Commentary from the Department Chair

Dr. Rosai and Dr. Kilometro on June 3, 1991 – our first day at MSK – looking at consult cases he brought with him from Yale.

He pushed us to do new things – subspecialization, digital pathology, even molecular characterization of tumors – but he also fiercely defended the power of the microscope and the ability of skilled pathologists to produce enormous quantities of information from simple H&E slides.

Much has been written about Dr. Juan Rosai since he passed away a little over one year ago, including the article in this issue of the MSK Pathology Review that details his years in our department. Tributes and memorials have been published, and more are forthcoming (including a detailed tribute I co-authored with Robin Young that will appear soon in Am J Surg Pathol). These works clearly detail Dr. Rosai’s life history, his contributions to patient care, research, education, and advocacy, and some provide glimpses into his personal interests and personality as well. But I had a very close relationship with Juan over many years, my early career was mentored by him, and my recollections and anecdotes may provide a bit more color about this man, whose influence on the practice of surgical pathology was so profound.

I first encountered Dr. Rosai in 1985, during the 2nd year pathology course at Yale. He had only recently joined the faculty there, and his reputation as a superb diagnostician and teacher preceded him. His lecture to the students was on skin cancer, and I remember him explaining why basal cell carcinomas should be considered malignant – not because of any significant metastatic potential but because of their local invasiveness, which he illustrated with an image of a patient’s face nearly replaced by a neglected BCC. The photo was shocking, but it illustrated how the lessons Dr. Rosai taught frequently touched on more fundamental issues in pathology – in this case the illusive definition of “malignancy” – than the simple criteria to make a diagnosis. Rarely were his lectures simply didactic, as he sought to understand the mechanistic explanations for the morphologic findings he observed.

After spending a 4th year medical student rotation in the Yale Pathology Department, I decided to train in that department, where Dr. Rosai was both the Director of AP and the residency program director. His clinical practice at that time was essentially limited to his personal consultation cases, but the residents had plenty of interactions with him through his weekly gross and microscopic conferences. These conferences were exemplars of Socratic teaching, in which Dr. Rosai peppered the trainees with questions, often asking why the answer was given, to understand the resident’s thought process and correct any errant deductions. These conferences were quite stressful for the residents, since no one likes to demonstrate ignorance publicly, but the process was extremely educational and motivated a lot of late night reading!

After I served as the administrative chief resident in my 3rd year, I had been accepted as one of Dr. Rosai’s consult fellows, to begin in July, 1991. In the spring of that year, rumors began circulating that he was considering another position. With the residents, he kept his cards very close to his chest. Only after he had formally accepted the position as Chair of Pathology at MSK did he openly discuss the situation. Naturally, I was distraught. I was supposed to spend 2 years splitting my time equally between reviewing his consults and working on research projects with him, and he was...
leaving. Luckily, Dr. Rosai was able to create an additional fellowship position for me at MSK that allowed me to spend half of the year looking at his consultations, and for the other half I would rotate with the other oncologic pathology fellows. Dr. Rosai’s consults included neoplastic entities from essentially every organ, but thyroid, thymus, and soft tissue tumors were particularly abundant. He received 15-20 cases per day, and the responsible fellow was to review them and present the findings to him at a group session around the multi-headed microscope in his consultation room, which also contained all of his old cases (consults and seminar cases), every issue of every major pathology journal, and paper reprints of articles from other journals. All of his material was catalogued in his custom computer system, but often he did not need it. Dr. Rosai had a true photographic memory, and he could recall a similar case that he had seen, or a report that was germane to the discussion, and often he could retrieve it from the slide files or journal without the need to look it up. As in his conferences, he liked to explore the reasoning with which the fellow arrived at a diagnosis, and he would allow you to go down the wrong path if it could be educational. I remember a soft tissue tumor that looked malignant and had both osteoid and chondroid matrix. I reasoned that it must be a chondroblastic osteosarcoma, and I proudly defended my diagnosis in front of the whole group. “You are right, that a malignant tumor with chondroid and osteoid ought to be an osteosarcoma,” he said. “But in this case, this is not a malignant tumor. Have you heard of myositis ossificans?” I neglected this case, this is not a malignant tumor. Have you heard of myositis ossificans? I neglected the clinical history of recent, rapid growth and asked if Sibel and I were looking forward to the trip to Granada. It did get us the honeymoon suite at the Alhambra Palace Hotel, so I think it was a good deal in the end! In all of my dealings with Dr. Rosai, I was always impressed by his knowledge, work ethic, and dedication to the field of pathology. He pushed us to do new things – subspecialization, digital pathology, even molecular characterization of tumors – but he also fiercely defended the power of the microscope and the ability of skilled pathologists to produce enormous quantities of information from simple H&E slides. Through his many publications, books (including his remarkable near-single authored textbook on surgical pathology), editorships, and lectures, Juan Rosai left an indelible impression on our field. As his mentee, I believe it was through teaching that he made his most lasting contributions, and dozens of fellows who trained with him at MSK during his 8 years here have added to the 100s who worked with him elsewhere in extending his influence across the globe. When he returned to MSK to receive the Fred Waldorf Stewart award, the response was tremendous, and I believe it was the largest alumni turn-out we have ever had.

Many things have changed at MSK since Dr. Rosai left in 1995 and some he would not have approved of. But I think the course our department has taken has extended many of the principles he espoused, and he told me, very near the end of his life, that the years he spent with us were the most satisfying and enjoyable of his professional career. I know how he felt.

- David Klimstra, MD

**Case of the Quarter**

55 year old female was found to have left humeral lytic lesion with cortical destruction and extraneous soft tissue component, measuring 3.4 x 2.6 x 3.8 cm by MRI. She also presented with a lymph adenopathy in the right cervical lymph node. Biopsy was performed from the bone lesion and the right cervical lymph node.

