INSIDE PATHOLOGY

MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

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INSIDE PATHOLOGY

ON THE COVER

Original Artwork: Bailey Fraker
Illustration representing the various machines and processing used within our labs.

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Regents of the University of Michigan: Jordan B. Acker, Michael J. Behm, Mark J. Bernstein, Paul W. Brown, Sarah Hubbard, Denise Ilitch, Ron Weiser, Katherine E. White, Santa Ono, *ex officio*.

Technological advances are growing at an exponential rate across all sectors of healthcare, including Pathology. To stay abreast of these developments, the Department of Pathology has invested heavily in advanced instruments and expert faculty and staff to position us to meet the diagnostic needs of patients today and in the future.

In this issue, you will read about cutting edge research, new technologies being implemented in our clinical laboratories, and the translation of research into clinical care and some of the complexities this entails. Our Pathology Informatics staff will discuss their involvement in supporting these advances and you will hear how social media is being utilized to spread the word about all the great things we are doing in Pathology.

You will also have the opportunity to look back over the career of Dr. David Gordon and the changes he has seen in cardiovascular pathology through the years, then read the perspective of Michael Pitter, a newly minted PhD graduating from our Molecular and Cellular Pathology program.

I hope you enjoy this issue of *Inside Pathology* magazine!

Charles A. Parkos, MD, PhD
Carl V. Weller Professor and Chair
Department of Pathology
Michigan Medicine

ON SOCIAL MEDIA

Find out what's new on our social media channels! Stay updated about our events, participate in our weekly cases, and listen to our pod casts.

Case of the Week
Read interesting cases and guess if you know the diagnosis.
#COTW

The Path Report
Hear interviews with our faculty on a range of different topics related to pathology.
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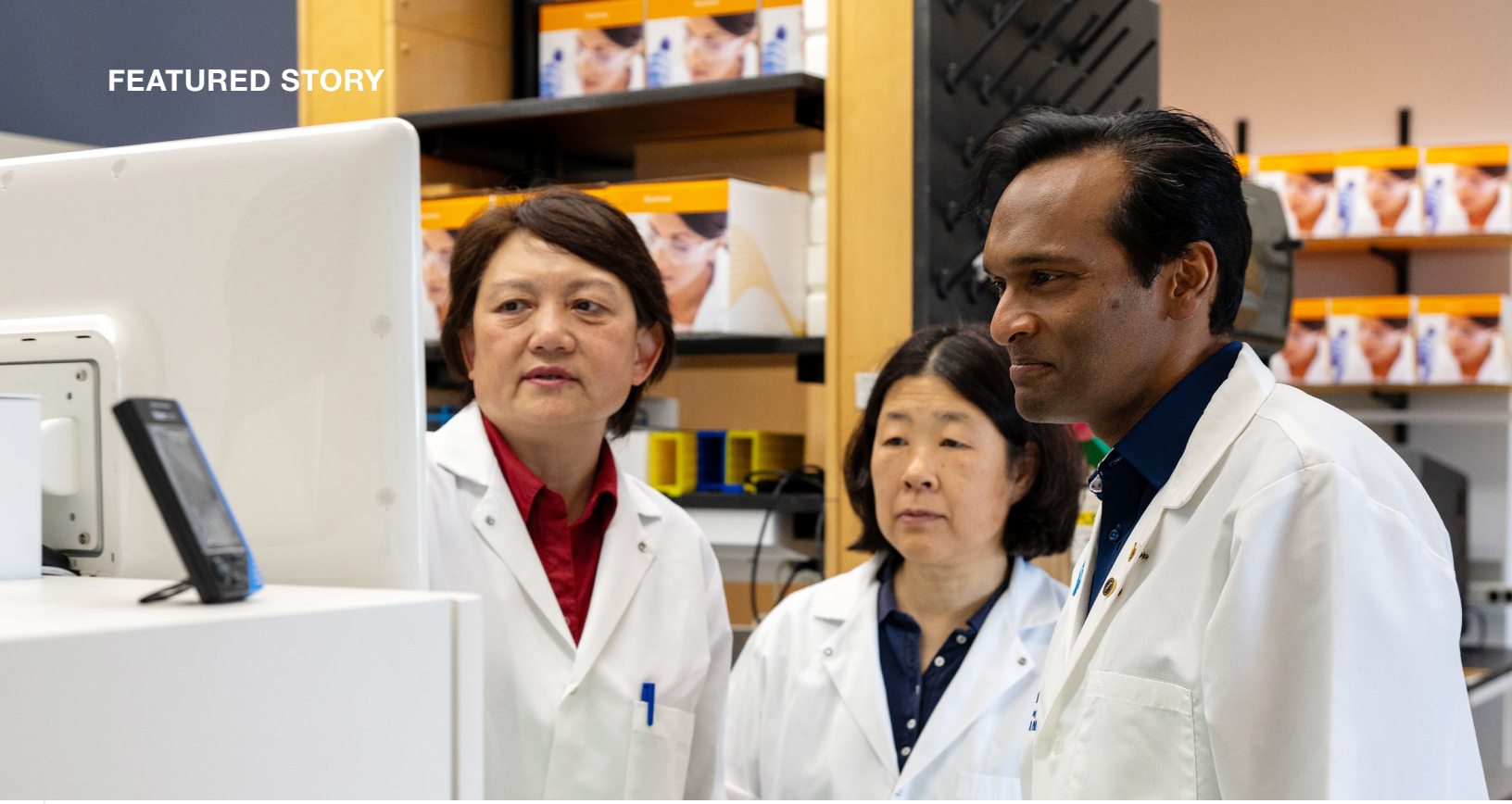
OUR WEBSITE

Large study identifies biomarkers for rare kidney tumors
May 15, 2024

Drs. Rouba Ali-Fehmi and Lee Schroeder win Global Health Equity Awards
March 6, 2024

Study provides mechanistic link of diet to inhibition of colitis in Crohn's disease
Nov 16, 2023



Above:
Dr. Arul Chinnaiyan stands with Xuhong Cao (left) and Rui Wang (middle).

The Genomic Revolution in Oncology: Tracing the Development of MiOncoSeq

by Lynn A. McCain, MHSA

The first versions of the human genome sequence were completed in 2001, as Arul Chinnaiyan, MD, PhD accepted his first faculty position as an Assistant Professor of Pathology and Urology Surgery at the University of Michigan. The first Next Generation Sequencer, the Genome Sequencer 20, was introduced in Germany in 2005. Technological and scientific advances in molecular pathology exploded over the next decade. Amid this milieu, Chinnaiyan envisioned a revolutionary research project that would sequence a large panel of genes to identify somatic and germline mutations that may be present in patients with metastatic cancer and for whom current therapies had been ineffective. By 2007, the Michigan Center for Translational Pathology (MCTP) was launched in the Department of Pathology at the University of Michigan in collaboration with the Rogel Cancer Center, with Chinnaiyan, now a full professor, at the helm. One year later, the MiOncoSeq assay was born and by late 2010, Chinnaiyan received IRB approval to utilize this test for clinical research. Chinnaiyan wanted to be able to report results to the patients' clinicians, so he pursued, and in 2013, obtained both CLIA and CAP certification for his laboratory to conduct testing to meet the medical needs of patients who had run out of options. "When Arul built this assay, there was nothing equivalent to it being run for clinical purposes. He was so far ahead of his time," praised Dr. Bryan Betz, Associate Professor and Technical Director of the Molecular Diagnostics Laboratory in the Department of Pathology.

In the era of single-gene testing, Chinnaiyan and his MCTP team proposed to use MiOncoSeq to examine the full genome (~20,000 genes) or large panels of as many as 1,800 potential cancer-related genes to identify which mutations are present in a patient. "Unlike others at the time, MiOncoSeq ran tumor matched to normal tissues in DNA and RNA analyses," stated Dr. Dan Robinson, Research Associate Professor in the MCTP. "Still today, other places generally

run just DNA on tumor samples only. They do not match to the normal tissues, nor do they run RNA sequencing. We find a lot of useful data in the RNA and we can also determine if mutations are germline or somatic by matching the tumor and normal tissues, which the others miss." At the time, insurers were reluctant to pay for single-gene testing, much less 1,800 genes. Costs were prohibitive for patients to self-fund this testing, so Chinnaiyan obtained funding to support testing through the National Institutes of Health grant mechanisms, foundation grants, and charitable donations. Most of these funds designated a focus on prostate and breast cancers, two of the most common cancers, or on very rare cancers, such as sarcomas. As such, Chinnaiyan's greatest impacts have been in these areas.

"In the early years, it took 14 days for the sequencer to run through all the bases in a sample. This is on top of the 3.5 days to prepare the samples to be sequenced," Robinson recalled. Nearly three weeks will pass before patients' test results finally come back in an extremely large dataset with millions of variants identified. Most of these are random variants and not changes related to any type of disease. Of the remaining mutations, some of these may be grouped such that they all trace back to similar genetic pathways. Other times both germline (inherited) and somatic (developed) mutations are discovered in the same or different genes. Extensive data review and analytics are needed to identify the truncal cause of the presenting cancer. "When we started, it would take a month to analyze the data and report back to the provider," recalled Chinnaiyan. "With advances in technologies, and programs developed in our lab, it now takes a week." In the future, Chinnaiyan envisions that machine learning and artificial intelligence (AI) will further streamline the data analysis and be able to find more complex associations. Beyond that, he foresees that AI will be able to help identify which therapeutics, or combinations thereof, will best treat a patient's cancer, leading to lasting remission and even cures.

MiOncoSeq continued to be refined for the next 14 years as technology advanced and knowledge of the human genome grew exponentially. "As more people began sequencing cancers, we were able to identify the genetic alterations that are significant. When we saw the same alterations repeat, we could focus on those genes to better understand them," Robinson explained. The laboratory began to trim the number of genes sequenced to about 1,200, which still allowed for ongoing research and discovery and remains considerably more than commercial laboratories whose largest panels run about 500 genes.

In 2023, the Department of Pathology recruited Dr. Annette Kim to lead the Division of Diagnostic Genetics and Genomics. One of her goals is to bring MiOncoSeq into the clinical molecular diagnostics laboratory to be offered to newly diagnosed cancer patients, enabling identification of the specific mutations and the best treatment protocols for those patients. Conducting large-scale testing, however, requires new equipment, programs, and vast data storage capabilities. The department invested in the Illumina NovaSeq X, the most advanced sequencer on the market, capable of 52 billion reads per run every 48 hours, producing up to 8 terabytes of data per run. This is complemented by robotic liquid handlers to automate pipetting, reducing stress on laboratory technicians, and the Covaris machine. "The Covaris uses sonic vibrations to shake apart the DNA into specific size pieces for analysis," explains Kim. In addition, a piece of equipment used during the COVID-19 peak, the Kingfisher, is being evaluated for its potential to be reallocated for DNA and RNA extraction for the MiOncoSeq platform.

Purchasing the equipment was just one step in the process to bring MiOncoSeq to the clinical laboratory, a process that is more challenging than it sounds. When bringing a molecular test into the clinical lab, one must address both the wet bench work and the "dry" analytics. The wet bench is running the actual test with patient specimens. Each component of the assay must be validated, and the performance specifications established to ensure the reliability of the results. Betz explained, "This test is very involved to set up because it includes both DNA and RNA procedures that can take several days to complete. There are dozens of steps. We need to be sure the work is set up optimally, the infrastructure is right to scale and streamline processes, and the test is implemented in a compliant manner." The panel to be sequenced in the clinical laboratory is a 1,023 gene panel which will also be used in the next version of the research panel used in the MCTP.

