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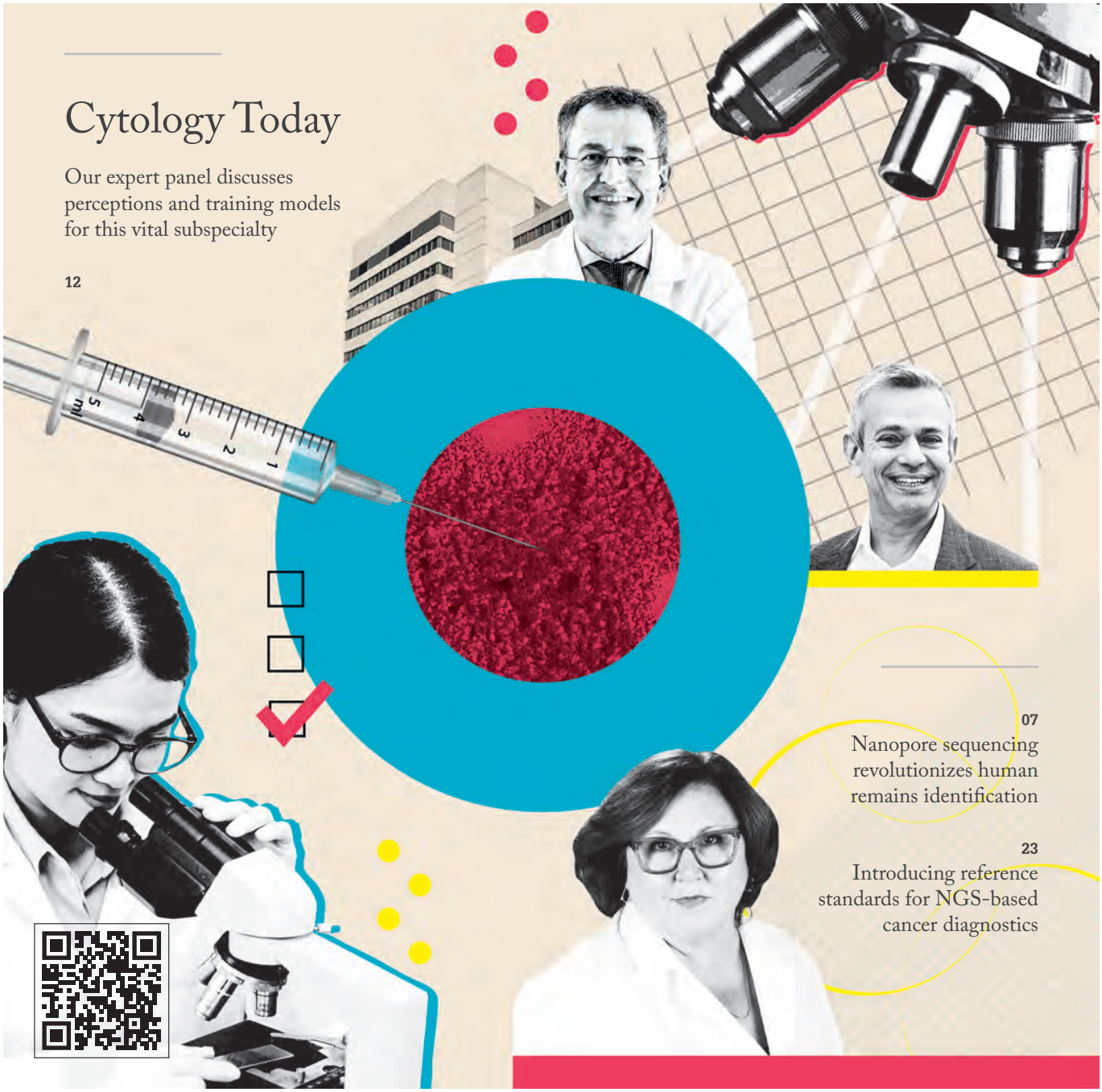

Cytology Today

Our expert panel discusses perceptions and training models for this vital subspecialty

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The Lasting Legacy of SARS-CoV-2

As the list of long-COVID symptoms continues to grow, should we all be taking this disease more seriously?

Four years on from the start of the COVID-19 pandemic, SARS-CoV-2 continues to plague individuals globally. In 2021, researchers identified over 200 symptoms of long COVID (1), with around 65 million people estimated to have the condition (2). Today, the world still faces a lack of access to diagnostics and therapeutics for COVID-19 – especially in low- and middle-income countries. Should we be taking more precautions?

Long COVID is often characterized by extreme fatigue, shortness of breath, and dizziness, but as time progresses, researchers identify more obscure effects in patients. A 2022 study identified secondary osteonecrosis of the knee caused by prolonged effects of COVID-19 infection in some patients (3); but this is arguably related to steroid therapy during hospitalization.

With so many varying symptoms, diagnosis remains challenging. Currently, clinicians take a mixed approach: asking patients about their health history, performing physical examinations, and ordering bloodwork. But another hurdle is a lack of understanding – both from the public and medical professionals – regarding the seriousness and wide-ranging symptoms of long COVID. And if a patient doesn't show a specific abnormality, they may not receive the necessary medical attention and support.

"There's a proportion of people who have difficulty accepting long COVID because the science hasn't caught up with it," says pulmonologist Denyse Lutchmansingh in an article with Yale Medicine (4). And this might seem understandable when we consider the huge variety of symptoms presented.

Should we be investing more in long COVID research? Or should priorities now lie elsewhere? Join the debate: *edit@thepathologist.com*

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See references online

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Bartonella on the Brain?

Bacterial DNA research links psychosis with Bartonella infection

Credit: Image for collage sourced from Adobe Stock and Pixabay

Researchers at North Carolina State University discovered that patients diagnosed with psychosis are three times more likely to have Bartonella DNA in their blood, suggesting that vector-borne pathogens play a role in mental illness (1).

Bartonella, a group of vector-borne bacteria transmitted by arthropods and animals, has at least 45 different known species – 18 of which have been found to infect humans (2). This research journey has been in progress since the early 1990s, shortly after infections with *Bartonella henselae* and *Bartonella quintana* were documented in AIDS patients in the United States (3). Beforehand, there was no knowledge of Bartonella infecting animals or humans in North America.

As technology advances, researchers have developed methods of diagnosing Bartonella in patients with various chronic illnesses, leading groups to question a link between the bacteria and chronic ailments. With this in mind, a team of researchers at North Carolina State University aimed to explore connections between Bartonella DNA and psychosis.