The correct diagnosis will be provided in the next issue of the MSK Pathology Review and on Twitter at @MSKPathology

**DIAGNOSIS: LAST ISSUE**

Metastatic adenocarcinoma with lepidic growth, consistent with metastasis from primary biliary adenocarcinoma. Based on molecular profiling, the tumors are clonally related. The lung metastasis have gained a few additional alterations. TFE-1 was retrospectively performed on the cholangiocarcinoma and was positive; Napsin A were negative in both tumors.
Research Profile

Caleb Ho, MD, Searches for Hidden Insights

By Kaye Sukei

Caleb Ho, MD, a pathologist with the Memorial Sloan Kettering Cancer Center (MSK) Hematopathology and Diagnostic Molecular Pathology Services, got scant exposure to pathology before his final year of medical school. Then came a life-changing blood banking rotation.

“Like many medical students, I didn’t really know all that much about what pathologists did until that rotation,” said Dr. Ho. “There, and then in a later rotation, I spent a lot of time working with slides. I liked that there were so many factors to consider. To get to the right diagnosis, you have to gather a lot of different and interesting information and put it all together. I really liked the investigative part of it.”

The desire to continue such investigations led him to specialize in hematopathology—a field that requires extensive integration of information ranging from microscopic examination to flow cytometry. Ho also liked that the subspecialty places heavy emphasis on findings from molecular diagnostics, which offer critical insights into hematologic cancers. Dr. Ho came to MSK in 2015 as a Molecular Genetics Pathology Fellow and remained as a faculty member after his year of training.

“One of the benefits of working at MSK is that there are a lot of tools available here that can help us understand the nuances of a patient’s cancer,” he explained. “For example, if I’m doing flow cytometry and looking at the cell markers there, I can use that as a way to sort out different cell populations. By separating different cell types, we can look at each type’s mutation profile or cytogenetic changes.” Those nuances, he said, make targeted diagnoses and prognoses possible for each patient. And they’re what make pathology so interesting.

THE RIGHT TEST

Understanding all those nuances is what drives Dr. Ho’s research. For example, multiple myeloma, a cancer of the bone marrow, shows variability in disease behavior based on a combination of different genetics and clinical factors, which increases the difficulty for clinicians to choose the right treatment. Even if clinicians can provide an effective intervention, patients who have been diagnosed with this form of cancer can potentially relapse later. Molecular tests that can pinpoint minimal residual disease (MRD), or traces of the cancer, make it possible to identify the return of cancer before it becomes too advanced to treat.

“It can be difficult to make the right decision about what’s appropriate for the patient from a treatment perspective with many of these cancers,” said Ho. “But it is also important to understand what molecular tests should be done and the implications of those tests to the entire clinical picture. There are a lot of new molecular tests out there that could help us but knowing the different methodologies available, the sensitivity levels of such tests, and the indications on the clinical side for a particular test over another is important.”

Dr. Ho and his colleagues have been working with a commercially available molecular assay, called LymphoTrack™, that helps pathologists detect very low levels of different cancers in patient samples. Currently, most pathologists would use flow cytometry to accomplish the same objective. Dr. Ho and his colleagues have determined that the molecular assay is comparable in technical performance for measurable/minimal residual disease (MRD) detection, giving clinicians crucial information so they know when to monitor patients more closely or even provide some form of early intervention to prevent a relapse.

“It’s been well established in myeloma that patients with even a very low level of disease don’t do well in comparison to patients who are completely negative for cancer,” he said. “The prognostic value of MRD is well known. But what we still do not always know is the best method for detecting MRD, or the clinical indications that might make one test better than another in certain situations.”

PROVIDING A CLEAR PICTURE

Like most pathologists, Dr. Ho’s goal is to provide each oncologist with a pathology report that uses the right tests to elucidate the biology of the tumor. That, in turn, offers a clear clinical picture of a patient’s disease. But he said the best results come from pathologists and oncologists working together, talking through all aspects of each particular case.

“The diagnostic process is very dynamic, and the kind of technology that is now available to help us come up with that diagnosis is amazing,’ he said. ‘But when pathologists can work with clinicians from the start, and clinicians can give a little bit more clinical information, it can help us decide which tests should be run and what information we need...’”
Looks Closely
CECILIA LEZCANO, MD

Cecilia Lezcano, MD,  
Looks Closely
By Kayt Sukel

According to the American Cancer Society, more than 100,000 new melanomas will be diagnosed this year. But for a correct and timely diagnosis, an individual— or his or her dermatologist— needs to recognize that a particular mole or area of pigmented skin should be biopsied and reviewed more closely by a pathologist with the right tools and expertise.

“Normally, the vast majority of melanocytic lesions of the skin can be fairly easily classified by pathologists as benign or malignant on the basis of their histomorphology” said Cecilia Lezcano, MD, a dermatopathologist at Memorial Sloan Kettering Cancer Center (MSK). “However, there is a subset of cases that are difficult to confidently determine the biological potential of a lesion. Having the right tools available to help us in the evaluation of melanocytic pathology where not only the diagnosis but also staging or margin assessment can be occasionally challenging is very important.”

At MSK since 2017, Dr. Lezcano has been diligently working in the study of a biomarker, PRAME, which stands for Preferentially expressed Antigen in Melanoma. Teaming up with Drs. Busam and Jungbluth, Dr. Lezcano focused on the practical applications of the detection of PRAME expression by immunohistochemistry in melanocytic lesions.