The "dry" work is all the bioinformatic data analytics and supporting infrastructure necessary for testing to be conducted. "This is the most comprehensive and complex analysis pipeline that we have ever been involved with," said Betz. The work is being coordinated by Assistant Professor Dr. Robert C. Bell, a clinical informatician, molecular pathologist, and hematopathologist. "We are creating our own data visualization and

reporting portal application that will encompass not just MiOncoSeq, but also our myeloid NGS panel, bone and solid tumor panels, the Archer FusionPlex, germline sequencing, and more. These all need to integrate with Soft Laboratory Information System and the Epic medical record software," explained Bell. "We will be able to look at the whole transcriptome of tumors to see what is expressed in the tumor, as well as comparing the tumor to a patient's normal tissues to see copy number variations, identify germline mutations, determine the tumor mutation burden. It will also be used for lymphomas and leukemias," Bell added. "There are so many possibilities for how this can be used to care for our patients." This work is receiving support from Pathology Informatics, HITS, and University ITS.

Above:
Dr. Rahul Mannan stands and speaks with Chelsea Decker while Amanda Miller (left) and Dawn Neff (sitting) conduct lab work.

Dr. Noah Brown, Associate Professor and Director of Molecular Diagnostics, emphasized the importance of getting the process right for reporting out the results to clinicians. "In our reporting, we really highlight which alterations are most clinically actionable. Getting the report right is going to be a critical part of this process, because clinicians are getting an enormous amount of data, and it's up to us as molecular pathologists to communicate that to them in a way that they can distill quickly to figure out what this means for their patient."

Kim is systematically approaching the process of transitioning MiOncoSeq to the clinical laboratory and believes that all the pieces will be in place to begin offering this test in late 2024. To ensure the molecular diagnostic laboratory is positioned to scale the MiOncoSeq test as demand grows, an entire new suite of informatics resources is needed. "I am very appreciative of the support from leadership at all levels and the entire team working on this project. The MCTP colleagues, including Arul, Dan, Jamie Estill, and Xuhong Cao and their entire teams, have provided incredibly generous support and collaboration. Robert has done an amazing job spearheading the informatics efforts with our staff, Hardik Joshi and Brandon Newell. We are also thrilled to have Dr. Marcin Cieslik, who has transitioned to join our efforts as well as our new DGG Director of Bioinformatics and will also soon add our current informatics fellow, Dr. Saguna Narayan, to our faculty team. In addition, we have engaged our future informatics fellow, Vincent Laufer, in helping us. We are hiring a new director of informatics to allow us to tie together all the pre-analytics, tracking through the wet bench processes, the bioinformatics pipeline, and post analytic steps, including data visualization and report generation, into a single informatics ecosystem. Pathology informatics and the medical school HITS have all been invaluable. Rarely have I seen such all-inclusive support for a project. The team is incredible."

A New Era in Pathology

by Christine Baker

"Our new Pathology space is an opportunity to do better what we already do well today… for a future we can't imagine.", says Dr. Jeffrey Myers, Vice Chair for Clinical Affairs and Quality.

A long, long journey for the Department of Pathology is coming to an end. With the trainees' move into their new space within University Hospital in late April, the PRR project team is celebrating the final project move. After formally closing out the project and associated documentation, the now 10-year project is coming to an end.

The quotation above was a guiding force in the early days of the PRR Project. In the summer of 2014, the PRR Committee sat in cramped conference rooms in Med Sci 1 and developed the Guiding Principles and overarching precepts that were the foundation of this decade-long project.

In the time since, we have spent thousands of hours, collectively as a department, meeting together to study our current processes and space, looking to the future and designing our new spaces. We did this iteratively, progressively becoming more detailed in our vision, using Lean Facility design tools to help us along the journey. We studied specimen flow and how supplies and waste move in and out of the lab. We looked to new and novel solutions, frequently including automation, and combined like processes into the same spaces as much as possible. We completed an entire parallel project completely devoted to non-laboratory space, and even built out (and occupied) a temporary office mock-up to further develop the workspace vision. Eventually, through much effort and creative thinking, that future state was first codified in construction documents and then finally came to fruition with the help of our construction partners.

In the summer of 2018, the first major phase was completed as we moved over 500 people and untold numbers of pieces of lab equipment to the new Pathology space at NCRC. Now, six years later, the original vision of flexible and innovative spaces has paid off as nearly every lab has brought in new equipment or pursued new ways of doing their work—and the sustainable and flexible lab design has enabled these changes to occur.

We soon followed with the 5-phase UH Renovation, and the teams at UH proved to be dynamic and adaptable as the temporary construction walls were erected, removed, and then put up once again. Today, we have an open and expansive core lab with automation at its center, and a state-of-the-art Transfusion Medicine "neighborhood" housing the Blood Bank, the Cellular Therapy Lab and our new Apheresis Patient Care Unit—to name a few of the new spaces at the main hospital complex.

On all phases of the project, we carried forth the vision for open, collaborative, and welcoming spaces for all of Pathology and our visitors. We carried forth Dr. Myer's vision to improve the work that was already done so well by the faculty and staff within our department. And now, with the final small phase of construction closing out, the transformative Pathology Relocation and Renovation project is coming to an end.

Beyond the Microscope: The Unknown World of Pathology Informatics

by Anastazia Hartman, MBA, MS

In the bustling environment of the University of Michigan's Department of Pathology, it's not just medical professionals who are pivotal in the maze of patient care. Some operate behind the scenes, like Josh Jacques, Monica Tetreault, Nancy Fritzemeier, Ivan Holland, and Todd Kandow from the Department of Pathology's Pathology Informatics team. Pathology Informatics, or Path Informatics (PI), might not be a widely recognized field, but it is instrumental in transforming and modernizing the diagnostic processes used by pathologists and lab members.

At the University of Michigan's Department of Pathology, Path Informatics is integral to clinical laboratory outcomes. Behind the scenes, this diverse group of team members each contribute their specialized skills to facilitate the department's seamless operation. To shed light on the broad scope of Path Informatics, various team members shared insights into their specific functions and how they enhance patient care.

Nancy Fritzemeier, Clinical Business Analyst

Nancy Fritzemeier is enthusiastic and dedicated to her role within PI. Having transitioned to pathology informatics after ten years in anatomic pathology management, her career in pathology spans several esteemed institutions. However, the University of Michigan is where she feels her contributions are most impactful, partly owing to the collaborative and positive work environment. Fritzemeier specifically supports anatomic pathology, which includes services like autopsy, cytopathology, and surgical pathology. The team works to ensure that software systems like Soft, the laboratory information system, are running smoothly and that any issues or new implementations are addressed efficiently.

"My role as a business analyst allows me to support individuals in anatomic pathology and our laboratory information system, Soft. Our team has multiple other business analysts and we are each experts in our specific modules. That way we can support each other and the labs," said Fritzemeier. "I'm also communicating with the end user in our laboratories and with our software vendor if needed to create customizations or fix bugs so that they can get their results out."

Fritzemeier emphasizes the significance of pathology informatics in urgent scenarios where, for instance, if a critical machine malfunctions in a laboratory, the path informatics team is there to provide immediate support. According to her, this immediate response capability demonstrates the importance of their own IT group, fundamental in facilitating quick result turnarounds for patient care.

Beyond her technical contributions, Fritzemeier is passionate about pathology. "Every individual is, knowingly or unknowingly, impacted by the work of pathologists. From a simple blood draw, to a biopsy and beyond." Fritzemeier also commented that the commitment to patient care, rather than just being a slogan, is a deeply ingrained ethos that sets Michigan Medicine apart. "I think pathology touches every aspect of our patient care throughout our entire medical institution, which is vast, as we know. We all are here because of the patients."

Ivan Holland, System Programmer

Ivan Holland has been a member of the Department of Pathology for nine years, more specifically within the PI team. Holland began working in IT at the Detroit Medical Center before arriving at Michigan Medicine. The former User Support Specialist now turned System Programmer has a breadth of knowledge

Above:
Group shot of the entire Pathology Informatics team.

and experience in understanding the importance of his role and PI as a whole. To Holland, transitioning to a new role doesn't mean leaving behind old responsibilities; it means building upon them. The new role encompasses liaison work with vendors, incorporating new devices into the existing network, and ensuring data is properly communicated between systems—adding layers of complexity to what was previously managed.

"As a Support Specialist, I worked to help members of the department replace broken technology items, created new workstations, and got them up and running on the network, a whole wide range of things that in turn benefit our patients", said Holland. "In my new role, I work with vendors, placing new equipment and ensuring that they can connect to our networks. A lot of this also includes working with Health Information Technologies Services first to test products and ensure their installation causes the least interference with our lab's daily operations."

To Holland, this transition makes it clear that there are endless possibilities for the work that PI does and that there is a clear trajectory to advance not only the tools used in patient care, but a career as well. However, it's not the tasks and growth alone that make the work gratifying. It's the sense of belonging, the camaraderie, and the department's family-like atmosphere that resonates with Holland. "They emphasize the notion of a collective—a dedicated group providing relentless support where personal and professional lines often merge to create a network of caring colleagues."

Holland noted that what sets this department apart is the mutual respect and support that binds its members together. It's that familial dynamic that makes Path Informatics—and by extension, the University of Michigan's Pathology Department—not just a workplace, but a home for innovation, collaboration, and dedicated care.

Josh Jacques, Manager, Application Development and DevOps

Josh Jacques has spent nearly two decades transitioning from research to a key position in Pathology Informatics (PI), where he is currently managing the application development and DevOps teams, which are essential parts of patient care. His role includes managing teams, protecting patient data, bringing in new technologies, and improving laboratory efficiency. Leveraging his biology background and coding skills, Jacques is crucial to the technology enabling tests and analysis in healthcare, ensuring the smooth functioning of clinical systems and data confidentiality.

"To me, Path Informatics is the support needed for the labs to do everything they need to do from the technology side of things as we move forward in the future," said Jacques. "We make sure that everything's up and running and done the right way, and making sure we are in compliance with all

different regulations.

"Many people don't know that every single test that runs through the hospital goes through pathology, and every single one of those things requires an electronic component to make sure that it's finished on the instrument itself, which has a network connection."

Jacques is excited about the growth of digital pathology and AI diagnostics, which are part of the evolving landscape of PI. This field's commitment to innovation, patient care, and data security solidifies its crucial role in the healthcare system. "The digital pathology space is going to revolutionize how we do things by automating some of those tasks that don't need that really specialized human eye to see."

Todd Kandow, Database Administrator

Todd Kandow is intimately familiar with the world of Path Informatics and recently ascended to the role of Lead Program Analyst. When discussing the world of PI, Kandow emphasized that without PI, the data critical for patient care would simply not find its way from the laboratories to the clinicians who need it.

At the unique intersection of medicine and technology, acting as the conduit through which lab data is collected, analyzed, and distributed, Kandow has dedicated his career to enhancing the department's technological capabilities. He and his team create applications that streamline and improve various processes, such as clinical lab billing and patient order entry. The goal is always clear: improving the systems that impact patient care. "We're kind of the heartbeat of pathology, the lab system, the clinical labs, because without us, our data goes nowhere."

Kandow's passion for his work is evident when he discusses the direct and indirect ways in which Pathology and PI contribute to patient care. Although they do not provide face-to-face interaction with patients, the intrinsic motivation of the staff is to improve the quality of the patient's experience and care. This motivation is equally strong in both the clinical and research segments of pathology, suggesting that the work of PI extends beyond the immediate laboratory context into broader university research initiatives.

Monica Tetreault, Business Analyst

Business Analysts like Monica Tetreault play a pivotal role in optimizing the flow of critical information between laboratory systems and hospital databases. Tetreault's journey in medical informatics began almost three years ago, after 18 years at a another institution. Her work focuses on creating and maintaining connections, not only between data systems but also among the people running them.

"I have been here almost three years and I worked at another institution for 18 years before that, and I can really say that there is a feeling of collaboration here with my colleagues and everybody is approachable, willing to help each other."