"As a veterinary internist and an infectious disease researcher, I believe that blood-borne infection should be critically examined as a potential cause of diseases for which the etiology (cause) is unclear or unknown," says Edward Breitschwerdt, Professor of Internal Medicine at NC State's College of Veterinary Medicine and corresponding author. "With an increasing number of newly discovered bacteria inducing zoonotic infections in humans, in conjunction with a lack of sensitive diagnostic testing modalities, we have faced an uphill battle in conducting our research."

The 116 participants were split into different groups (control, prodromal, patients with a confirmed psychosis diagnosis, and close relatives of patients diagnosed with psychosis) before donating blood for analysis. Researchers used immunofluorescence assays and droplet digital PCR testing to detect and amplify DNA in the blood samples. Of participants diagnosed with psychosis, 43 percent were found to have Bartonella DNA in their blood, while 14 percent were Bartonella DNA positive in the control group.

"This does not prove Bartonella caused these conditions, but it confirms that a subset of patients with these diagnoses have the bacteria in their blood, and potentially their brain," explains Breitschwerdt. "We hope to continue pursuing studies related to the genus Bartonella and neurological diseases".

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Scaled Down

The essence of surgical pathology, captured in miniature

This 1/12 scale diorama of the frozen section room at UPMC Presbyterian, by Karen Schoedel, features her colleagues Samuel Yousem and Robert Peel at the microscope. The pathologist's assistant preparing the slides is Walter Bugielski. "Sadly, Yousem has since passed away, but his commitment to excellence in diagnosis is an example for us to follow," says Schoedel.

Credit: Karen Schoedel, Professor of Pathology, University of Pittsburgh Department of Pathology, Pennsylvania, USA

Unlocking Blood's Secrets

From blood draws to personalized treatments – liquid biopsy is revolutionizing cancer care

By Jurgi Camblong, Co-founder and CEO of SOPHiA Genetics, Rolle, Switzerland

Determining the right cancer treatment is often a labyrinthian task. Doctors are frequently faced with tough challenges, such as insufficient material, poor tissue quality, or the need for a less invasive method to assess the patient's tumor. The advent of liquid biopsy in the early 2010s introduced a powerful tool to unlock the valuable and potentially life saving data hidden in our blood.

This relatively new test has proven to be a useful tool to complement traditional solid tumor biopsy. Its overall sensitivity ranges from 60 percent to 85 percent (1); specificity and sensitivity vary according to tumor type, patient health, and other clinical factors.

Liquid biopsy also offers hope as an alternative test for patients who are not candidates for solid tissue biopsies. Studies have shown that nearly 30 percent of non-small cell lung cancers and 20 percent of breast cancers are ineligible for molecular profiling through traditional tissue biopsy. For these patients, liquid biopsy could open the door to more data-driven treatments.

And the evidence surrounding the benefits of liquid biopsy continues to grow. Today, there are over 200 clinical trials evaluating the clinical utility of liquid biopsy, and organizations such as the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the American Society of Clinical Oncology provide guidelines including recommendations that support liquid biopsy as an alternative for certain cancers.

From every vial of blood drawn, clinicians, virtually anywhere, can unlock a wealth of genomic insights about their patient's cancer. By detecting tumor DNA shed into the bloodstream, doctors and researchers can identify the specific mutations driving a patient's cancer – information that was previously unattainable without invasive tissue biopsies. This opens up a myriad of possibilities: from faster selection of targeted therapies to monitoring treatment response more efficiently – all with minimal discomfort for the patient.

But to truly realize the full potential of precision medicine, liquid biopsy needs to be accessible to labs and patients everywhere, requiring worldwide collaboration across many constituencies. Today, we are getting closer to this goal. The market for liquid biopsy testing is expanding as more companies develop their own tests. Additionally, some corporations have recognized the power of partnerships and are joining forces with others to optimize, streamline, and increase access to these assays worldwide.

Decentralizing tests will continue to elevate the field of liquid biopsy and make it available to more patients in more areas of the globe. Though tissue biopsy is still the gold standard, we need all involved in cancer care to realize – and demand – that liquid biopsy becomes a routine part of the diagnosis and treatment process.

To make a change, clinicians must advocate for these tests for patients. Researchers must continue to generate the clinical evidence needed to make liquid biopsy part of the standard of care. Policymakers and payers must remove barriers to access and reimbursement. Diagnostic companies must prioritize approaches that democratize capabilities. And patients and families must demand the most advanced cancer testing available.

Together, we can envision a future where every cancer patient has access to powerful precision oncology insights from a simple blood draw. And cutting edge liquid biopsy testing becomes as routine as standard lab tests, securing timely and personalized treatment for all.

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The Future of Forensics

With additional forensic-specific analysis software, nanopore sequencing platforms look set to revolutionize the industry

By Roxanne Zascavage, Assistant Professor, University of North Texas Health Science Center, US

Human remains identification (HRID) is important in both crime scene investigation and live human identification. Methods used to test degraded remains can also be applied to traditional cases involving DNA left by victims and perpetrators. Additionally, HRID is used to identify victims of mass disasters and military operations. To give an idea of the scale of this task, as of December 31, 2022, the US National Crime Information Center reported 8,242 active unidentified persons cases, as well as 546,568 open cases for missing people (1).

In forensic investigation, current pitfalls mostly lie with trying to type damaged or degraded samples. The most common practices for human identification revolve around short tandem repeat sequences, which require intact fragments of nuclear DNA. However, this is often not accessible for human remains, as time and environmental exposure break down DNA. Other methods are available; for example, exploring mitochondrial DNA, but this is not an easy piece of evidence to work with. Many labs aren't equipped to perform mtDNA testing and those that are cannot individualize with DNA of this kind.

I was lucky enough to have the opportunity to work with nanopore sequencing technology when the instrument was first released to a small group of researchers for testing. Given its unique characteristics, I saw its potential to revolutionize the industry. For example, the cost of the instrument is minimal compared with other sequencers, making it accessible to crime labs on a budget. Additionally, nanopore sequencing technology has the potential for in-field use thanks to its small size and weight, which would help in reducing backlogs and turnaround times. Some instruments also have limitless data generation, enabling simultaneous assessment of multiple targets. And that means we can make the most of our samples by performing various analyses, traditional short tandem repeat typing alongside single nucleotide polymorphisms, mtDNA, or epigenetic analysis, even when traditional methods yield unreliable results.

The gold standard in forensic analysis would be capillary electrophoresis (CE) and perhaps mtDNA sequencing, but I'm working to develop a more streamlined process that doesn't rely on clunky traditional methods. With my team at the University of North Texas Health Science Center, I use nanopore sequencing technology for both whole genome and targeted analysis (post-PCR using standard commercially available forensic kits) (2).