“PRAME is an antigen that has been shown to be expressed in high levels in most melanomas and some carcinomas, sarcomas, and leukemia/lymphomas, while in benign neoplasms PRAME expression is either absent or only very low levels of it can be detected”. Dr. Lezcano adds “normal tissues also typically lack expression of PRAME with the exception of testis and few other tissues, placing PRAME in the category of cancer testis antigens: antigens characterized by their expression fairly restricted to malignancy and testis, which has implications for PRAME as a biomarker to aid in diagnosis as well as a potential target for therapy”

EVIDENCE FOR PRAME
Initial data by other groups identifying PRAME as a biomarker focused on its expression at the mRNA level. However, through the use of a commercially available antibody suitable for immunohistochemistry Dr. Lezcano and her colleagues were able to assess the in situ expression of PRAME protein in tissue sections. Their initial work included a cohort of 400 melanocytic lesions including metastatic melanomas, primary melanomas, and nevi.

The results were promising: “We saw a very clear difference in staining for PRAME in benign lesions there was little or no immunoreactivity, whereas in most malignant tumors we saw diffuse positive staining for PRAME”. This provided grounds for a subsequent study looking at PRAME immunostain in the assessment of melanocytic lesions with ambiguous histologic features. “PRAME is an antigen that has been shown to be expressed in high levels in most melanomas and some carcinomas, sarcomas, and leukemia/lymphomas, while in benign tumors with challenging histology and results from cytogenetic ancillary tests we have shown that immunohistochemistry for PRAME is a helpful piece of the puzzle”. Once a diagnosis of melanoma is established, surgery to remove the primary tumor is typically the treatment of choice. “Here again, PRAME immunostain can be helpful to establish margin status in excisions for melanoma especially when there is a lentigious in situ component with borders that are difficult to confidently determine on routine H&E sections alone.” Dr. Lezcano points to the frequent expression of PRAME in lentigo maligna which often occurs in skin with background increase in melanocyte density, and the fact that PRAME different from other melanocytic markers like Sox10 and Melan A- is normally negative in non-neoplastic melanocytes.

Further work by Dr. Lezcano has shown that immunohistochemistry for PRAME can assist in the evaluation of melanocytic deposits in lymph nodes. “Sentinel lymph node biopsy is a procedure offered to some patients with a recent melanoma diagnosis. The presence or absence of metastatic melanoma is a predictor of outcome, and pathologists have the important task of making this call. Because benign nevus can also occur in lymph nodes, it is key to distinguish them from melanoma metastases and we found that PRAME is a valuable tool to establish such important distinction.”

With clinical trials exploring PRAME as a target for therapy against cancer currently underway, it is possible that immunohistochemistry for PRAME will become relevant in selecting patient candidates for these trials. Regarding this, Dr. Lezcano mentions “it could certainly represent an additional opportunity for pathologists to help guide decisions on treatment.”

THE VALUE OF WHAT YOU CAN SEE
Dr. Lezcano said she originally pursued a specialty in pathology “inspired by the immense value of the information provided to patients through a pathologist’s eye.” “When I got into medical school, I didn’t really know that pathology existed, let alone what pathologists did,” she said. “But during my pathology rotation, I just fell in love with the fact that with a microscope and my eyes I had access to a new dimension, the microscopic features that underlie disease and have a tremendous impact in the lives of patients. It was absolutely fascinating to me. I knew right then I would pursue training to become a pathologist.”

Today, the idea that her research work is contributing to the ability of dermatopathologists to provide information for diagnosis and management of patients constitutes a big motivation. As she continues this important research, Dr. Lezcano said she is thrilled to be working with her dedicated colleagues at MSK and to have access to the wealth of samples, expertise, and all-around professional quality at MSK. “It is a privilege we have as pathologists to play such a crucial role in patients’ care.”
Juan Rosai, MD, Memorial Sloan Kettering’s former Pathology Chair, was a father of modern surgical pathology. His legacy shapes nearly every aspect of the department.

By Kayt Sukel

He was a giant among academic pathologists.

Known as the “last of the great generalists,” Juan Rosai, MD, stood apart from his contemporaries in the field. The co-author of *Surgical Pathology*, considered “the Bible” for those in the field, Dr. Rosai received just about every honor a pathologist might be nominated for, from the United States and Canadian Academy of Pathology’s Distinguished Pathologist Award and Maude Abbott Lectureship to the International Academy of Pathology’s Golden Medal. He authored hundreds of papers and was consulted on the most challenging and complex pathological cases. And while he spent time at several great institutions over the course of his career — Washington University in St. Louis, University of Minnesota, Yale University, and Milan’s Instituto Nazionale dei Tumori — in his eight years at Memorial Sloan Kettering (MSK) Cancer Center he provided the kind of foresight and leadership that have ensured the department will remain a leading force for decades to come.

When the pathology community learned of Dr. Rosai’s passing this summer after a prolonged illness, doctors around the globe mourned the loss. Ronald Ghossein, MD, Director for Head and Neck Pathology at MSK, credited Dr. Rosai with having the ability, knowledge, and grace to inspire an entire generation of academic pathologists. Not just an amazing pathologist, “he was an extremely cultured person, despite quite modest beginnings,” said Dr. Ghossein. “He didn’t grow up in a family of doctors or intellectuals. Yet, he found a way to study, learn, and become probably the most well-known surgical pathologist of his time.”

Perhaps more importantly, however, Dr. Rosai made sure to share his passion and knowledge with the generations of pathologists that followed him, ensuring that his legacy will live on at MSK and other institutions around the world.

“Our greatest gift to the department and to our patients are the people he trained here and brought here to MSK,” said David Klimstra, MD, current Department Chair. “Several faculty who Dr. Rosai brought on board are still here and hold leadership positions within the department. He trained hundreds of fellows during his tenure who are now taking their experience with him out into their own practices and academic institutions. It’s a legacy with tremendous reach.”

LOOKING TOWARD THE FUTURE

Dr. Rosai ascended to Chair at MSK’s pathology department in 1991, on the heels of six years at Yale University. What became apparent in his tenure, said Marc Rosenblum, MD, Director of Neuropathology, was his uncanny ability to see where and how the field should evolve.