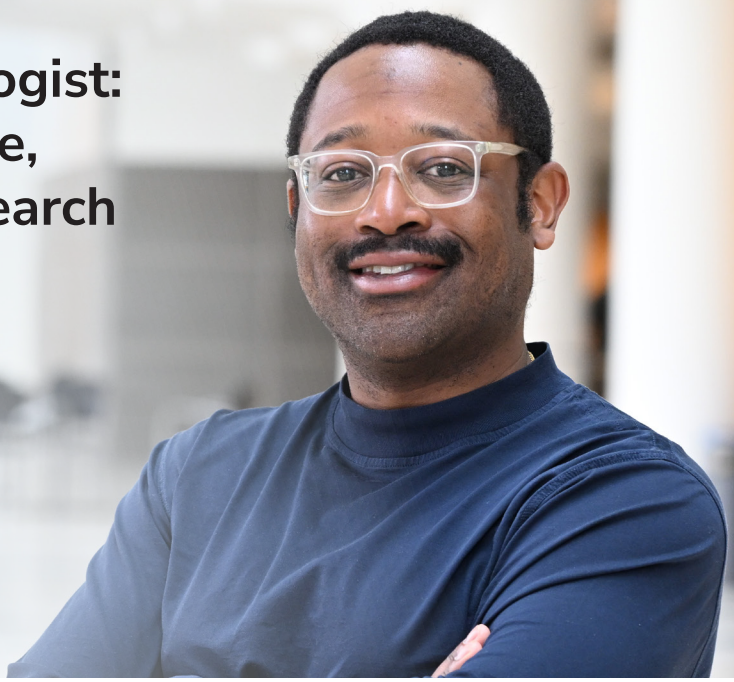
Pathology Informatics, as Tetreault describes, intermediates between the lab and hospital information systems. Laboratories rely heavily on specific software like SoftLab to manage patient data and test information, while hospitals utilize tools such as Epic — known as MyChart — to handle comprehensive patient and clinical data. The seamless transmission of data between the two, aided by the departmental interfaces Tetreault helps oversee, is nothing short of the circulatory system of the hospital infrastructure.

Tetreault credits the diversity within her department to success, where med techs bring laboratory perspectives that mesh with the technical insights of IT experts. This wealth of knowledge and expertise allows their department to stay ahead of the curve in testing and implementing system upgrades, new tests, and maintaining crucial equipment.

The leaders of Pathology Informatics like Josh Jacques, Nancy Fritzemeier, Ivan Holland, Todd Kandow, and Monica Tetreault, have carved an indispensable niche in healthcare that cannot be overstated. From optimizing the flow of crucial lab data to ensuring robust support for diagnostic technologies, this dedicated team operates at the forefront of innovation and patient care and serves as a bridge between technical advancement and clinical outcome.

The Makings of an Immunologist: A Journey Through Literature, Philosophy, and Cancer Research

by Michael Pitter, PhD



I took a non-traditional path towards pursuing a PhD. Although I majored in English and philosophy as an undergraduate, the combination of specific mentors and studies engendered within me the motivation to pursue medical research. Literary criticism, world history, existentialism, and human nature classes widened my perspective of the world and my role in it. Upon graduating, I realized that I needed to pursue a career which was universally relevant regardless of differences in language, culture, or ethnicity. Moreover, several early philosophers including Aristotle, Lucretius, and the Epicureans, were also early scientists. These realizations brought the prospect of becoming a medical researcher within reach.

I enrolled in a post-baccalaureate biomedical sciences program in which I took all the basic science classes. I also sought opportunities to work in a research laboratory to couple the classroom lectures with the real-world experiences of conducting research at the forefront of scientific knowledge. In the research lab environment, I quickly identified a sense of belonging and assumed the position as an investigator, contributing to the creation of knowledge. In this lab, my major projects were focused on behavioral neuroscience and neuroinflammation, piquing my interest in immunology. I then worked at a laboratory at Memorial Sloan Kettering Cancer Center focusing more directly on cancer immunotherapy. At this time, I was also surveying various PhD programs to develop my expertise in cancer immunology and immunotherapy. I received multiple offers but chose Michigan, eager to become a member of a cutting-edge laboratory in a large and interconnected research institution and university.

One of the major reasons for enrolling in the Program for the Biomedical Sciences (PIBS) at Michigan was the prospect of working in the lab of Dr. Weiping Zou. I had previously gained valuable laboratory experiences in cancer immunology and wanted to continue developing as an investigator in this field. Dr. Zou has had an illustrious and innovative career as one of the early pioneers in the understanding and development of immune checkpoint blockade therapy. While expanding my knowledge in and contributions to cancer immunology, I wanted to engage in research that would be translational or clinically relevant in the human context. These aspirations led me to inquire into whether I could rotate in and subsequently join the Zou Lab. Given, my past experiences in the large, post-doc–heavy lab at Memorial Sloan Kettering, I had some preconceived notions regarding the intensity and seriousness of researchers in the Zou Lab. However, I was pleasantly surprised. Although the researchers in the Zou Lab indeed are serious and work diligently, everybody exhibited a kind and warm demeanor and my relationship with lab members evolved to that resembling a family. Over the years, my experience in the lab both matched and

exceeded expectations.

In the Zou lab, projects mainly focus on elucidating novel mechanisms in either cancer cells or immune cells which may provide insights for improved means of treating cancer. My task was to study how certain, key post-translational modifications (PTMs) in immune cells could control immune cells' functions critical for the maintenance of anti-tumor immunity. We decided to study citrullination mediated by peptidyl arginine deiminases (PADs) because citrullination is among the few known enzymatic irreversible PTMs. Citrullination has been shown to play a role in cancer development however, citrullination

Above:
Dr. Pitter working in the lab with Dr. Zou.

in mononuclear immune cells has not been comprehensively shown. Moreover, immune cells, including T-cells and macrophages, play an indispensable role in determining tumor growth, progression, or regression. Therefore, my thesis work would endeavor to investigate the role of PADs in macrophages and T-cells.

We began by investigating the most well-studied PAD, PAD4, in T-cells. The post-doc training me and overseeing the project had to unexpectedly leave the lab earlier than anticipated, leaving me to continue to work on this early–developing project. Independently driving the project, I reproduced the results generated by the post-doc, yet one issue remained: we did not observe a consistent *in vivo* phenotype in the tumor-bearing mice with PAD4 specifically knocked out of the T-cells (Padi4fl/fl Cd4cre). We observed no difference in tumor sizes between wild-type (normal) mice and the Padi4fl/fl Cd4cre mice, indicating that PAD4 may not actually play a key role in T-cells, which may affect anti-tumor immunity.

The laboratories were then suddenly closed due to the COVID-19 pandemic. Working from home, I leveraged my bioinformatics/computational biology skills to analyze publicly available RNA-sequencing datasets. It became clear that PAD4 was more highly expressed in macrophages and PAD4 expression was associated with tumor–promoting functions and phenotypes in macrophages. When labs reopened, we changed the research focus from PAD4 in T-cells to PAD4 in macrophages and discovered that PAD4 negatively regulates MHC-II expression and function. MHC-II is a protein on the surface of innate immune cells which mediates the presentation of antigens to CD4+ T-cells.

We found that the genetic loss or the pharmacological inhibition of PAD4 resulted in the significant enhancement of MHC-II expression and MHC-II–mediated antigen presentation. Moreover, when we inoculated tumors into wild-type mice versus mice with PAD4 knocked out of the macrophages (Padi4fl/fl LysMcre mice), we observed that the Padi4fl/fl LysMcre mice developed significantly smaller tumors. This indicated that PAD4 activity in macrophages supported tumor growth and therefore, when inhibited, may serve as a novel target in the treatment of cancer. We also discovered that PAD4 citrullinated STAT1, controlling STAT1 transcriptional activity, and consequently, MHC-II expression and function in macrophages. This work featured multiple novel findings in macrophage biology which may be exploited for the treatment of cancer and which will inform future macrophage studies. Multiple pieces of bioinformatic analysis supplemented this work. In a dataset featuring the immune cells from triple negative breast cancer (TNBC) patients treated with immunotherapy (PDL1 blockade), we showed that the patients who did not respond to the therapy exhibited a higher expression of PAD4 in the macrophages, indicating that PAD4 in macrophages impairs anti-tumor immunity and immunotherapy. We further validated these findings with multiple mouse tumor models in which we found that the genetic loss or the pharmacological inhibition of PAD4 synergized with PDL1 blockade to abrogate tumor growth.

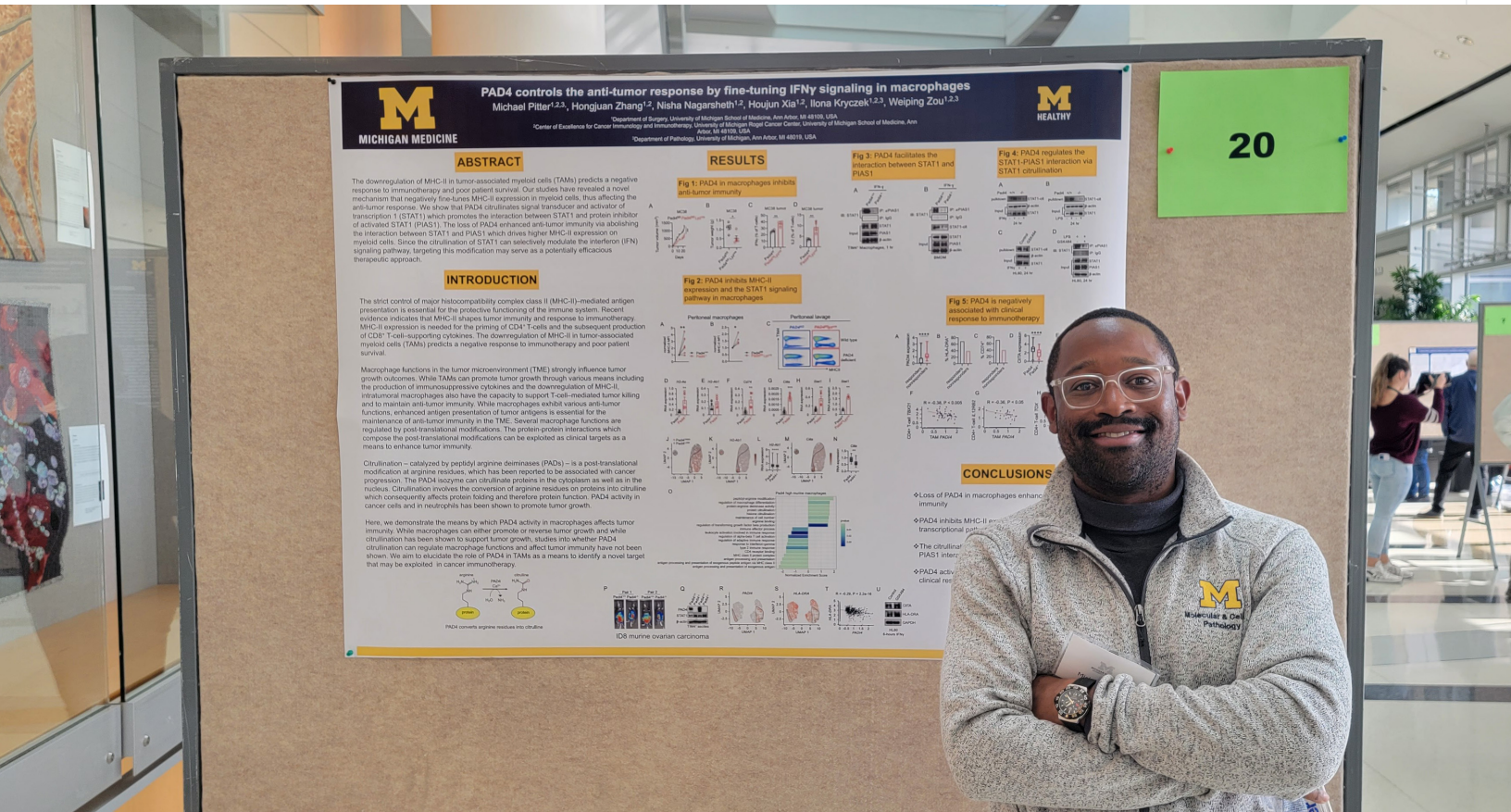
In addition to the science, the MCP graduate program, which is part of the PIBS program, provided a strong support network for students. As a first year PhD student, PIBS organized new students into so-called "houses" or subgroups of

the student body. Each house was given the task to seek out and engage in public service projects. Students proposed projects and voted on the one preferred by the group. I suggested that we volunteer with a church in Flint, Michigan which, in the wake of the Flint water crisis, played a central role in maintaining large stockpiles of food, water, and other provisions to supply community members in need. After meeting with church leaders to discuss their service efforts, we noticed that they documented their delivery metrics on paper. We discussed with them the development of an electronic system for documenting their deliveries and they said that this would greatly enhance their work. We set up a Google Forms system that they still use today. As a team, we were pleased that we could apply our inventiveness and humanitarianism to contributing to the great work done by this church.