We also designed RNA baits to target regions of interest – something that is new, but has resulted in increased enrichment of our target regions. Our results have shown improved discriminatory power from traditional methods because we are able to resolve isoalleles (alleles with the same length-based designation, but different sequence) that are indistinguishable through CE.

Moving forward, my team aims to expand upon our work with nanopore sequencing technology in forensics – working on a specific assessment of methylation for age estimation and body fluid identification. After working in this area for so many years, I still believe in building the capabilities of nanopore sequencing technology and its potential in forensics. As this area progresses, I hope to see less of the same instruments in labs. Instead, with different specialized options available, labs will be able to select instruments that best fit their needs to ensure proper validations and cross-platform comparisons.

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Olympians in the Laboratory

Early career laboratory medicine professionals must nurture the drive to excel to achieve success

By E. Blair Holladay

Summer is always a special time of year for the laboratory, as recent graduates and pathology residents join our teams and start their careers in the laboratory. This summer brings with it extra flair in the form of the Olympics, with world-class athletes from around the globe gathering in Paris, France, to compete. Though these athletes, who have trained for years to hone their sporting skills, have only a few weeks to show the world what they can accomplish, new-in-practice laboratory professionals and pathologists, and pathology residents are at the precipice of a lifelong career of creating change in pursuit of high-quality patient care.

As pathologists and medical laboratory scientists, we parallel many of the same qualities needed to succeed – and honing those skills starts from day one. What you might find in the heart of an athlete is not dissimilar to what you will find in the heart of a pathologist or laboratory professional who is equally dedicated to their craft.

Olympic athletes have an unyielding desire to excel and to push the boundaries of what is possible. They refuse to settle for mediocrity. So, too, do leaders in the laboratory. In the context of patient care, the drive to excel is paramount. We begin building our commitment to patient care from the first test we run and the first diagnosis we provide. We are just as committed to achieving the highest standards of quality, accuracy, innovation, and always seek ways to improve. Central to our training – whether at the beginning, middle, or end of our careers – is the understanding that the accuracy and reliability of our work can mean the difference between life and death. Just as an Olympian's drive to excel pushes them to break records and achieve new heights, a laboratory leader's drive ensures the highest level of performance in their laboratory. We don't do it for fame and recognition; we relentlessly pursue excellence because we understand that on the other end of the test is a patient whose life may depend on how well we do our job.

When we are at the beginning of our careers, the need and amount of learning that must be done can seem overwhelming. Unlike an Olympic athlete, whose goal may end at the gold, silver, or bronze medal, there is no end point of learning. Rather, the process of learning is what we adapt to throughout our careers, knowing that it is relentless and challenging work to stay abreast of evolving technologies, new and stringent regulations, and the constant vigilance of maintaining quality. Like an Olympic athlete, however, the process of learning allows us to improve, embrace new techniques and methods; moreover, our willingness to learn, ideate, and innovate is critical to our success.

> *"We relentlessly pursue excellence because we understand that on the other end of the test is a patient."*

For those starting their careers, know that you are an Olympian of the laboratory. Your skills and abilities are what make your role unique and imperative within patient care. Allowing your desire to excel flourish and keeping yourself open to learning and adaptable to change will create an unstoppable, winning career in the laboratory.

This summer is the start of so much and will be an inspiration for so many. Let your dedication, your achievements, and your willingness to learn shine as a role model of excellence and unwavering commitment to patient care.

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Optimizing Biomarker Testing For Solid Tumors

Oncology networks have the power to improve oncology outcomes

By Aleš Ryška, Chair, Department of Pathology, Charles University Medical Faculty, Hradec Králové, Czech Republic; immediate past president of the European Society of Pathology

Janssen Pharmaceutica NV, a Johnson & Johnson company, has funded the development and publication of this article, including a consultancy fee for Professor Aleš Ryška. The views expressed in the article are those of the authors and publisher, and do not necessarily reflect the views of Janssen Pharmaceutica NV and/or Johnson & Johnson. CP-465155 August 2024

Today's cancer diagnosis is based not only on tumor origin and stage but also on its molecular profile (1). Comprehensive biomarker testing, as part of the initial diagnostic process, can help ensure optimal systemic treatment selection and identify those patients who are most likely to respond to specific targeted therapies – but only if we work collaboratively (2). Multidisciplinary information flows within regional oncology networks hold the key to early diagnosis and optimal treatment selection for patients.

The current landscape of biomarker testing

In adult solid tumors, the greatest advancements in biomarker testing have been made in lung cancer. The rapid progress was driven largely by the discovery of novel treatments, such as kinase inhibitors, that have now been on the market for more than 15 years (3, 4). This led to a huge investment in biomarker research in order to match the right patients to each new therapy.

Another factor was the great number of genomic alterations in lung cancer – each of them presenting in a very small subset of the patient population. Whilst EGFR and KRAS G12C mutations are relatively common, other mutations constitute a very small population, which, combined, appear in around one third of all NSCLC tumors (5–9). It was important to look for those "needles in a haystack" via biomarker research in order to effectively treat as many patients as possible.

The good news is that progress in molecular profiling is also now being made in colorectal, ovarian, endometrial, urothelial, and gastric cancers, as well as in melanoma – a significant proportion of the landscape of solid oncology (1). However, investing in biomarker testing makes sense only if a corresponding treatment is available. In some countries, where the availability of new targeted treatments is quite limited, it follows that molecular profiling is also limited (10, 11).

Yet, even where targeted therapies are available, there is an urgent need for improved utilization of biomarker testing, particularly in bladder and prostate cancers, to help patients receive tailored therapy options earlier in their treatment journey.

Barriers to optimal use of biomarker testing

In genitourinary cancers, biomarker testing is far less established than in lung cancer, therefore education and awareness among pathologists and oncologists is less advanced (12). However, labs that are already fully equipped for biomarker testing in lung cancer will be well placed to introduce similar testing for those other cancer types.

"There is an urgent need for improved utilization of biomarker testing, particularly in bladder and prostate cancers."