“He really was the foremost general surgical pathologist of his generation,” said Dr. Rosenblum. “And when he trained them, pathologists who were bright and sufficiently experienced could function capably in any area of diagnostic pathology. I believe he really was one of the last of the great masters who could reasonably claim that kind of generalist expertise.”

And yet he was aware of the emerging need for subspecialization. “Whether you were talking about advances in breast pathology or neuropathology, things were becoming more and more complex. It was too much for any one pathologist to keep up with,” said Dr. Rosenblum. “Dr. Rosai knew, even as most pathologists at the time resisted this idea, that specialization was the future of the field.”

While Dr. Rosai was unable to make subspecialization happen within the department before he left in 1999, Dr. Klimstra said he laid the foundation such that these important changes could happen later. He also had the foresight to recognize the importance of molecular diagnostics and digital pathology to future work.

“He was, no doubt, a traditional surgical pathologist,” said Dr. Klimstra. “He was someone who relied heavily on the morphology of tumors to make his diagnoses and was a strong advocate for the discipline. Yet he was always looking for ways to improve the quality of the work. He saw the potential impact of molecular diagnostics and digital pathology early on and was a champion for both technologies.”

Yet even as he encouraged fellow pathologists to embrace the future, he made sure his trainees never forgot their morphological roots, said Victor Reuter, MD, Vice Chair of the department and Director of Genitourinary Pathology.
“He knew people could embrace these new technologies and encouraged them to go down those routes,” Reuter said. “But even as he did that, he made sure they never turned their back on the basics. He wanted them to remain true to morphology and the microscope, allowing them to have all the tools they need to become great pathologists.”

TRANSFORMING PATHOLOGY EDUCATION

Dr. Rosai was a stalwart supporter of strong fellowship training. He led the fellowship program while at Yale and wanted to ensure that MSK trainees received the highest quality education, too. To that end, he worked to transform the fellowship program at MSK to meet the evolving demands of clinical practice.

“He knew the fellowship training program in oncologic pathology could be made into a more valuable educational experience in several ways,” explained Dr. Rosenblum. “For decades, even when I was a fellow, only a portion of specimens that came through the department were the responsibility of fellows, who would examine them to try to arrive at a diagnosis before consulting with an attending. One of the first things Juan did when he came to MSK was to say, ‘Every single specimen should pass through the fellows’ hands.’ And he meant everything. He wanted the fellows to review not only the in-house surgical samples, but slides submitted through the offices of the hospital’s practitioners, the consult biopsies, consult specimens initially done in outside institutions, and even frozen sections.”

The staff was at first skeptical about this plan. But Dr. Rosai was convinced, and convinced in the faculty that once they saw the benefits of fellows “pre-digesting” all this material, they would never want to go back to how things were done before.

“This intense immersion into the diagnostic work of the department was of incredible benefit not only to our fellows but to our faculty pathologists,” said Dr. Rosenblum. “Juan was right. No one wanted to go back.”

Jinru Shia, MD, Director of Gastrointestinal Pathology, was a fellow at MSK toward the end of Dr. Rosai’s tenure. She remembers the doctor having a way of making pathology fun and interesting. “It was more than just his encyclopedic knowledge on the subject,” she said. “He was passionate about the work, and that made it interesting for us.”

One of the more memorable aspects of Dr. Shia’s fellowship was under Dr. Rosai’s early morning personal consultation meetings. Thanks to his reputation and renown, Dr. Rosai received complex consult cases from hospitals all over the world. He would host a weekly meeting to go over those consults with the fellows, allowing everyone to see the slide on a special 14-headed microscope.

“He would always go through those consults so early in the morning. No one liked to get up that early, but we all made sure to be there and didn’t complain,” said Dr. Shia. “It was just so amazing to sit with him and see him walk through all those fascinating cases.”

Kiki Tan, MD, an attending pathologist at MSK, was not only a fellow under Dr. Rosai, but also one of his residents back at Yale. She described rotations with Dr. Rosai, saying he would often put one of the fellows on the “hot seat,” asking the young doctor to explain what he saw on the slide. She said it ensured that all the trainees studied hard to stay at the top of their game.

“Everyone is looking at the slide at the same time and then he’d ask someone, ‘What do you think?’ Right in front of everyone else,” she said. “It could be stressful, because these were often extremely complicated cases. Yet, whether you were right or really far off on your diagnosis, he was incredibly kind and supportive. If you got it wrong, he would say, ‘I could see why you thought that,’ and explain what was really going on there.”

Dr. Tan appreciated how open Dr. Rosai was about the mistakes he himself had made over the course of his career. He even gave lectures on those mistakes. “As a trainer, it’s a powerful thing to have one of the greatest pathologists of his time owning up to errors,” she said. “It helped us gain the experience and the confidence we needed as we continued our own training.”

Dr. Shia added that her experience with Dr. Rosai, and the time he spent with students, has helped her become a better teacher as she works with her own trainees. “He had such a big influence on me, on why it’s so important to put fellows first,” she said. “He showed us how to make pathology interesting and how to help trainees gain the experience they need. Truly, he made us all better mentors.”

When you put it all together, said Dr. Ghossein, Dr. Rosai transformed the fellowship program to promote the education of the next generation of academic pathologists. “It’s just an incredible experience to work with someone with such broad knowledge of pathology across the board,” he said. “It wasn’t just about diagnoses, though those are of course important. It was about thinking about why tumors looked a certain way and considering how to answer that question through research. He made the department much more academic.”

GROWING BY LIFTING OTHERS UP

While Dr. Rosai will always be lauded for his many academic and professional achievements, those who knew him best say one of his best qualities was the way he lifted those around him up—from trainees to colleagues. Dr. Klimstra, who was also Dr. Rosai’s fellow, said that he gave trainees leadership responsibilities early on in their careers.