Other extra-curricular activities that we engaged in included golf and soccer. Soccer was a major activity as this was among the main recreational activities we all enjoyed. I, along with many other PhDs from around the country and the world, came together to play the global game that we all loved. Here, I made many friends as well.

Now that I have completed my PhD, I am eager to continue working as an immunologist and bioinformatician in the context of cancer and infectious disease. This exciting and burgeoning field holds a great deal of promise that the innovations therein will have huge impacts on health and medical treatment for the years to come. I am currently interviewing for scientist positions at several companies where I would be leveraging my immunology knowledge and techniques to support the development of drugs and therapeutics. In the Zou lab, I was the only graduate student among several post-docs, so I learned to remain self-motivated, work independently, and solve unforeseen problems. I am confident that I will be able to handle the rigors of working in industry.

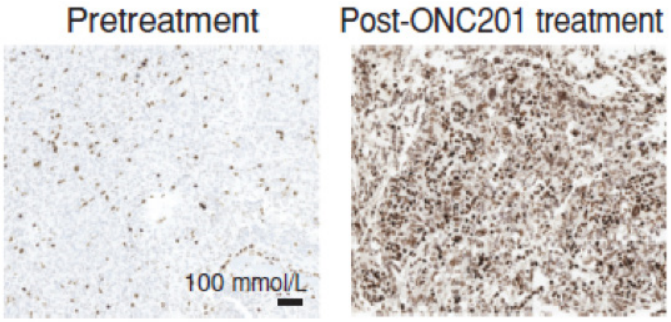
In looking over my experience in the MCP program, some key takeaways include the following: (1) With self-propelled motivation and persistence, nothing can stop you. I was an English and philosophy major who persevered to become a scientist. Looking back, I impressed myself with my level of perseverance. (2) We are in a golden age of science; an era in which our research tools have reached a level of advancement capable of deriving a great deal of meaning from the large volumes of data collected. (3) Diversity is essential for good science. Diversity regarding ethnicity, race, intellect, ideas, interests, and perspectives will ensure that when working towards the elucidation of novel mechanisms or phenomena, the group will inevitably arrive at a solution.



Below:
Dr. Pitter presenting his poster at the 2023 Research Symposium.

Clinical Efficacy of ONC201 in H3K27MMutant Diffuse Midline Gliomas Is Driven by Disruption of Integrated Metabolic and Epigenetic Pathways

Sriram Venneti, Abed Rahman Kawakibi, Sunjong Ji, …, and Carl Koschmann



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Patients with H3K27M-mutant diffuse midline glioma (DMG) have no proven effective therapies. ONC201 has recently demonstrated efficacy in these patients, but the mechanism behind this finding remains unknown. We assessed clinical outcomes, tumor sequencing, and tissue/cerebrospinal fluid (CSF) correlate samples from patients treated in two completed multisite clinical studies. Patients treated with ONC201 following initial radiation but prior to recurrence demonstrated a median overall survival of 21.7 months, whereas those treated after recurrence had a median overall survival of 9.3 months. Radiographic response was associated with increased expression of key tricarboxylic acid cycle–related genes in baseline tumor sequencing. ONC201 treatment increased 2-hydroxyglutarate levels in cultured H3K27M-DMG cells and patient CSF samples. This corresponded with increases in repressive H3K27me3 *in vitro* and in human tumors accompanied by epigenetic downregulation of cell-cycle regulation and neuroglial differentiation genes. Overall, ONC201 demonstrates efficacy in H3K27M-DMG by disrupting integrated metabolic and epigenetic pathways and reversing pathognomonic H3K27me3 reduction.

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Significance:
The clinical, radiographic, and molecular analyses included in this study demonstrate the efficacy of ONC201 in H3K27M-mutant DMG and support ONC201 as the first monotherapy to improve outcomes in H3K27M-mutant DMG beyond radiation. Mechanistically, ONC201 disrupts integrated metabolic and epigenetic pathways and reverses pathognomonic H3K27me3 reduction.

Mucosal IgA immune complex induces immunomodulatory responses in allergic airway and intestinal TH2 disease

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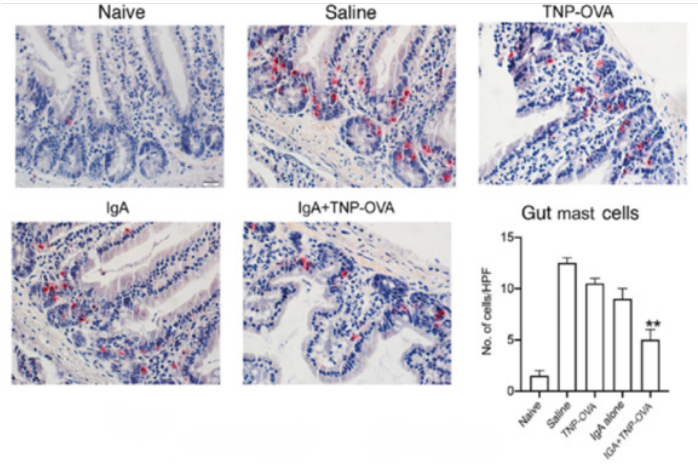
IgA is the most abundant immunoglobulin at the mucosal surface and although its role in regulating mucosal immunity is not fully understood, its presence is associated with protection from developing allergic disease. In this study, we sought to determine the role of IgA immune complexes for therapeutic application to mucosal allergic responses. We applied trinitrophenol (TNP)-specific IgA immune complexes using TNP-coupled ovalbumin (OVA) to airway and gut mucosal surfaces in systemically sensitized allergic animals to regulate allergen challenge responses. Animals were assessed for both pathologic and immune-mediated responses in the lung and gut, respectively, using established mouse models. We found that the mucosal application of IgA immune complexes in the lung and gut with TNP-OVA regulated TH2-driven allergic response in the lung and gut, reducing TH2 cytokines and mucus (lung) as well as diarrhea and temperature loss (gut), but increasing IL-10 and the number of regulatory T cells.



The IgA-OVA immune complex did not alter peanut-induced anaphylaxis, indicating antigen specificity. Using OVA-specific DO.11-green fluorescent protein IL-4 reporter mouse–derived TH2-skewed cells in a transfer model demonstrated that mucosal IgA immune complex treatment reduced TH2-cell expansion and increased the number of regulatory T cells. To address a potential mechanism of action, TGF-b and IL-10 were induced in bone marrow–derived dendritic cells when they were exposed to IgA immune complex, suggesting a regulatory

phenotype induced in dendritic cells that also led to an altered primary T-cell–mediated response in *in vitro* OVA-specific assays.

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Significance:
These studies highlight one possible mechanism of how allergen-specific IgA may provide a regulatory signal to reduce the development of allergic responses in the lung and gut.

IL-13–induced STAT3-dependent signaling networks regulate esophageal epithelial proliferation in eosinophilic esophagitis

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Basal zone hyperplasia (BZH) and dilated intercellular spaces (DISs) are thought to contribute to the clinical manifestations of eosinophilic esophagitis (EoE); however, the molecular pathways that drive BZH remain largely unexplored. In this study, we sought to define the role of IL-13–induced transcriptional programs in esophageal epithelial proliferation in EoE. We performed RNA sequencing, bioinformatics, Western blot, reverse transcriptase quantitative PCR, and histologic analyses on esophageal biopsies from healthy control and patients with EoE, primary esophageal cells derived from patients with EoE, and IL-13–stimulated esophageal epithelial keratinocytes grown at the air-liquid interface (EPC2-ALI). Genetic (shRNA) and pharmacologic (proteolysis-targeting chimera degrader) approaches and *in vivo* model of IL-13–induced esophageal epithelial remodeling (Krt5-rtTA x tetO-IL-13Tg) were used to define the role of signal transducer and activator of transcription 3 (STAT3) and STAT6 and secreted frizzled-related protein 1 (SFRP1) in esophageal epithelial proliferation. We found that RNA-sequencing analysis of esophageal biopsies (healthy control vs EoE) and EPC2-ALI revealed 82 common differentially expressed genes that were enriched for putative STAT3 target genes. *In vitro* and *in vivo* analyses revealed a link between IL-13–induced STAT3 and STAT6 phosphorylation, SFRP1 mRNA expression, and esophageal epithelial proliferation. *In vitro* studies showed that IL-13–induced esophageal epithelial proliferation was STAT3-dependent and regulated by the STAT3 target SFRP1. SFRP1 mRNA is increased in esophageal biopsies from patients with active EoE compared with healthy controls or patients in remission and identifies an esophageal suprabasal epithelial cell subpopulation that uniquely expressed the core EoE proinflammatory transcriptome genes (CCL26, ALOX15, CAPN14, ANO1, and TNFAIP6).

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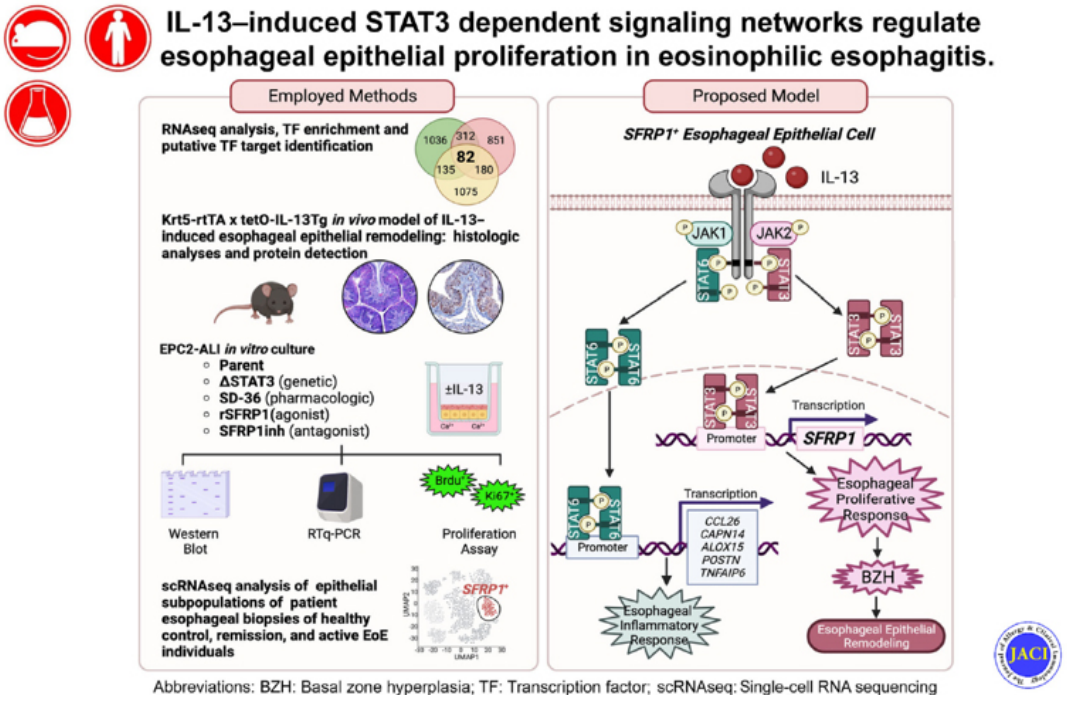
Significance:
These studies identify SFRP1 as a key regulator of IL-13–induced and STAT3-dependent esophageal proliferation and BZH in EoE and link SFRP11 esophageal epithelial cells with the proinflammatory and epithelial remodeling response in EoE.