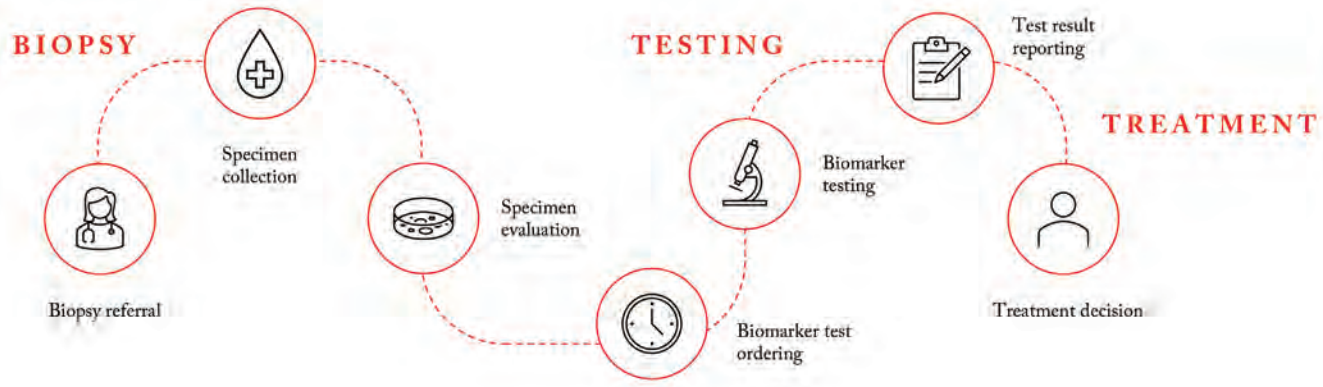
Of course, for any lab introducing a new testing capability, the first major hurdle is funding. Where this is not available internally, alternative means such as sponsorship or financing through research projects are sought (11). Sadly, such sources are neither reliable nor sustainable (11).

Another barrier is the size of the lab and the volume of work. In-house next-generation sequencing isn't economically viable for every single small (low-throughput) pathology department (13). For this reason, in certain cases it makes sense to establish more centralized testing centers – or centers of excellence – for molecular testing.

In the Czech Republic, among our seventy or so pathology departments, around fourteen of them provide molecular testing. When lung cancer is diagnosed in one of the small labs, the specimen will be sent reflexively to one of the centralized testing labs. Immediately, this reduces patient leakage from the precision pathway due to lack of referrals. Results are returned to the source efficiently and, if positive for targetable mutation, we advise the local oncologist to send the patient to the Comprehensive Cancer Center to access the appropriate treatment.

However, for such centralized services to succeed, well-designed logistics are essential to ensure fast turnaround times.

The Oncology Precision Medicine Pathway



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Smooth-running programs require careful organization and, ideally, involvement of the national pathology society, healthcare payers, and patient organizations.

The connected approach

The official opinion of the European Society of Pathology is that the genomic testing of cancer for somatic molecular alterations should be performed by pathologists (14). This is because pathologists have full oversight of the whole testing process – from the pre-analytic and analytic phases, through interpretation of the data, to reporting. The society also advocates for pathologists participating in (or even leading) multidisciplinary teams to ensure patients are referred to the right specialists earlier in their treatment pathway, have the right tests conducted, and have access to the latest targeted treatments.

Molecular tumor boards are also crucial for correct interpretation of the data from genetic sequencing. Led by pathologists, our molecular tumor board at Charles University Medical Faculty connects oncologists from our own Comprehensive Cancer Center with those from local hospitals in the region. We discuss their patients and advise on which cases to refer to our center for targeted treatment. This prevents the leakage of patients with actionable mutations from appropriate and timely treatment pathways.

Education is key

In establishing our cancer networks in the Czech Republic, we took time to educate the local pathologists on accessing comprehensive care for their patients. We set out a clear process for ordering testing from the central testing labs, and found the system was adopted very quickly as a result.

In close collaboration with our national oncology society, we have also established a program of education for oncologists on treatment advances and the benefits of precision oncology, to maximize the uptake. For us, it was essential to establish this network of collaboration with regional oncology.

Picking up on the importance of digital learning, the European Society of Pathology offers several virtual preceptorships, which are online educational programs for specific cancers (15). Every society member has access to this fantastic, accredited platform at their fingertips.

The evidence base

We live in the world of evidence-based medicine. Diagnosis of rare cancers such as angiosarcoma, where the evidence base is lacking, can be very challenging (16). Additionally, monitoring the quality of biomarker testing in individual laboratories may be difficult. I strongly believe in the value of national oncology registries to fill this void.

For example, in the Czech Republic we have had a breast cancer registry for more than 10 years that monitored biomarker testing – primarily HER2, but other biomarkers, such as Ki67, ER and PR were also recorded (17). This allowed us to compare diagnostic performance across the fourteen central testing laboratories and provided objective feedback. Similarly, our non-small cell lung cancer (NSCLC) registry collects data on molecular testing methods, specific mutations detected, and turnaround times in all newly diagnosed cases of NSCLC (18). Again, this provides crucial data: from turnaround time and performance of individual labs, to comparison of test method sensitivities and technology purchasing decisions.

The ideal world

The optimal model for cancer diagnostics, in my opinion, incorporates a well-established network of laboratories, including smaller local departments providing the specimens, centralized

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regional testing centers, multidisciplinary teams collaborating on interpretation of results, and molecular tumor boards advising on cases across the network.

In an ideal world, this all works together efficiently to deliver the right diagnosis to each patient in clinically sufficient time, with no delays. In my dream, molecular test results are reliable and clinically significant, with all costs covered by healthcare insurance or systemic funding.

With this vision in mind, my call to action to the medical community is twofold: continued education on biomarker testing and its importance, and greater involvement of the pathologist in clinical decision making. Only if the clinicians have all the information on grading, staging, and molecular testing of an individual patient, are they in a position to make a qualified decision about that patient's cancer treatment. In this respect, the pathologist is now the keystone of the oncology decision making process.