“He not only taught me how to think about pathology—to ask the research questions to better understand why tumors might look the way they do and what mechanisms may be behind that—he also made sure that there were opportunities to grow in other ways. For example, he asked me to run the fellowship program while I was still a fellow.”

Despite being a top name in the field, Dr. Rosai allowed his colleagues to shine whenever possible, said Dr. Klimstra. He rememberes a series of articles on which he and Dr. Rosai collaborated where Dr. Rosai was the senior author. “By the time we got to the third article, I gave him the manuscript. He reviewed it and told me to take his name off it,” he said. “At first, I thought he didn’t think it was good enough for his name to be on it. But later realized that he did this so it would be seen as my work. He was setting me up so I could be the expert on the pancreas. It was such a gracious and generous gesture that really helped me make my own name in the field.”

Dr. Rosenblum had similar stories about himself and countless other colleagues. “I remember him asking me to rewrite the neuropathology chapter in Surgical Pathology,” he said. “This was the Bible. And he was asking me to contribute. It gave me a lot more visibility than I had at that time. He gave me an opportunity to improve my academic bastard.”

But he did that sort of thing for others all the time.”

Dr. Rosai set an enormously high standard for the department and all its members, but he did so with grace, humor, and care, said Dr. Klimstra. That winning combination benefitted and continues to benefit the department.

“He is not only the most brilliant pathologist I’ve ever known, but also the kindest,” said Dr. Tan. “You don’t come across that combination of greatness and kindness very often. He was a remarkable teacher and a remarkable man. And we all still benefit from all the many lessons he taught us.”

His greatest gift to the department and to our patients are the people he trained here and brought here to MSK. Several faculty who Dr. Rosai brought on board are still here and hold leadership positions within the department. He trained hundreds of fellows during his tenure who are now taking their experience with him out into their own practices and academic institutions. It’s a legacy with tremendous reach.”

- Dr. David Klimstra

From left to right: Peter Rosen, MD, Marc K. Rosenblum, MD, Cynthia Lieberman, Juan Rosai, MD, ****, and Victor E. Reuter, MD.
**MAKING CHANGE HAPPEN: The OpEx Digital Pathology Project**

A silver lining to the COVID-19 cloud? How the pathology department effected a nearly seamless shift to digital platforms without sacrificing patient care.

By Kayt Sukel

Even before the COVID-19 pandemic hit, the Department of Pathology at Memorial Sloan Kettering (MSK) Cancer Center had long planned to increase its reliance on digital pathology. Doing so would reap many benefits including improved analysis, productivity, and patient outcomes. Yet any change of that magnitude would have to rely on a strong management process and a steady, more comprehensive overhaul. “This was the emergency, just-in-time effort. Now, working with OpEx is allowing for a steadier, more comprehensive overhaul,” said Dr. Hanna. That was the emergency, just-in-time effort. Now, working with OpEx is allowing for a steadier, more comprehensive overhaul. “This gives us the institutional resources and support to push a much larger-scale effort where we can look at the entire workflow, from specimen receipt to digital slide distribution, create the right efficiencies and operational gains across the board, and make the digital pipeline work for all of our service lines.”

Moira Hameed, MD, Chief of the Surgical Pathology Service, said it is vital that the department take the time to understand any potential concerns or bottlenecks that may interfere with future digital pathology implementations. “It’s really about processing where we are with digital pathology as well as what we can do with these platforms,” she said. “Having teams that will look at every level, at each spot that a digital pathology workflow may touch, is important. MSK is a busy lab with very different services and workflows. We need to create an infrastructure and a workflow that’s able to support each one of our pathologists.”

**WORKING GROUPS FOR SUCCESS**

The OpEx Digital Pathology project currently consists of four distinct working groups: technical and information technology (IT) infrastructure; laboratory procedures and workflows; ergonomics and user experience; and training, education, and communications.

**Historical Timeline**

- **1884**: Bausch & Lomb introduced the universal microscope
- **1950**: Whole Slide Imaging (WSI) scanners introduced commercially
- **1996**: MSK Department of Pathology tests its first WSI scanner
- **1998**: MSK Department of Pathology acquires its first WSI scanner
- **2006**: In house biopsy specimens scanned
- **2012**: Bar-coding and tracking
- **2015**: Introduction and utilization of telemedicine
- **2016**: Equivalency and Efficiency study published
- **2018**: In house biopsy specimens scanned
- **2020**: Bar-coding and tracking

**The Numbers**

- **3 Million Slides**: Currently we scan, on average, 30K slides per week.
- **26 Scanners**: We have 26 scanners at 3 different locations.
- **30K**: Total of 3 million slides scanned as of November 2020.
Specimens are triaged and delivered to the gross room where they are scientifically dissected and added to tissue processing machines. Once the specimens are waxed and embedded, blocks are trimmed and ribbon of tissue sections are cut and floated in a water bath before being added to a glass slide. Stained slides are dried in an oven and cover slipped. The case is assembled and verified into CoPath verifying the number of slides. Each slide is placed on a whole slide scanner in the laboratory or adjacent scanning rooms. The patient’s results are electronically reported.
Each working group meets regularly, as well as reaches out to key stakeholders through surveys and other means, to understand exactly what is needed to support the transition to digital pathology, now and into the future.

While each working group has its own “slice of the pie,” said S. Joseph Sirintrapun, MD, an attending in genitourinary pathology, “we have different stakeholders who will be affected. A person working in the lab is not going to have the same interests or concerns that a pathologist or fellow might,” said Dr. Sirintrapun. “Having a message that resonates for everyone can help us move from the current state to the new state with less friction.”

FORGING AHEAD  
MSK has traditionally fostered a culture of innovation and continuous improvement, and the OpEx Digital Pathology project takes that mission very seriously. By doing the important upfront work, stakeholders for the project hope to promote acceptance of the changes involved with a digital pathology implementation and help the entire department understand its value to a strong care delivery model.