Abbreviations: BZH: Basal zone hyperplasia; TF: Transcription factor; scRNAseq: Single-cell RNA sequencing

A Model of Multidisciplinary Patient Care: How an Idea Led to a New Interdisciplinary Clinic within U-M

by Anastazia Hartman, MBA, MS

In the Department of Pathology, new and innovative approaches to patient care are always at the forefront of faculty, trainees, and staff minds. Dr. Rouba Ali-Fehmi, Director of Breast Pathology at the University of Michigan, was inspired by a conversation with Dr. Jeffrey Myers, Vice Chair of Clinical Affairs and Quality, years ago to step out from behind the microscope and engage more directly with patients. From there, the U-M Breast Pathology Clinic was born.

While Dr. Myers played a prominent role in the clinic's ideation and implementation, published research and information drawn from anecdotal experience were collected and curated by the department's Patient and Family Advisory Council (PFAC) and a Pathology Clinics Project Team launched by the ASCP's Patient Champions Steering Committee (PCSC). Dr. Myers, together with his PFAC Co-Chair and Michigan Medicine Patient and Family Advisor (PFA), Michele Mitchell, served on the ASCP Project Team which proved helpful in moving forward with work begun by our PFAC prior to the pandemic. Together, work done by our PFAC and the ASCP converged with the reporting requirements of the 21st Century Cares Act to drive the idea of pathology clinics into reality. "There are many factors that have come to light after the COVID-19 pandemic that led to the implementation of the Breast Pathology Clinic here at the University of Michigan," said Myers. "Some ideas came to life before Rouba Ali-Fehmi arrived at the Department of Pathology. Once she arrived, I approached her to begin this exciting and patient-valued project."

While other institutions are beginning their pilot programs, Ali-Fehmi shared insight into the clinic's beginnings at the University of Michigan. "It all started with an idea mentioned by Dr. Myers during a Michigan Society of Pathology panel in 2014," said Ali-Fehmi. "The seed was planted in my mind and stayed there for many years before I came to the University of Michigan." Once Ali-Fehmi arrived at Michigan Medicine, Dr. Myers, Michele Mitchell, and members of our PFAC immediately began work to establish the pathology clinic. Ali-Fehmi noted that starting the clinic was no small feat. Many layers had to be discussed and evaluated, with a lengthy preparation phase involving collaboration with both internal and external pathologists who had completed similar projects. Through the delays, Ali-Fehmi pushed on, and with the support of three other breast pathologists, Dr. Ellen Chapel, Dr. Sara Abbott, and Dr. Mustafa Yousif, the Breast Pathology Clinic officially opened on April 8, 2024.

The clinic fosters an environment where face-to-face interactions enable patients to better understand their medical diagnoses, reducing stress and promoting compliance with treatment plans. Digitalization plays a crucial role in making patient slides accessible and easily shareable during consultations. Not only do patients meet with a pathologist, but also a multidisciplinary team of surgeons and oncologists, which, in one visit, paints a holistic picture of each patient's care goals. Through studies conducted so far, many patients have found a benefit in better understanding their diagnoses, and pathologists have enjoyed demonstrating firsthand how their work benefits patients during all aspects of their care.

"What sets this clinic apart is its tangible goals: to demystify pathology reports for patients and to alleviate the anxiety that accompanies a breast cancer diagnosis," Ali-Fehmi said. "By allowing patients to meet with the pathologists

Above:
The department's Breast Pathology team comprised of Drs. Chapel, Ali-Fehmi, Abbott, and Yousif (left to right).

who examine their slides, the breast cancer care experience becomes less daunting and far more informative. Patients express immense gratitude upon realizing there's a real person behind the report, someone who can explain the nuances of their condition and the implications of their pathology results."

Ali-Fehmi noted that the hope is that this breast pathology clinic will not only serve its patients but also become a blueprint for nationwide replication—demonstrating a transformative form of care where multidisciplinary teams work together, and pathologists are at the forefront of patient communication. In the future, Dr. Ali-Fehmi, Dr. Chapel, Dr. Abbott, and Dr. Yousif are committed to working alongside patients and furthering the reach of the clinic's goals. Ali-Fehmi also noted that much of what she and her team do would not be possible without Anju Verma, Breast Services Administrative Assistant, and Dr. Marya Wahidi, Research Fellow. "We are grateful for all Anju and Dr. Wahidi do to help us achieve our goals with this clinic."

The clinic's beneficial effects promise a revolution in patient care, a future where pathology steps into a more visible and patient-interactive role. The clinic exemplifies how knowledge can empower patients in their healthcare journey and how connecting more intimately with the individuals behind the analysis can humanize and enrich the patient experience.

As the breast pathology clinic team navigates the intricacies of this new model, their eyes are set on the horizon. The Breast Pathology Clinic is more than just a new venture at the University of Michigan; it's a beacon of what patient-centered care can look like when barriers between disciplines are broken down. It's the fruition of a long-held belief that engaging patients with all members of their care team, including pathologists, can not only inform but also transform both their experience of care but also their health outcomes.

Above:
Dr. Mustafa Yousif stands in the new digital pathology space located in the North Campus Research Complex.

The Future of Pathology Now: How Michigan Medicine's Experts are Harnessing Tech for Better Care

Three experts describe the dramatic advances in technology being implemented within the Department of Pathology.

The field of pathology has made dramatic advances over the past several years with incorporation of novel technologies, robotics, machine learning, and artificial intelligence into laboratory workflows. This is resulting in increased efficiencies, lower costs, more standardization with less human error, and better patient care. At Michigan Medicine, the Department of Pathology is staying at the forefront of these advances. We recently spoke with three Pathology faculty who are spearheading the introduction of advanced technologies in our laboratories:

- Dr. Carmen Gherasim, Assistant Professor of Chemical Pathology. Dr. Gherasim shared with us the introduction of the cobas® p512 and p612 pre-analytic robotic analyzers into our specimen processing unit.
- Dr. Mustafa Yousif, Assistant Professor of Informatics and Breast Pathology. Dr. Yousif described the implementation of a digital pathology workflow within the department.
- Dr. Annette Kim, Henry Clay Bryant Professor of Pathology and the Director of the Division of Diagnostic Genetics and Genomics (DGG). Dr. Kim details the incorporation of advanced technologies and the validation of these technologies in the DGG laboratory.

Dr. Carmen Gherasim: Pre-analytical Automation to Enhance Laboratory Efficiency and Accuracy

Healthcare providers rely on laboratory test results to make informed clinical decisions for patient care. According to a survey of specialist clinicians (Rohr et al., 2016), 60-70% of clinical decisions were affected by laboratory test results, highlighting the crucial role of the laboratories in providing accurate and timely test results. Although it is commonly perceived that the performance of a laboratory test is reflected by its analytical accuracy, the quality of the specimen can significantly affect the reliability and accuracy of the test results, impacting clinical decisions and ultimately the clinical outcomes. Blood sample

quality depends on several factors including patient preparation, sample collection, handling, and transportation, all of which take place outside the laboratory in the pre-analytical phase of the testing process. Hemolysis, insufficient sample volume, wrong tube type, clotting, and contamination are among the commonly encountered pre-analytical errors that should be identified, ideally prior to testing, to avoid any preventable errors. Due to the significant contributions the pre-analytical errors have on results, laboratories are increasingly investing in optimizing the pre-analytical phase to ensure the quality of the specimens tested and to improve standardization of specimen processing to reduce specimen processing time and decrease the overall turnaround time (TAT).

Closing the Gaps to Achieve a Standardized, Efficient, and Reliable Pre-analytic Processing

The Clinical Laboratories at Michigan Medicine process millions of specimens/year that are received from various hospitals, health centers, and outpatient clinics nationwide and are handled by our dedicated specimen processing department. Each specimen must be manually "received" and updated in our laboratory information system (LIS) by the staff to allow tracking of the specimen. Our staff inspect the specimen to ensure that it meets general specimen labeling requirements and the specific criteria defined for each test. Specimens are manually sorted and either routed to clinical laboratories at University Hospital (UH) and the North Campus Research Complex (NCRC) that perform the testing in-house or specimens may be sent out to reference laboratories for specialized testing. A large staff cohort support specimen processing, gatekeeping the quality of the specimens received by the testing labs. High quality specimens don't just mean better results and better patient care, but also significantly impact the flow of specimens through the testing cycle. Specimens that do not meet the expected standards (e.g., missing information, quality concerns) require additional investigations that can impact the TAT of the results. These processes may be very manual, with many touch points that are the ideal target for automation to help standardize and improve specimen processing, ultimately improving quality in our clinical laboratories.

Pre-analytical Systems Hold the Promise to Improve Specimen Processing at Michigan Medicine

In recent years, many sections of the Clinical Laboratories at Michigan Medicine have adopted or updated automation solutions to improve their processes. The Pathology Relocation and Renovation (PRR) project allowed us to redesign clinical laboratory space at UH to accommodate automated solutions for the pre-analytical processes. Two new standalone systems (Cobas® p512 and p612) have been validated for use to automate and simplify the pre-analytical processes with the ability to automatically receive the specimens and perform a comprehensive inspection of the sample quality including tube type, liquid level detection, and blood sample quality (hemolysis, lipemia, icterus). The systems can process up to 1,400 tubes/hour, sorting the specimens based on the downstream testing requirements. This automation is an exciting step forward in our commitment to improve the quality of our laboratory testing processes. In addition to improving the workflow, the systems collect valuable quality indicators that can spur improvement in the pre-analytical processes.

Dr. Mustafa Yousif: Advanced Technologies Transforming Pathology: Michigan Medicine's Digital Revolution

In medical sciences, the evolution of technology is a beacon of hope, promising enhanced precision, efficiency, and patient care. Particularly in pathology, a field historically reliant on microscopes and physical slides, the advent of digital pathology (DP) represents a paradigm shift. Michigan Medicine's Pathology Department is at the forefront of this transformation, embracing digital workflows to redefine diagnostic practices. This article delves into the transformative impact of digital pathology on Michigan Medicine's operations, patient care, and the broader field of pathology.

Digital Pathology: Beyond the Microscope

Digital pathology transcends the conventional microscope, offering a digital window to current and historical cases. This innovation allows pathologists to access and analyze medical images from anywhere, at any time, ushering in an era of unparalleled convenience and efficiency. Slide digitization streamlines the review process and opens the door to second opinions and specialist

Above:
Dr. Kim stands with her team next to the department's new Novaseq X Plus machine.

consultations with a mere click. This digital leap facilitates integrated diagnostic workflows, fostering collaboration across medical disciplines and enhancing the quality of patient care.

Implementing Digital Pathology: A Multidisciplinary Approach

The shift to digital pathology is not merely a technological upgrade but a strategic transformation involving a multidisciplinary team of pathologists, technicians, and IT experts. Michigan Medicine's phased integration of DP focuses on optimizing areas where digital adoption yields the most significant benefits. The core of this initiative is the remarkable transformation of the histopathology lab, which now features an array of specialized scanners, each tailored for a specific function within the realm of advanced slide scanning. Beyond their capabilities for bright-field scanning, these sophisticated devices support a variety of imaging techniques, including dark-field microscopy and immunofluorescence. This diversification in scanning technology represents a significant advancement in the lab's diagnostic potential.