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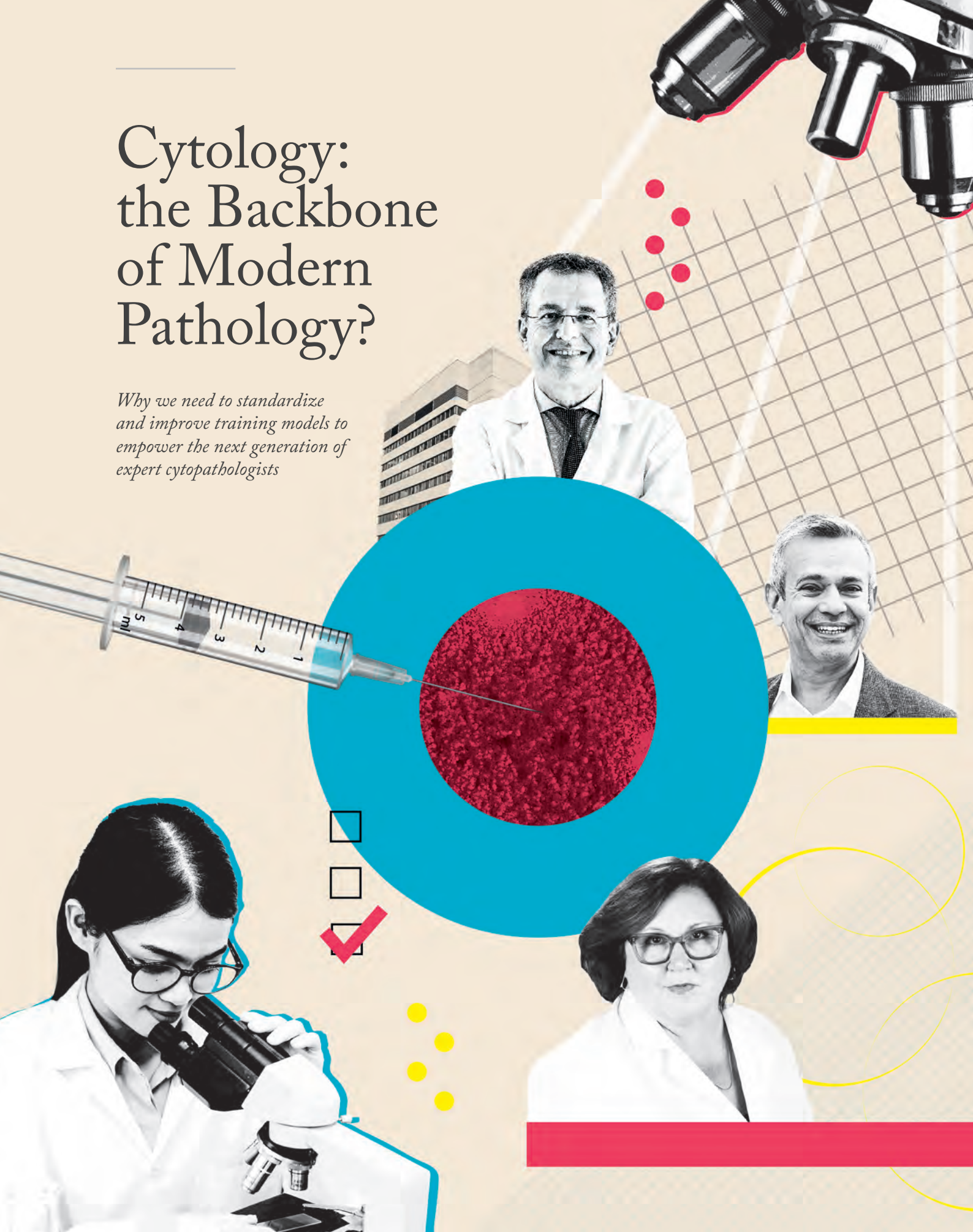
Cytology: the Backbone of Modern Pathology?

Why we need to standardize and improve training models to empower the next generation of expert cytopathologists



Are cytopathologists a dying breed – soon to be extinct? Is cytology a disregarded specialty, pushed to the bottom of the training checklist? These experts think not.

In this round table, hosted by The Pathologist, three renowned cytopathologists challenge the view that cytology is an endangered specialty. Our expert panel discussed perceptions of cytology, training models in the US, UK, and Europe, how to maintain and improve competency in these regions, and why it will be vital to patient outcomes to do so.

How would you describe the status of cytology within the modern pathology lab?

Fernando Schmitt: I think that cytology is the backbone of the modern pathology department in three different areas: screening, diagnosis, and, especially, for establishing prognosis and predictive markers. The specialty has received a great boost in the last few years thanks to advances in lung cancer diagnosis that now use, for 50 percent of cases, the cytology materials for molecular tests. And this is now expanding from blood to other liquids, such as effusions, urine, and cerebrospinal fluid.

In the past, cytology has perhaps been considered as a second division, providing a preliminary diagnostic service. But now, if you consider that surgical pathology has progressed recently due to the use of biomarker testing to select the best treatment for patients – well, cytology is the same. This has served to elevate the role of cytology to equal that of surgical pathology in the modern pathology department.

Ashish Chandra: I absolutely agree with that perception. I also think it's important for cytopathologists to establish its position as an important subspecialty within the department and the institution. There should be a clear organizational structure within the subspecialty with a lead and a named team of consultants. We should ensure the visibility of the cytology services in the institution. This goal can be achieved in a number of ways. As Fernando was saying, we should advertise the clear benefits to our users and clinicians, both in the institution and beyond. For instance, fine needle aspiration cytology may be a more suitable alternative to core biopsy and should be easily available. Ancillary tests are available on cytology samples as easy alternatives to those being performed on core biopsy or other types of histology specimens.

Saying that, we could also contribute to the popularity and the visibility of cytology via grand rounds and educational activities. There are many ways in which a modern pathology department can stand out with all its subspecialties – but we need to make space for each of them, including cytology.

Eva Wojcik: I'm in complete agreement with both Fernando and Ashish. However, I would expand on this – I would even say that cytology, in many instances, is superior to surgical pathology.

Currently, with all the developments in imaging techniques, smaller and smaller lesions are being detected. From those lesions, we can practically obtain the best sample by using cytological techniques like fine needle aspiration. In my department, cytology is the main service for dealing with all the newly developed lesions in lung cancer. That's because – as Fernando mentioned – during this procedure, we not only make the diagnosis of the presence of malignancy, we make the diagnosis of the specific type of malignancy.

What's more, we also stage the patients. We use those fine needle aspirations for sampling of the lymph nodes. So we already understand the extent of the disease, and, most importantly, we collect the material for molecular studies, which are critical in lung cancer. So, with one relatively simple procedure, cytopathologists are answering all the diagnostic questions.

In many instances, those patients – based on cytology results – are treated with appropriate chemoimmunotherapy, and potentially resections; in other words, we are the first line of diagnosis as well as prognosis. With the expansion of our knowledge and experience, and development of new molecular testing, this service will expand to practically every organ and every type of specimen.

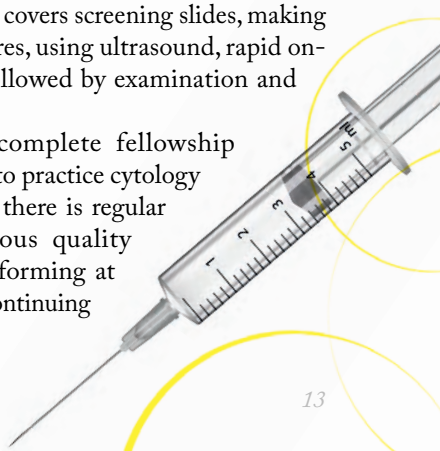
So, the role of cytology has never been so crucial. We are truly becoming one of the most important specialties in pathology.