“Our success is highly dependent on our working groups building a blueprint so that we can easily make further transitions into these newer technologies later on.”

As technologies continue to advance in the digital pathology realm, Dr. Hanna added that he hopes this kind of improvement process will also allow the department to easily implement new innovations as they become available.

“We will know how well we’ve done by how well the next phases play out, and how easily we are able to leapfrog on today’s efforts to add new technologies and other ancillary applications that digital pathology can offer,” he said. “What we create today will provide the right kind of blueprint so that we can easily make further transitions into these newer technologies later on.”

OpEx Digital Pathology Project Teams

Executive Sponsorship

Judy Hagerty-Paglia  
Senior Vice President, Hospital Leadership

Clinical Champions

Dr. Victor E. Reuter  
Vice Chairman, Department of Pathology  
Attending Pathologist

Dr. Meera R. Jameed  
Chief, Surgical Pathology Service  
Attending Pathologist

Pathology Leadership

Dr. David Klimstra  
Chair, Department of Pathology  
Attending Pathologist

Christine England  
Senior Director, Department of Pathology

Core Group

Dr. Orly Ardon  
Scientific Manager, Digital Pathology Diagnostics

Dr. Matthew Hanna  
Director, Digital Pathology Informatics  
Assistant Attending Pathologist

Joseph Aloise  
Senior Process Improvement Engineer, Operational Excellence

Michelle Battista  
Project Manager, Operational Excellence
LORA HEDRICK ELLENSON, MD

From the start, Lora Hedrick Ellenson, MD, Memorial Sloan Kettering Cancer Center’s (MSK) Director of Gynecologic Pathology, said she was looking to combine her clinical work and research interests. She found that sweet spot in pathology. “Growing up, I had three PhDs in the family. My father and brothers were all scientists,” she said. “Perhaps I was inspired by example to take the same path.” Dr. Ellenson eventually spent her days working in the lab where the principal investigator was a pathologist. “The light bulb turned on: ‘I knew that’s where I wanted to be.’”

Since arriving at MSK in late 2019, Dr. Ellenson has continued her groundbreaking work into the molecular signatures of endometrial cancer, diseases that are, she said, unique and, unfortunately, increasing both in incidence and mortality.

“There’s a big push to understand these cancers at the molecular level,” Dr. Ellenson said. “We need to develop a deeper sense of why they develop, why they recur, and why they can be so hard to treat. To address those fundamental questions, Dr. Ellenson and her colleagues are applying sophisticated molecular techniques in the lab. “Once we better understand these diseases, we can begin to apply targeted therapies that treat the patients more effectively.”

UNDERSTUDIED DISEASES

As a veteran researcher in gynecologic cancers, Dr. Ellenson knows more than most that patients diagnosed with these diseases are asking questions that, thus far, research hasn’t adequately addressed. “Like many diseases which primarily affect women, these cancers have, historically, been understudied,” she explained. “It’s clear that research into these tumors has been largely underfunded, especially when compared to diseases with similar incidences.” This is not, she noted, an uncommon story in medicine.

Many different types of gynecologic cancer affect the entire female reproductive system, from the ovaries to the vulva, requiring a closer look, she said. While there is some overlap in the types of tumors that may develop in these areas, each part of this organ system has its own set of unique diseases. An evidence-based molecular classification system, based both on genetic changes seen in the tumors themselves as well as the overall tumor microenvironment, could help both pathologists and oncologists better understand these diseases and select the right interventions to treat them.

Early in her career, Dr. Ellenson’s laboratory was one of the first to identify distinct molecular differences in different types of endometrial cancer. “We used to think of endometrial cancer as a disease divided into two major clinical types of disease,” she said. “However, using molecular techniques, we now understand there are actually four molecular classes of endometrioid and serous carcinomas, which comprise the most common types of endometrial cancer.”

“Like many diseases which primarily affect women, these cancers have, historically, been understudied,” she explained. “It’s clear that research into these tumors has been largely underfunded, especially when compared to diseases with similar incidences.” This is not, she noted, an uncommon story in medicine.

“More than 90 percent of all patients diagnosed with endometrial cancer are women,” she added. “We talk a lot about personalized medicine, but understanding the molecular underpinnings of the copy number high categories of these tumors, the development of tumor organoids, simple, three-dimensional in vitro models to study the ruminations of the molecular changes, and mouse models to study the development of the tumors in vivo. Our goal over the next few years is to really parse out the molecular diversity of these different tumors,” said Dr. Ellenson.

“We talk a lot about personalized medicine, but understanding the molecular changes and evaluating those changes within the landscape of each individual’s tumor,” she said. “We are trying to tease out the molecular changes which drive tumor behavior.”

Pursuing this groundbreaking research alongside her many clinical responsibilities has indeed provided Dr. Ellenson with the career she envisioned all those years ago. “In pathology, we’ve had an understanding of tumors at a more global level,” she said. “But using these techniques, we can understand the evolution of tumors in individual patients will also afford her team the opportunity to translate those granular changes into potential therapeutics.

“Understand each individual’s tumor better—perhaps why the tumor developed in the first place, why one person’s tumor metastasizes and another’s doesn’t, and even why one tumor responds to therapy while another one doesn’t. The more we can understand about what’s going on at the single-cell level—and how the tumor interacts with the host—the more we can utilize that information to treat and potentially prevent endometrial carcinoma. That mission is at the heart of our research.”

...using molecular techniques, we now understand there are actually four molecular classes of endometrioid and serous carcinomas, which comprise the most common types of endometrial cancer, and it has changed the way we think about these diseases."