The LEAN Workflow Optimization

Adopting a LEAN approach, Michigan Medicine has reengineered its lab workflows to minimize unnecessary movement and enhance efficiency. Michigan Medicine has implemented a state-of-the-art dashboard system to complement the capabilities of these advanced scanners and maximize their efficiency. This digital platform is a central hub for monitoring and managing the scanning workflow, offering real-time insights into scanner operations, sample throughput, and diagnostic progress. The dashboard allows lab technicians and pathologists to track the status of each slide, from scanning to analysis, ensuring a seamless transition between steps and minimizing wait times. The introduction of eight scan technicians, operating round the clock, exemplifies the department's commitment to optimizing lab throughput and maintaining a seamless workflow in both new and legacy systems. Michigan Medicine's commitment to digital pathology extends to upgrading its infrastructure, including reading rooms and faculty offices, to support an interactive digital environment. Comprehensive training programs and town hall meetings ensure the staff is well-versed in digital protocols, facilitating a smooth transition to the new digital landscape.

The Future is Digital: Integrating Pathology and Radiology

By July 2024, Michigan Medicine is set to achieve a groundbreaking milestone by fully integrating digital pathology into its comprehensive enterprise solution, encompassing a wide range of imaging modules, including radiology, cardiology, orthopedics, and ophthalmology. This ambitious integration aims to establish a unified diagnostic hub, significantly enhancing diagnostic precision and efficiency. Digital pathology's immediate access to images, alongside radiological and other medical images, enables more effective case discussions and diagnostics. The facility for rapid case retrieval, simultaneous case reviews, and more precise diagnostic audit trails significantly enhance service quality. Moreover, the digital sharing of images facilitates external consultations and second opinions, potentially reducing patient wait times and improving treatment outcomes.

Digital pathology optimizes workload distribution and case management, contributing to rapid and accurate diagnoses. The reduced need for physical slide handling streamlines the

diagnostic process and enhances pathologists' satisfaction by enabling remote work, educational opportunities, and better ergonomics. Furthermore, digital pathology is a valuable research resource, supporting the development of new diagnostic techniques and treatments. Michigan Medicine's strategic embrace of digital pathology marks a significant leap towards setting new standards in healthcare excellence. By harmonizing traditional expertise with digital innovation, Michigan Medicine is enhancing patient care and diagnostic accuracy and positioning itself as a leader in the future of medical sciences. The transition to digital pathology, characterized by its collaborative, efficient, and patient-centered approach, heralds a new healthcare era, promising better patient outcomes and a more rewarding work environment for medical professionals.

Dr. Annette Kim: Advancing Diagnostic Genetic and Genomic Testing in Pathology

The division of Diagnostic Genetics and Genomics (DGG) is in the midst of several assay validations that will bring state-of-the-art molecular diagnostics to Michigan Medicine (MM). Two different assay validations are underway on the Novaseq X Plus® that arrived in fall of 2023. This powerhouse sequencer has the highest sequencing capability and the most advanced onboard bioinformatics tools on the market, capable of generating 16 Tb of data in just a little over one day. Other new innovative platforms have been introduced as well.

DGG plans to validate an assay analogous to MiOncoSeq for clinical testing at scale, in collaboration with the MCTP team under Arul Chinnaiyan, MD, PhD. This paired tumor-normal pan-cancer panel is capable of detecting single nucleotide variants, insertions/deletions, copy number alterations, structural variants such as fusions, mutational signatures, and other complex biomarkers (such as TMB). In addition, the panel includes several hereditary cancer predisposition genes from which germline alterations may be identified. DGG is designing this assay to handle high volumes with the aid of pre-sequencing automation, high-capacity sequencers, and an expansive informatic ecosystem that tracks specimens and data through pre-analytic, analytic, and post-analytic workflows, with a user-friendly interface for rapid generation of reports. This entire system will back onto modern variant and interpretation databases. DGG is also validating a complementary, rapid molecular oncology assay (from DNA/RNA to sequence in 27 hours) using the Genexus® sequencer which requires only 10 ng of DNA/RNA or less, perfect for small biopsies.

Also utilizing the NovaSeq, DGG plans to concomitantly validate a whole genome sequencing platform. This platform does not require either a lengthy hybridization step nor a bias-prone PCR step, enabling a wet-bench procedure that takes an astounding 90 minutes rather than 3 days and provides more uniform coverage than the current germline NGS targeted panel. This platform will be used initially to replace the current set of many small orderables (currently encompassing 297 genes) but will be amenable to subsequent validation of whole exome (WES) and whole genome (WGS) reporting. This assay is also most cost-effective at larger batch sizes and is therefore built for scale.

DGG is also validating optical genome mapping (OGM), a novel genome-wide platform that will complement karyotype and replace some reflex FISH tests and chromosomal microarrays (CMA). The Saphyr® OGM instrument utilizes extra-long DNA molecules from which a whole genome view of structural variants, copy number alterations, and copy neutral loss of heterozygosity can be assessed. Compared to targeted assays such as FISH, low resolution karyotype, and CMAs which cannot assess balanced rearrangements, OGM can detect all types of genomic variants, including novel fusion detection, at high resolution. In addition, other instruments have also been introduced to automate harvesting for karyotype and FISH studies.

These advanced technologies in the laboratory will allow the lab to expand testing volumes to better serve MM patients and accommodate the growing MLabs outreach clients. In addition, DGG will be able to recover significant testing currently sent out to reference laboratories (especially NGS oncology panels, WES, and WGS). In doing so, MM clinicians and researchers will benefit from interactions with their pathologists, access to personalized data review, and access to the primary data, which is unavailable from commercial labs, for MM clinical, research, and educational missions.

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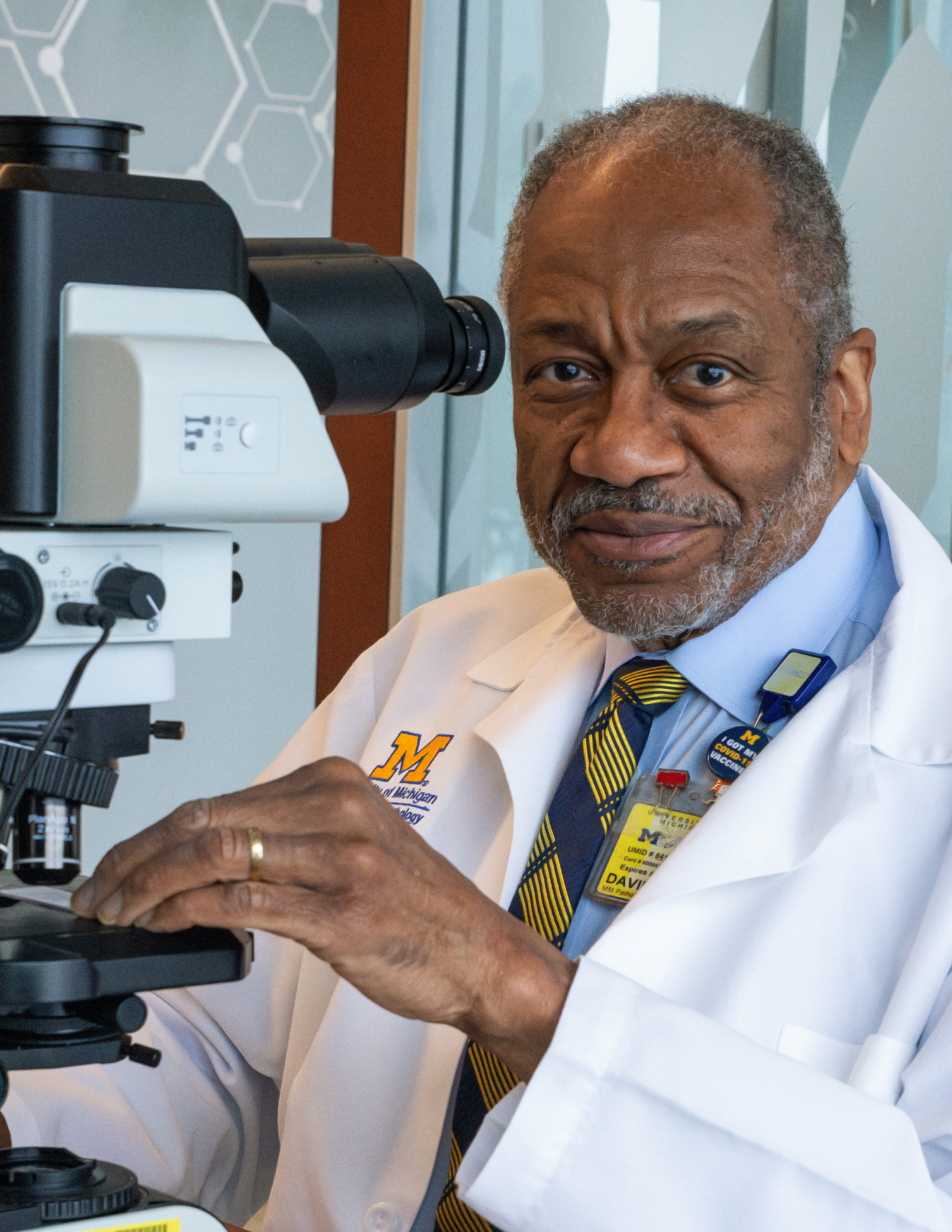


The Adaptable Dr. David Gordon: Highlights from His 55-Year Career

by Lynn A. McCain, MHSA

David Gordon describes his storied career spanning six decades of cardiovascular pathology with multiple detours along the way.

Fifty-five years ago, Dr. David Gordon graduated from Harvard Medical School and launched his storied career. Born the middle son in his family, Gordon's father served as a United States diplomat. While his early years were spent in the United States, by the time Gordon reached elementary school, his family was staying in Ghana, West Africa. He also spent time in Nigeria and 1.5 years in Sweden, with stints in the United States between each of his father's diplomatic appointments. Gordon and his family returned to the United States where he completed high school and attended Amherst College, obtaining a degree in Chemistry. "It was a good experience being in these different countries", recounted Gordon. "I discovered that though we speak different languages and have different cultures and ways of doing things, people are, at the core, pretty much the same. For example, the kinds of pranks that kids play on substitute teachers in this country are the same as goes on in Nigeria and in Sweden. Kids are not really that inherently different in terms of the kinds of things that they like to do." His ability to adapt to major changes set the stage for the rest of Gordon's career.

While at Harvard Medical School, Gordon got involved in vascular biology research, spending two years focused on research. "From a career point of view, I wanted to pick a field where people were having a lot of health problems with a high death rate, because I knew that is where the monies for research would be appropriated," Gordon explained. "Even though cardiovascular research was not as advanced as cancer and immunology, it was a good field in which to make a mark and really make headway in our understanding of the disease." As he worked on his vascular biology research, the lab's primary investigator, Dr. Morrisa Karnovsky, "kept whispering in my ear, 'Think of pathology, young man.'" Yet, convinced that internal medicine was his path, he applied to the internal medicine residency match. Then his last rotation in medical school turned out to be pathology. "That's when I decided I should really go into pathology. It is a much more cell biology approach to medicine compared to all the other specialties. But I had committed myself to at least one year of an internal medicine internship." Following his internship, Gordon went to the University of Washington, Seattle to complete pathology residency training and a postdoctoral fellowship in experimental cardiovascular pathology under Dr. Stephen Schwartz and cardiovascular pathology mentor, Dr. Dennis Reichenbach.