What are the current training models for cytopathologists in your regions?

EW: For us to provide this vital service, we have to be well trained. One of the reasons that cytology is underestimated is that many pathologists don't feel comfortable dealing with this type of specimen. The problem isn't cytology – it's that people without sufficient training and competence are trying to perform cytology. And, therefore, the answer is proper training and gaining sufficient expertise.

In the US, we are fortunate – cytology training is very well established. Cytology is recognized as a subspecialty in the residency programs here, which usually takes the form of two or three months of dedicated training. However, I would say that the majority of pathologists who are practicing cytology in the US are fellowship trained, which involves one year of dedicated cytology training that covers screening slides, making diagnoses, performing procedures, using ultrasound, rapid on-site examination, and so on, followed by examination and board certification.

As a result, people who complete fellowship training are very well equipped to practice cytology independently. On top of this, there is regular proficiency testing and various quality measures to ensure we are performing at the appropriate level, as well as continuing professional development.



Meet the panelists

Eva M. Wojcik is Chair of the Department of Pathology and Helen M. and Raymond M. Galvin Professor of Pathology at Loyola University Stritch School of Medicine in Maywood, Illinois, USA

Fernando Schmitt is Professor of Pathology Medical Faculty of University Porto, Portugal, Coordinator of RISE (Health Research Network), and President of the International Academy of Cytology (IAC)

Ashish Chandra is Lead consultant for Urological Histopathology and Cytopathology at Guy's and St Thomas' NHS Foundation Trust, UK, Vice President of the IAC, and a member of the Specialist Advisory Committee of the Royal College of Pathology

AC: Back in the days when I trained, in the UK, there was a year-long training program in cytology, culminating in an exam, which awarded a diploma. Sadly, a few years after I achieved my diploma, the exam was discontinued, mainly due to a lack of applicants. This was a bit of a blow to cytology as a subspecialty and, ever since, we have been playing catch up. We've had to look at how we can draw people into the specialty early enough in their careers and how we can provide opportunities for fellowships or for dedicated training time to develop their interest in cytology. That is still work in progress in the UK.

At present, cytology forms just one unit of a five-year integrated cellular pathology training program. But the training does define the minimum number of cytology cases that the trainee must see per year. For example, in the first year, the trainee might be required to assess 150 cervical cytology samples and 150 non-cervical samples. These might be new cases or self-assessment-type teaching cases, with appropriate, structured feedback from a trainer. The number of required cases increases each year; however, by the third year, the trainees have the option to drop cervical cytology cases because the demand for these has dropped since HPV primary cervical screening was adopted.

As trainees progress, they may be expected to report 300 non-cervical cytology cases per year. By year four, they might be able to report cases independently. In short, the level of exposure and responsibility increases over the course of the program.

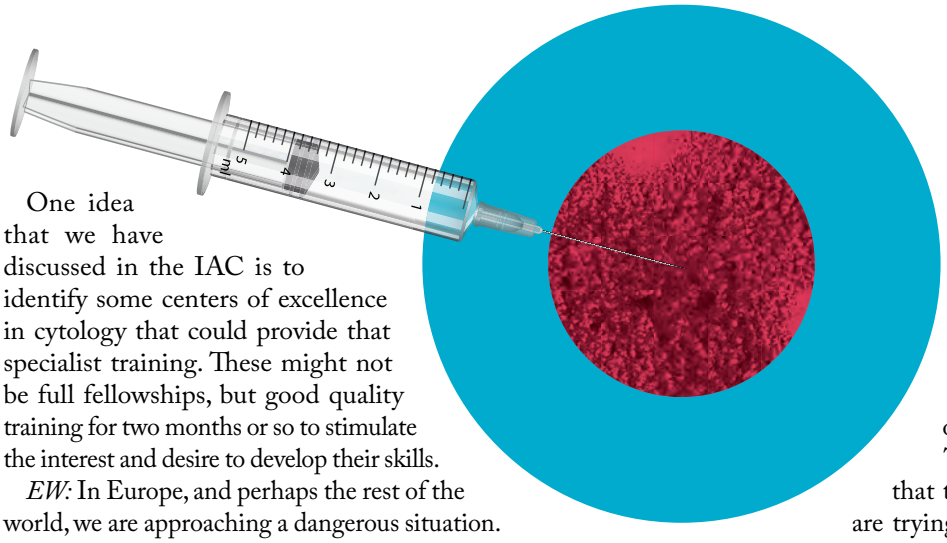
The reality is that trainees will only spend a few weeks of the year on their cytology training, and this training is region dependent in terms of the scope of the cytology service and supervisor resources.

Clearly, there is work to be done to try to meet the high standards we would like to see for cytology training in the UK.

FS: In Europe, cytology training is extremely heterogeneous, both between the countries and inside the countries. For example, in some countries, during five years of pathology residency, some residents spend only one month in cytology. In other countries, it might be a few months, or a specified number of cases, like in the UK, but it is highly dependent on the place.

You can see there is an imbalance there. In my first comment, I talked about the rising importance of cytology, but in Europe we are seeing less and less training to support the need.

Another problem is that there are not enough senior people who are adequately trained in cytology in Europe who can train or mentor the less experienced pathologists. The pool is shrinking. I find this very curious, because when pathology leaders are planning resources, we see the gaps and we know we must recruit more young people into cytology. But we can't find enough young people, which is a consequence of this inadequate training.



One idea that we have discussed in the IAC is to identify some centers of excellence in cytology that could provide that specialist training. These might not be full fellowships, but good quality training for two months or so to stimulate the interest and desire to develop their skills.

EW: In Europe, and perhaps the rest of the world, we are approaching a dangerous situation. As we said at the beginning of this discussion, the role of cytology is becoming increasingly important to patient care. Having samples analyzed by appropriately trained cytopathologists is best for patients. Yet, we are approaching a situation where, as a profession, we won't be able to provide this crucial service. As Fernando said, if we don't have teachers and role models, no-one will follow. We became cytopathologists because we were fortunate enough to meet some amazing role models who inspired us.

But I also want to say that I truly believe that no-one can become a great cytopathologist if they are not also a great surgical pathologist. I heard that there are certain countries that train cytopathologists completely separately from surgical pathologists. I don't agree with that approach. I think it's even more dangerous than the model described by Ashish and Fernando.