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**Service Spotlight**

**HEMATOPATHOLOGY SERVICE**

When Ahmet Dogan, MD, PhD, was recruited to launch the Hematopathology Service at Memorial Sloan Kettering Cancer Center (MSK) in 2013, he knew challenges lay ahead. It isn’t easy to create an entirely new service from scratch. But, after a long stint at the Mayo Clinic in a variety of leadership roles, including Medical Director of Immunostains, Chair of the Clinical Proteomics Laboratory and Vice Chair of the Division of Anatomic Pathology, he was more than ready to meet those challenges head on. “We knew, from the beginning, we had to create this service that would meet the clinical mission to support diagnosis and care for cancers of the blood, but we had to do so without disrupting existing services at MSK as we grew,” said Dr. Dogan. “Hematopathology, because of all that it offers, requires a rather unique infrastructure. So gradually bringing in more than a dozen new faculty, as well as many, many technologists into existing structures, space, and IT infrastructure required a delicate balance so we could evolve the way we needed to within the department.”

Seven years later, Dr. Dogan can safely say he and his team have now evolved into one of the strongest pathology service lines at MSK. The Hematopathology Service is considered a world leader in hematology-oncology flow cytometry, molecular testing, protein chemistry, and lymphoma pathology. They clear a volume of nearly 25,000 cases each year and are engaging in groundbreaking research in immuno-oncology, proteomics, and cytogenetics.

“We are lucky to have a relatively young faculty with a mixture of different talents and skillsets that complement one another,” said Dr. Dogan. “We are making sure we have good educators within that mix to train the next generation of pathologists, and also developing a cohort of true physician-scientists who are doing incredible research. When you put it all together, we have a lot of diversity that really sets the Hematopathology Service apart.”

**LEADING THE WAY IN RESEARCH**

As a subspeciality, hematopathology has always been at the forefront of integrating innovative new methods. That work continues with the research currently being conducted by the Hematopathology Service at MSK. Several service members hold positions in the Molecular Diagnostics Service as well, giving them access to the latest molecular techniques. Dr. Dogan said there are many exciting areas of research being heralded by Hematopathology Service members. But two research areas, for him, stand out above the others. The first involves using single cell phenotyping and sequencing to map the tumor cells and the microenvironment in hematological malignancies.

"Immunotherapies can be very effective. Unfortunately, they do not work for all patients,“ he explained. "If we can better understand what is happening in the microenvironment, we could use what we know to better predict who will respond to a particular treatment.”

Researchers in the Hematopathology Service are using next-generation sequencing (NGS) techniques to identify the specific genetic and phenotypic features that may be working to promote the growth of abnormal cells.

“When you know the proteins expressed by a single cell, as well as the mutations present in that cell, it gives you an advantage in providing the right diagnosis,” he said. “With this additional information, you can diagnose and classify each tumor very precisely at the very beginning. When you know that you are dealing with a specific disease, you can help guide the clinician to the most precise and effective therapy.”

The second area of research that Dr. Dogan highlighted involves new ways to detect measurable residual disease (MRD). Unfortunately, many patients with blood cancers will see those cancers return later in their lifetime. Currently, it is quite challenging to predict who will experience a recurrence of leukemia or multiple myeloma, and how quickly they may face it. "When you are talking about hematological cancers, there is always the risk of disease returning,” Dogan said. “But when you can assess MRD, actually detect the cancer cells that may be circulating in the blood, you can detect by different technological methods like flow cytometry and genetic techniques. In that respect, hematopathology has always been at the cutting edge of pathology and has really been at the forefront of the process of integrating innovative new methods.”

**25,000 They clear a volume of nearly 25,000 cases each year and are engaging in groundbreaking research in immunogenetics, proteomics, and cytogenetics.**
can do a better job of understanding who is at risk of their disease coming back. We are working to measure MRD effectively and then integrate it into our overall clinical management for patients.”

Hematopathology service researchers, alongside scientists who specialize in molecular pathology and flow cytometry, are hard at work developing novel assays that can identify residual tumor cells at very low levels in blood or bone marrow—to the tune of one in one million cells.

The hope is that such assays will not only detect MRD but also identify just what kind of cells are present, using single-cell sequencing techniques. Dr. Dogan said MRD is representative of high-risk cells, but some may be more aggressive forms of cancer compared to others. That, again, matters when determining a particular patient’s course of treatment. This information can help clinicians come up with precise, individualized care.

“You can look at these cells and try to see their characteristics. Are they all identical when it comes to disease progression? Or are some more benign?” he said. “This can help determine whether someone who may be in remission needs extra therapy now, before a new tumor develops. It makes a difference in whether we can say this patient is cured or not, and what kinds of treatments are most appropriate. You don’t want to give therapies if they aren’t needed. But you don’t want to miss an opportunity to give a therapy and help a patient before the disease advances either.”

IN PARTNERSHIP FOR PATIENTS

MSK boasts five clinical hematopathology services. Dr. Dogan said the Hematopathology Service feels much like the sixth clinical service because they are so well integrated into the clinical decision-making process for patients.

“We work closely with our colleagues, participating in tumor boards and even doing a lot of research projects in common,” Dr. Dogan said. “We have strong mutual respect and a willingness to work together and that makes all the difference for patients.”

Moving forward, Dr. Dogan believes the Hematopathology Service will continue to grow and evolve, providing valuable analyses and research efforts to fuel innovations in the field of hematopathology cancer care.

“Our service at MSK is one of the biggest in the United States—possibly the world,” said Dr. Dogan. “We are dedicated to moving the field forward to provide the best diagnoses, prognoses and treatment selections we can for our patients. And I think we are fulfilling our role in supporting hematopathology-oncology and MSK’s patients quite successfully.”