After serving on faculty at Washington University from 1984 – 1991, Dr. Peter Ward, former Chair of Pathology, recruited Gordon to the University of Michigan as an Associate Professor of Pathology. "I have been affiliated with the University of Michigan Pathology ever since, in some capacity, even though I have had a few detours, as I like to call it." From 1997-2001, Gordon detoured to Parke-Davis/Pfizer while maintaining an adjunct appointment in Pathology. He returned full-time to the department as a professor in 2001 and launched the Diversity and

Above:
Dr. Gordon speaks to medical students during their autopsy rotation.

Career Development office, a forerunner to today's Office for Health Equity and Inclusion. "I was the Assistant Dean (1994-1997) and then later Associate Dean (2004-2011) of Diversity and Career Development, working between faculty affairs and student affairs to improve the whole pipeline of underserved, disadvantaged students all the way from pre-high school to pre-med, medical school recruitment and retention, house officer recruitment and retention, through faculty recruitment and retention. I even worked to start the African American Alumni Association, the Fitzbutler-Jones Society, during that time (named after the first African American male and female UM Medical School graduates)." He continued practicing cardiovascular pathology, teaching residents and fellows along the way. "I handled a lot of the unexplained heart deaths in autopsy, supported the heart transplant service, and monitored transplant rejection. Today, we see a lot more aneurysms and other cardiovascular pathology."

"One of the most important tools we have to improve the quality of patient care is the autopsy. That is where we find things that, if the condition had been known when the patient was alive, would have changed treatment. It helps us to continue to educate physicians about things they should be looking for." The autopsy is also useful to find hereditary conditions and thus run in families. As an example, Gordon mentions young athletes who suddenly drop dead, only to find hypertrophic cardiomyopathy during the autopsy, which is an inherited condition causing an enlarged heart. "There could be other members of the family affected by that condition and at risk. It is important to identify those things and to have discussions with the family so they can be screened." Autopsies also expose unknown risks associated with new devices, such as a stinted valve conduit that gets tangled up in one of the other valves of the heart. When complications such as this are identified in autopsy, the pathologist informs the cardiologist to increase risk awareness when putting in a new device. "A lot of data came from autopsy studies that historically led to things like seatbelts and airbags in motor vehicles. The autopsy showed how people were dying from concussions, ripped aortas, and things like that. The evidence for those safety measures came from autopsy studies."

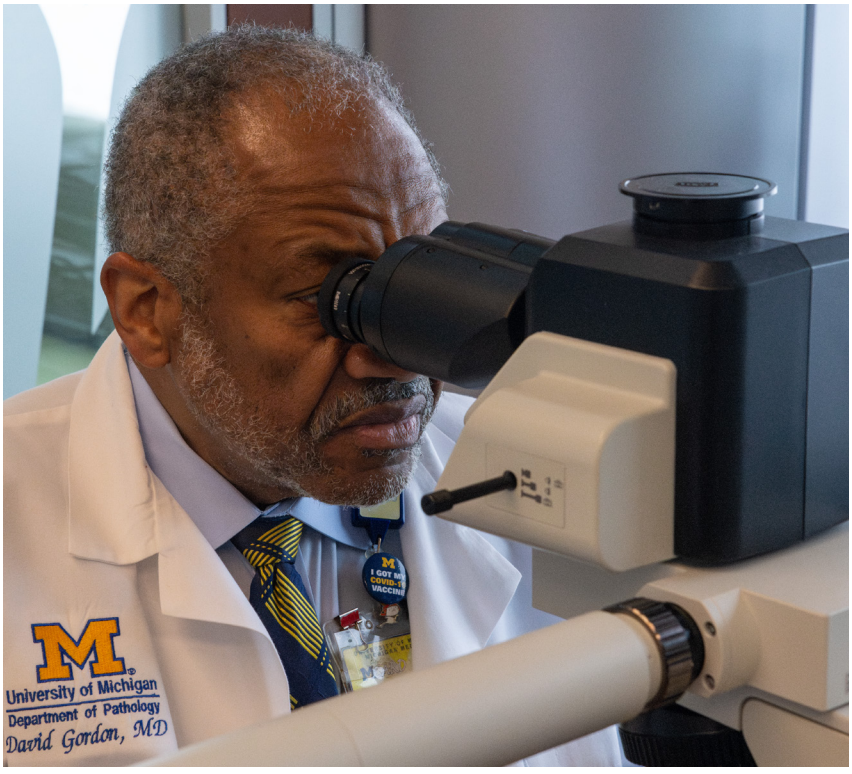
Healthcare disparities is another area of passion for Gordon. These are often seen on the autopsy table as well. Conditions that could have been treated were neglected and led to death. He tells the story, "I remember seeing one patient, a pregnant African American woman with severe hypertension. She died as a result of a stroke. It made me wonder what kind of prenatal care she received. I don't think there was much of any. It is just an individual case, but it highlights the kinds of problems and disparities that people have

pointed to in larger studies. We need to do better as pathologists in going out and doing community education. We are considered educators within medical schools and health systems. There is no reason we cannot be doing community outreach types of efforts." Gordon frequently gives talks to churches and in other community settings about health and answers attendees' questions. For example, he explains the different types of dementia, some of which are reversible. He talks about aneurysms and explains the importance of annual checkups to spot things that are still asymptomatic. "If I had a wish for pathology in terms of improving our pathology services and training programs, it would be to get a little more involved in these types of activities. There is a lot we can do."

Gordon faced another change as he accepted the role of Dean at the University of Michigan, Flint's School of Health Professions and Studies in 2011. "Even though we are bo th a part of the University of Michigan system, there was little affiliation between our Ann Arbor School of Nursing and Flint's department of nursing and between our Ann Arbor School of Public Health and their department of public health. One major administrative role I played was increasing the collaboration between these two University of Michigan campuses." In 2016, The University of Akron in Ohio recruited Gordon as the founding Dean of the College of Health Professions. This expanded his administrative experience, dealing with budgets, faculty promotions, careers, and multiple departments all competing for resources. "I learned a lot about diplomacy. My father was a diplomat, so maybe I inherited some diplomacy genes from him. The bottom line is you need to care about people to be able to work through people's differences and point them toward a useful goal that is going to be beneficial for most people, if not everybody."

New presidential leadership at the University of Akron led to sweeping changes in leadership and Gordon was faced with another opportunity to adapt. "I came back from Akron and served as the Associate Medical Director for a Federally Qualified Health Center (FQHC) in Genesee County, Michigan, the Hamilton Network. The FQHC exposed me to dealing with an indigent population in a safety net clinic for the first time." Gordon learned about many issues this population faces, such as the difficulty in attracting healthcare providers to these clinics. He increased ties with the University of Michigan and ran some programs jointly. "I had to unlearn some things about the community and learn other things that would be helpful for certain disadvantaged populations. That has been my passion all along – ultimately really helping disadvantaged patients."

Throughout this entire time, Gordon maintained an appointment in the Department of Pathology, consulting on cardiovascular cases. He returned more fully to the Department as an active professor emeritus, where he continues to serve in the autopsy suite and sign out cardiovascular cases. He is also the Director of Faculty Programs for the Office for Health, Equity, and Inclusion. In this position, he recruits, coaches, and works to retain faculty who come from underrepresented backgrounds. "I cast a broad net in that regard. It is not just simply people who are African American, Hispanic, or Native American. It is anyone who comes from socioeconomically poor background or is otherwise disadvantaged. I am here to help advocate for them, coach them, explain to them how the university system works. If need be, I will go and talk with their chairs or their division heads to get clarity in terms of what is going on with them. I try to make the faculty and trainees aware of their different career opportunities. That is my overarching mission. I want to train faculty and new leaders who will go on and make headway in terms of improving the health of underserved and disadvantaged populations. That is what I do."

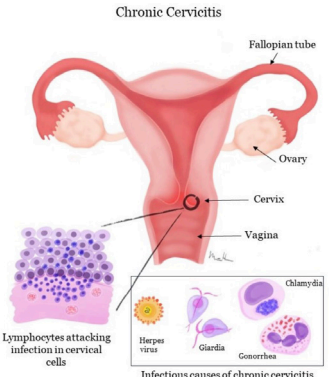


Below:
Dr. Gordon sits at a scope while reviewing cases.

Pathology in the Digital Age: Harnessing Social Media for Education, Outreach, and Collaboration

by Zoe Shafiezadeh

The prominence of digital technologies, notably social media, has surged across various spheres in recent years. These platforms can be great for collaboration, creativity, and more, but users must be cautious when interacting with different types of information. Many believe that the benefits of utilizing these tools outweigh the potential risks as long as they are handled cautiously, especially in professional spheres. Michigan Medicine is known for its innovative spirit and ability to adapt to new technologies. Social media might not traditionally be associated with the medical field, especially pathology, yet numerous staff members have adeptly integrated it into their professional lives. Dr. Meredith Herman, a first-year resident, is a large proponent of social media. She understands that while social media can be seen as trivial; she believes "many don't realize the impact that having a social media footprint has in medicine" especially as the field gains more recognition.



The impact of social media is particularly profound for younger generations and aspiring pathologists. Although it is not an authoritative resource for academic or diagnostic purposes, it excels in sparking interest. Pathology is a widely unknown field for many entering the medical sphere and social media can be a great way to introduce undergraduate and medical students to this specialty. "By posting and reposting about related medical topics, the effects bubble over, raising awareness about the use of tumor banks to perform cutting edge research and then highlighting that pathologists are essential for this to occur allows people to see how it's all connected," says Dr. Analisa Difeo, Associate Professor and Associate Director of the Doctoral Program in Cancer Biology. Herman reflected on her time as a medical student where information about pathology was disseminated, "all through word of mouth… I didn't know any pathologists." "Social media can be used as a place to touch base and for medical trainees to understand what pathology is, which brings an element of outreach to the platform," according to Dr. Kamran Mirza, Assistant Chair for Education. He believes that to inspire and teach the next generation of pathologists, those in the field now must be proactive.

When pathologists and others post about pathology prospective students are exposed to the field and begin to think about it as a possible career choice. Social media also allows for some of the medical hierarchy to dissipate as students can connect and interact with pathologists who are established in the field. "I want to be someone that a student can reach out to and ask questions because that is what I would have wanted," Herman stated, understanding how valuable it is for students to get insight from someone currently in the field. Difeo is proud to have students from a range of educational levels present in her lab. "Sometimes it is a question from a high school student that could change the trajectory of our research," she said, "It is important to recognize how their insight is incredibly valuable." Social media's use goes far beyond posting educational material; it also helps to create it by crowdsourcing information. "We've been able to create a website with over 1.2 million views which provides free education that is accessible to everyone including people from low-resource countries," said Mirza. Uses like these actively strive to make the medical field a more diverse, equitable, and inclusive community.

Social media is also an incredible resource because of its ability to deliver fast and widespread communication. X, formally known as Twitter, has become the main space for the pathology community, allowing pathologists to connect

with people in and outside of the field. Dr. Rohit Mehra, Professor of Pathology, finds that posting is a great way to get people talking about research topics. "I try to post interesting cases to share and disseminate knowledge about Genitourinary Pathology." He found that by sharing his work other institutions are more inclined to contribute and share theirs, enhancing collective knowledge about various subjects that are less widely known. Difeo uses her lab-based account to not only advertise research but also members of the lab. She is happy to use their collective platform to promote the success of lab members and help them gain exposure in the field. Some may not feel comfortable posting on these platforms but there are still many other ways to interact that are less direct. Reposting content from other reputable organizations can amplify awareness of a pathologist's endeavors and related subjects. This method is instrumental for Mehra in his work with the Prostate Cancer Foundation and for Difeo in her work with the Michigan Ovarian Cancer Alliance. "In a field like cancer research, it is very important to have it on social media and have people who aren't in the sphere of pathology or cancer be able to see that and interact with it," said Mehra. Reposting content from these organizations is an effective and easy way to distribute their messages and their important work to more audiences, increasing cognizance about the field.