FS: I completely agree. The readers will appreciate that the history of cytology starts with non-pathologists. Many years ago it was regarded as completely separate from the rest of pathology.

Here's a story that illustrates the problem. The President of a country had a nodule in the thyroid. The nodule was aspirated and presented to the country's most revered surgical pathologist who, unfortunately, had never studied cytology. Nevertheless, trusting his skills, he diagnosed cancer. Based on this, the nodule was removed – however, it was discovered to be benign. Subsequently, when the slides were shown to cytopathologists, they diagnosed follicular benign nodules. The President could have been spared from unnecessary surgery had the correct experts been consulted.

Cytopathologists should have dedicated, specialist training, built on to a foundation of surgical pathology knowledge.

What needs to be put into place to standardize and improve cytology training models?

FS: The American model appears to work well. Cytology training needs to start in the pathology residency and continue with a dedicated fellowship led by excellent cytopathologists in a recognized center of excellence. Further, it must include all the latest techniques and technologies.

EW: What Fernando describes is certainly the ideal, but the starting point is currently quite low. I also find it surprising that pathologists in Europe can practice in different countries, where competency standards might be completely different to their own, without additional training.

To address this problem, I'm aware that the IAC, as well as European societies, are trying to standardize training curricula and requirements across countries, while exposing early-career pathologists to cytology. The IAC also sets exams for its cytology fellowships, which ideally should set the standards for competency everywhere.

FS: The current reality exposes the gap between regulatory bodies and the practices. I agree that, ideally, the regulatory bodies should require standardized exam certification to practice across regions such as Europe. You might gain a European diploma, for example.

At present, we have the United Medical Education Consortium (UMEC) Medical Society (UMS) in Europe, which covers all medical specialities. They have the goal of standardizing medical practice in Europe, but it is a very slow and political process. It seems they have a great many meetings with very little consensus and few decisions. Many years later, we are still waiting for them to issue the Europe-wide examination they promised.

In the US, the regulatory bodies do require certification by examination to practice. We recognize that examinations aren't everything, of course – but at least it's something.

AC: In the UK, the Royal College of Pathology created a syllabus for histopathology higher speciality training, which recommends the minimum number of cytology cases that post-graduate trainees should see, in each year of training, to achieve competence. This provides the opportunity for uniformity in competencies across the UK. It also sets out the training expectations for a department to be recognized as a specialist center for cytology.

However, this is a self-surveillance program, and we have no way of monitoring uptake or measuring the results. So, whilst regulatory bodies can lay out the ground rules, they are not in a position to make them mandatory.

In many cases, trainees, having not received the recommended training for the specialty, find themselves doing "crash courses" in cytology before an impending exam. It's like trying to learn a new language just before a holiday!

The exam itself includes just eight cytology cases. Hence, many candidates might prepare by focusing on the eight most likely case types, and then consider themselves competent if they pass the exam.

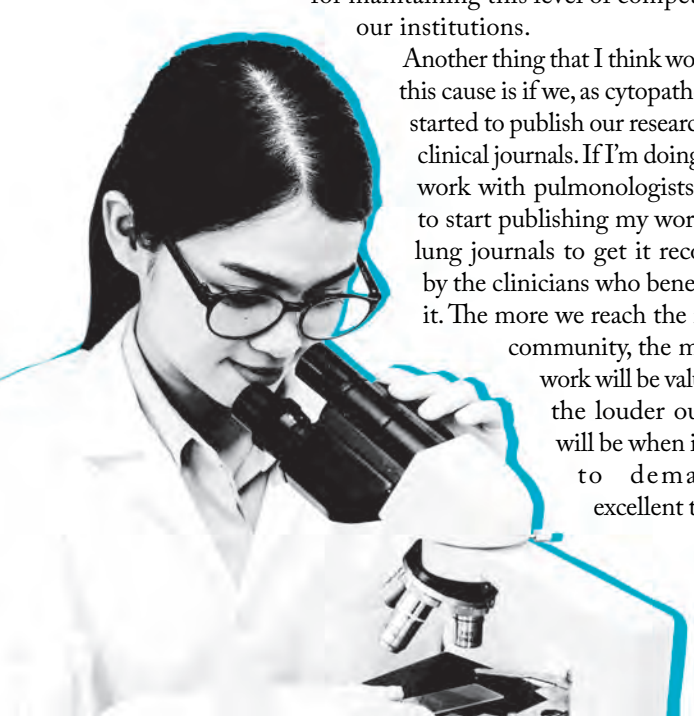
However, for those trainees who are committed to dedicated training, recognized departments like mine will offer a period of observership, as long as the visiting trainee's institution is prepared to fund it.

EW: It's interesting that we, as cytopathologists, are trying to solve this training problem ourselves. Perhaps we should be asking our clinical colleagues to support us. The recognition of cytology as an essential service for patients and the requirement for competent people within the institution to provide that service, could be very powerful. Radiologists, pulmonologists, gastroenterologists – they all need us! They need us to interpret the results of the tests they have ordered and specimens obtained during procedures they performed. Without competent cytopathologists, their efforts will be in vain.

AC: Eva is absolutely right. At my institution, we established our endobronchial ultrasound (EBUS) and pancreaticobiliary cytology (EUS) services on the request of the physicians who needed them. They sought the training to be able to take the samples, but are reliant on the pathologists to read them. It was challenging to get off the ground, but it was exciting, and has drawn more pathologists and cytotechnologists into cytology.

These services are greatly valued in the hospital. We need these drivers to set things in motion, so that we can build on our successes – and then the sky's the limit.

FS: I think Eva and Ashish can both testify to something that perhaps looks very simple from the outside: urine cytology. But when the urologists realize the value of urine cytology in terms of its diagnostic powers, they also start to value cytopathologists, asking for us by name to analyze their patients' samples. In these situations, the other specialists do realize the importance of having well trained cytopathologists in place to look at their cases. We need to encourage them to keep advocating for maintaining this level of competence in our institutions.



Another thing that I think would help this cause is if we, as cytopathologists, started to publish our research in the clinical journals. If I'm doing a lot of work with pulmonologists, I need to start publishing my work in the lung journals to get it recognized by the clinicians who benefit from it. The more we reach the medical community, the more our work will be valued, and the louder our voice will be when it comes to demanding excellent training.

Who should be accrediting the training models?

FS: This brings us back to the problem I mentioned before. We have regulatory bodies and scientific societies, and they serve very different purposes. IAC is a scientific society. It can put a seal of approval against a training course, but it can't make it mandatory for accreditation.

Each country in Europe creates its own exams, but there is really no need for this when the IAC can provide good quality, standardized examinations to ensure competency standards worldwide.