“You can look at these cells and try to see their characteristics. Are they all identical when it comes to disease progression? Or are some more benign? This can help determine whether someone who may be in remission needs extra therapy now, before a new tumor develops.”
We are excited to highlight @MSKPathology Faculty & Fellows presentations at @TheUSCAP Annual Meeting #USCAP2021VNI (Virtual ‘N Interactive) @sloan_kettering

Dr. Meera Hameed
#gipath #USCAP2021VNI @MSKPathology
Neuroendocrine Neoplasms of Pancreatobiliary & Gastrointestinal Tract
New Concepts & Controversies in the Diagnosis
Short Course #09: Drs. Olca Basturk @OlcaBasturk & David Klimstra
#bstpath #USCAP2021VNI @MSKPathology
Specialty Conference
Bone & Soft Tissue Pathology “Evening”
My Favorite Mistake and How to Avoid Making It
@MSKPathology

Dr. Tejasa Bate @MSKPathology
Clinical Sequencing of Cell Free DNA from CSF in Brain Tumor Patients
Association for Molecular Pathology Companion Meeting
#amopath #asmpath #USCAP2021VNI @MSKPathology

Dr. Marina Baine @mkbaine
Platform - #cytopath
“Identification of Small Cell Lung Carcinoma Subtypes Defined by ASCLL1, NEUROD1, YAP1 and POU2F3 in Cytology Specimens”

Dr. Anjelica Hodgson @dochodgson
#USCAP2021VNI @MSKPathology Fellows
Cytologic Features of Gynecologic Tract Germ Cell Tumors and Carcinomas
Cytologic Features of Gestational Trophoblastic Neoplasms and Somatic Neoplasms Exhibiting Trophoblastic Differentiation

Dr. Marina Baine @mkbaine
Platform - #cytopath
“Tuft Cell Master Regulator POU2F3 is a Novel Helpful Diagnostic IHC Marker in Neuroendocrine-Less Small Cell Lung Carcinomas”

Dr. Samson Fine @revvinguscap & @DrClaudiaRegg
Short Course #33: Dynamic Evolution in Prostate Cancer Diagnosis & Reporting: What the Pathologist Needs to Know
#gupath #prostatecancer #USCAP2021VNI @MSKPathology

Dr. Ying-Hsia Chu @yhc_uh
The Dr. L. Clarke, Jr. and Elaine F. Needs to Know
Diagnosis & Reporting: What the Pathologist
Dynamic Evolution in Prostate Cancer
Short Course #33: DrCristinaMagi
Dr. Samson Fine @rovingatuscap & @DrClaudiaRegg

Dr. Marina Baine @mkbaine
Platform - #cytopath
Cytologic Features of Gynecologic Tract Germ Cell Tumors and Carcinomas
Cytologic Features of Gestational Trophoblastic Neoplasms and Somatic Neoplasms Exhibiting Trophoblastic Differentiation

Dr. Elena Papaemmanuil @elpapaemmanuilLab (@ @sloan_kettering
Mutational Landscapes in CHOP and Myeloid Diseases such as MDS & AML
Society for Hematopathology Companion Meeting
#hemopath #molecpath #USCAP2021VNI @MSKPathology

Dr. Olca Basturk @OlcaBasturk & David Klimstra
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Pathology at MSK at USCAP 2021

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**Q&A**

**MONIKA KAMALSKA-CYGANIK**

Quality Assurance Manager for the Molecular Diagnostics Service  
By Kayt Sukel

**Q** How did you come to Memorial Sloan Kettering (MSK) Cancer Center?

**A** My adventure with MSK started in 2010 when I was still a student at Hunter College, studying laboratory sciences. I did my professional practice here and thought it would be so nice to come back as an employee someday. When I started job hunting after graduation, I asked the manager I had worked with at MSK for a recommendation letter. She told me that they were looking for someone to be a technologist in the Microbiology Laboratory in the Department of Laboratory Medicine. She thought I'd be perfect for the job. It was serendipity!

**Q** What does the role of Quality Assurance Manager entail?

**A** Simply put, we support quality efforts in the service, but what we do changes and adapts depending on what is happening in the department at a given time. To do the job, you have to find a way to mold yourself to fit. You need a wide array of skills, from problem solving to documentation to even basic programming. In the Molecular Service, we have a large volume of operations. I make sure that we have all our i’s dotted and t’s crossed so we can meet quality regulations and manage any inspections. But my day-to-day role is to troubleshoot any potential quality issues, and to help come up with technology solutions to assist the department with their needs. You have to constantly learn new things, especially as molecular service is always changing. There are always new assays and innovations to consider. With that kind of growth and evolution, we work hard to ensure we have the infrastructure and systems communications to support it—and still provide the highest quality testing for our patients.

**Q** What is your favorite part of your job?

**A** I like the problem-solving aspect of the job. I enjoy thinking on my feet and solving issues. If I’m called in to help figure out an issue, I have the opportunity to open up and educate our staff about new tools, and to help them improve their workflow. Does it add any benefit or is it causing a problem? How can we do things better? I enjoy being able to help streamline our processes to make sure that our testing is the best it can be.

**Q** What is the most surprising aspect of your job?

**A** When I talk to others about quality assurance outside of MSK, especially other laboratory professionals, they think it’s mostly about regulations. But MSK goes the extra mile when it comes to quality. Our quality teams are much more involved in the day-to-day processes. We aren’t there just when there is a problem. We work very proactively, beyond just regulatory concerns, to promote safety, communication and the highest quality testing.
INQUIRIES about the MSK PATHOLOGY REVIEW should be addressed to
Memorial Sloan Kettering Cancer Center Attn: Sarah Virgo
1275 York Avenue
Department of Pathology
H-504
New York, NY 10065
212-639-5696
cooks@mskcc.org
www.mskcc.org/departments/pathology

Twitter & Instagram:
@MSKPathology

2nd Quarter 2021
Research Profile
Darren J. Buonocore, MD
Filiz Sen, MD
Timothy D’Alfonso, MD

Service Spotlight
Head and Neck Pathology

Cover
Mission: Africa

@MSKPathology stands firmly with our Asian colleagues and patients and together with @sloan_kettering in continuing to foster an environment where everyone feels respected and one that is committed to equality, diversity and inclusion.