The audience for posts related to pathology consists mostly of students or professionals in the medical field, but these tools can also reach patients. Social media has emerged as a valuable tool for simplifying medical information, enabling a more accessible and visual approach to understanding complex diagnoses. Herman has been using her passion for art combined with her career in pathology to illustrate diagnoses for patients and share them with the public. When patients research a diagnosis online or have it explained by a doctor it can be difficult for the patient or their loved ones to grasp the concept due to unfamiliarity with the medical terminology. By creating a simple visual and making it publicly accessible, Herman is helping simplify a time in their life that can be very confusing and overwhelming depending on the severity of the diagnosis. Herman mostly shares these images on Instagram and X. Mirza has found a space on TikTok by partnering with patient advocacy groups to talk directly to patients. While he is not offering medical advice, he is able to explain a disease in more detail and make diagnoses easier to digest. Allowing patients to interact with doctors through a mediated form of communication makes patients more comfortable asking questions to understand topics more deeply.

There are copious benefits to using social media, especially in a professional sphere such as pathology, yet caution must be taken when interacting with content. Misinformation is rampant across all platforms and it is important to protect yourself and others. This may make some hesitant to join social media. Consider, however, that if pathologists are not distributing accurate information and participating in these conversations, others will, presenting less well-curated information. Luckily, according to Mirza, the online pathology community is relatively on top of the information circulating. "If someone makes a mistake or goes down the wrong path, people are willing to step in and respectfully correct the information." Social media is still relatively new in comparison to many other facets of technology so there are bound to be challenges society must overcome as it is applied more broadly. While there is a learning curve, Herman urges people to think about how, "it is not just posting; it is intentionally continuing to grow and contributing to the growing community of pathology on a global scale."

Connect with Our Faculty

Analisa Difeo, PhD
X @DiFeoLab

Meredith Herman, DO
X @MeredithKHerman
@WhiteCoatArtistry

Kamran Mirza, MD, PhD
X @KMirza
@Kampathdoc
@Kampathdoc
www.pathelective.com

Rohit Mehra, MD
X @drmehrarohit

Supporting the Department of Pathology

Supporting key initiatives within the Department of Pathology helps the next generation of trainees, researchers, and physicians. With these funds, you are enhancing the training of our up-and-coming pathologists, improving the education of faculty from the earliest stages through senior levels, and providing opportunities for ongoing research as we work to find the underlying causes of disease and identify ways to improve patient outcomes.

Departmental Initiatives

- **Pathology Annual Fund:** Provides the Department of Pathology with funds to be used where they are most immediately needed, or opportunities are greatest.
- **Appelman Family Junior Faculty Enhancement Fund:** This fund is designed to enhance the development of our junior faculty in the areas of teaching, clinical research, service, administration, and overall professional development.
- **Clinical Pathology Gift Fund:** Your contribution will help advance innovative research, education, and patient care inititatives in the Department of Pathology.
- **Clinical Pathology Staff Enhancement Fund:** This fund supports educational initiatives for clinical laboratory staff and clinical laboratory science/phlebotomy interns in the Department of Pathology.
- **Pathology Faculty Research Fund:** Your gift will support faculty who are international leaders in diagnostic pathology, education, and research and aid in the continuation of their research efforts.
- **Pathology Residents Research Fund:** Gifts to this fund enable our residents to take on research projects during their training to help better understand diseases and disease progression, as well as uncover novel pathways that may lead to therapeutic solutions for patients.
- **Pathology Fellowship Fund:** Pathology Fellows are focused on becoming experts in a subspecialty area of Pathology. This fund will enhance their ability to undertake a scientific investigation, pursue educational leadership development, and expand their clinical expertise as they prepare to launch their careers.

For more information email:
path-development@umich.edu

Retirements — 2022-2023

Douglas R. Fullen, MD
Clinical Professor
Retired: Jul 1, 2022

Denise E. Sulavik
Pathologist Assistant
Retired: Oct 22, 2022

Lore P. Krzewina
Medical Technologist Specialist
Retired: Dec 6, 2022

Nancy L. Tague
Histotechnologist
Retired: Jan 11, 2023

Rong Wu, MD
Associate Research Scientist
Retired: Apr 1, 2023

Linda Dawson
Cytotechnologist
Retired: May 20, 2023

Jeffrey Harrison
Histotechnologist
Retired: Jul 6, 2022

Yinhong Shen
Medical Technologist
Retired: Nov 8, 2022

Diana Khiterer
Allied Health Assoc.
Retired: Dec 31, 2022

Charles Howison
Lab Technician
Retired: Feb 14, 2023

Nancy Czerwinski
Medical Technologist
Retired: Apr 14, 2023

Lori Hufstedler
Word Processing Operator Sr.
Retired: Jun 1, 2023

Michelle Bensette
Medical Technologist Specialist
Retired: Aug 13, 2022

Lena Muchkina-Livshiz
Medical Technologist Specialist
Retired: Nov 11, 2022

David R. Lucas, MD
Clinical Professor
Retired: Jan 3, 2023

Jill Gosselin
Phlebotomy Specialist
Retired: Feb 22, 2023

Sylvia Zelenka-Wang
Research Lab Specialist Inter.
Retired: May 11, 2023

Laurie Chopko
Admin Asst. Sr. Healthcare
Retired: Jun 3, 2023

Those We've Lost — In Memoriam

Eugene Silverman, MD
Associate Professor Emeritus
Jun 1938 - Feb 2024

David Ferguson, MD, PhD
Associate Professor
Jun 1966 - Jan 2024

Hope Jones
Lab Technician
May 2024

Dena Ryan
Manager, MediaLab
May 1977 - Apr 2024

Scan the QR Code
Read their Full Obituaries.

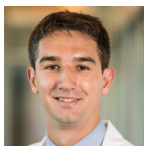
GRADUATES 2024

Clinical Instructors

Heather Chen-Yost, MD
Pulmonary/Thoracic Pathology
Clinical Assistant Professor
Michigan Medicine

Sabina Desar, MD
Genitourinary Surgical Pathology
Assistant Professor
Virginia Commonwealth University

Efrain Gutierrez-Lanz, MD
Surgical Pathololgy
Hematopathologist
LabCorp



Geoffrey Halling, MD
Gynecologic Surgical Pathology
Head & Neck Pathololgy Fellowship
Michigan Medicine

Suguna Narayan, MD
Informatics
Clinical Assistant Profressor
Michigan Medicine

William Perry, MD
Head/Neck Pathology
Clinical Assistant Professor
Michigan Medicine

Julianne Szczepanski, MD
Breast Surgical Pathology
Molecular Genetic Pathology Fellowship
Michigan Medicine

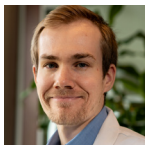
Kriti Tiwari, MD
Surgical Pathology
Breast Pathology Fellowship
Mount Sinai Hospital, New York

Mary Torrez, MD
Surgical Pathology
Cytopathology Fellowship
University of New Mexico

Katelyn Zebrowski, MD
Gastrointestinal Surgical Pathology
Surgical Pathologist
Michigan Pathology Specialists

ACGME Fellows

Matthew Bayes, MD
Chemical Pathology Fellow
Molecular Genetic Pathology Fellowship
Johns Hopkins, Baltimore, MD



Hans Magne Hamnvag, MD
Hematopathology Fellow
Surgical Pathology Fellowship
Mayo Clinic, Rochester, MN

Anup Jnawali, MBBS
Hematopathology Fellow
GI & Liver Pathology Fellowship
Beth Israel Deaconess, Boston, MA

Vincent Laufer, MD, PhD
Molecular Genetic Pathology Fellow
Pathology Informatics Fellowship
Michigan Medicine

Jaclyn Plotzke, MD
Dermatopathology Fellow
Dermatology
Michigan Medicine

Arjun Reddy, MD
Molecular Genetic Pathology Fellow
Tempus Corporate Lab
Chicago, Illinois

Andrew Schuler, MD
Dermatopathology Fellow
Dermatopathologist
UM Health West

Residents

Haley Amoth, MD
Hematopathology Fellowship
Michigan Medicine

Thomas Herb, MD
Forensic Pathology Fellowship
Michigan Medicine

Nathan McCammon, MD
Clinical Instructor-Surg. Path Fellowship
Michigan Medicine

Corey Post, MD
Hematopathology Fellowship
Michigan Medicine

Fysal Shennib, MD
Clinical Instructor-Surgical Pathology Fellowship
Michigan Medicine

Nicole Tomm, MD
Clinical Instructor-Gastrointestinal Surgical Pathology Fellowship
Michigan Medicine

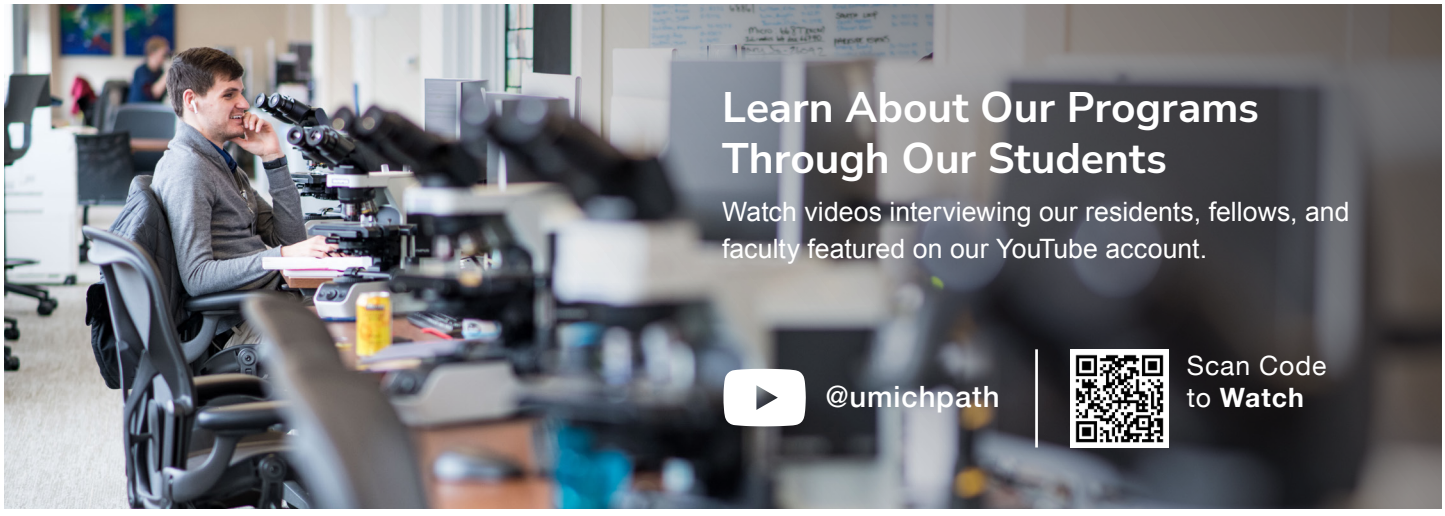
Maxwell Wang, MD
Women's Pathology Fellowship
NYU Langone Health

Molecular & Cellular Pathology - PhD

Derek Dang, PhD
Defended / January 19, 2024
Mentor / Dr. Sriram Venneti
Position / Scientist
Beyond the Warburg Effect: A study of metabolic alterations in malignancies of the posterior fossa

Sahiti Marella, PhD
Defended / December 6, 2023
Mentor / Dr. Simon Hogan
Position / Postdoctoral Fellow
Regulatory Networks that Govern the Esophageal Epithelial Proliferative Response in Eosinophilic Esophagitis Endotypes

Michael Pitter, PhD
Defended / March 15, 2024
Mentor / Dr. Weiping Zou
Position / Scientist
The Role of Peptidyl Arginine Deiminases in Regulating Anti-tumor Responses in Immune Cells



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UNIVERSITY OF MICHIGAN

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