellows-in-Training Subcommittee. She was elected to Alpha Omega Alpha, a prestigious national medical honor society, in 2017.

"In 2016, Nadia became a U.S. citizen," says her friend and colleague, Phil Seo, M.D. "She remained tremendously proud of her Jamaican heritage, and often quoted the Jamaican motto, 'Out of Many, One People.' She used this as a way of reminding us that the aspects of life that drew us together were far more important than the quirks that drew us apart."

Nadia "had a fierce, independent streak and a drive to succeed," Seo adds. This was "softened by her tremendous compassion for others, which she shared with patients and colleagues alike. She had a magnetic personality and a commanding presence; you could instantly tell when she walked into a room. Like the ginger beer she liked to drink, she was sweetness, tempered with a bit of spice. She is irreplaceable. She will be missed."

Interviewed for the Winter 2018 issue of *LEAP*, one year before her death, Morgan said that in her hometown of 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, that 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?"



JOHNS HOPKINS

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The publication of *LEAP* is made possible through a grant from the Jerome L. Greene Foundation



“There’s been a revolution in computing, and in measurement, and in connectivity. I wouldn’t say we’ve been taking baby steps, but I do think we can accelerate the research. Maybe we’re at a point where we can make **LEAPS**, instead of incremental steps in discovery.”

— Ami Shah, M.D., M.H.S., Director of Clinical and Translational Research at the Johns Hopkins Scleroderma Center