The ideal situation is that the regulatory body in each country mandates the IAC exams, for example, as proof of competency to practice cytology in that country. This is actually the situation in Japan for cytotechnologists. For other countries, we have a long way to go. There is some political work to do to convince the local regulatory bodies to accept international standards.

How might the establishment of cytology centers of excellence help improve standards?

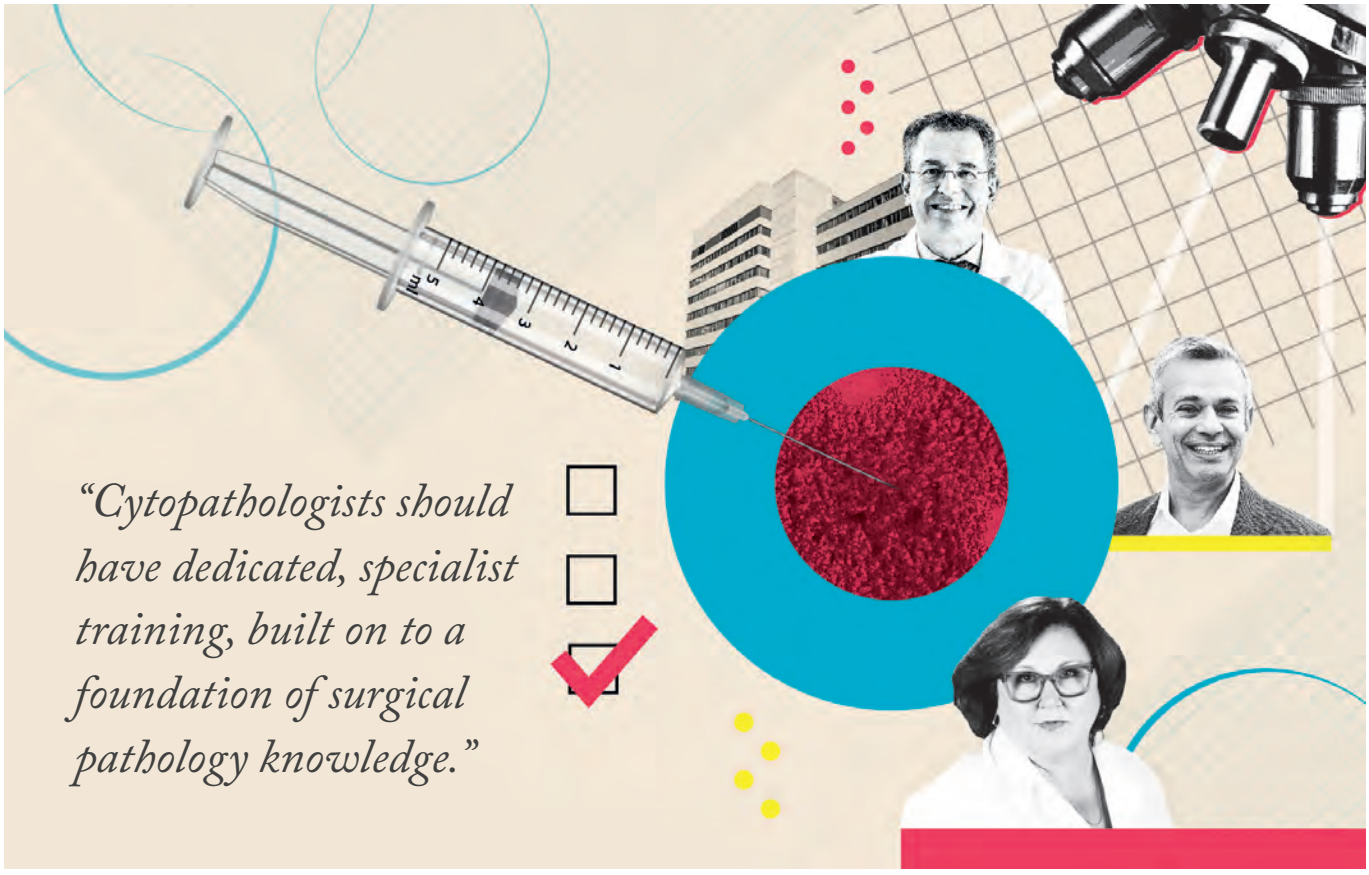
AC: As Fernando explained, the IAC cannot directly influence what happens at an institutional or national level. What we try to do is identify leaders in different countries who either have the potential to host, or are already hosting, high standard cytology fellowships. We look for people who have policies in place in their departments to be able to offer training to people in their own countries and, ideally, from other countries whether in the form of observerships, fellowships, or mentorship.

For example, in my institution, we can accept observers free of charge for a stipulated period of time. Participants don't receive a certificate, but we can write a reference-type letter to confirm their participation and level of interest.

The IAC's role in this is to identify the centers and individuals who can offer these opportunities, and to publish a register so that interested individuals can approach them; however, it is unable to govern the process.

EW: I think centers of excellence is a great idea, overall, for recognizing those institutions that are strong in cytology. One benefit is exposure of young pathologists to cytology, so they can see all the things cytopathologists can do, and even help them meet potential mentors.

Regarding observerships, we have always offered those in our department. Some trainees might spend up to a month with us, and even have a chance to do a preliminary review of some cases. However, recently it has become much more difficult to offer these opportunities. Everything was put on hold during the COVID-19 pandemic, and our official policy still states that we cannot accept observers in our labs. This is mostly due to safety and liability reasons. There are also patient confidentiality restrictions – observers cannot have any access to patient medical



records. This also affects their ability to contribute to research projects. Then we have to consider cyber security and IT access. And so, though we are all willing to share our experience with the younger generation, we are battling against so many restrictions to do so.

And that is why the development of those robust and regulated training programs is so important.

The good news is that there are opportunities for international fellowships, for those individuals who can secure funding. Virtual fellowships are also available for those who cannot travel. The technology we need to deliver these programs is already in place, and there is a wealth of material available online. But, in my opinion, nothing beats that hands-on experience of being in the EBUS lab and making important clinical decisions about whether a patient needs a procedure or not, for example.

Any closing message for our readers?

FS: Thank you for the opportunity to share our ideas. I think this activity is very important for cytology. Many cytopathologists see The Pathologist and maybe our discussion will inspire some thoughts and ideas for them.

And let's all take some responsibility for cytology training. We can offer webinars and tutorials, for example. We had a fantastic experience earlier this year when we organized a virtual tutorial which reached two or three hundred people in Africa – free of charge. Technology opens up huge potential for offering training all round the world.

Finally, cytology will not disappear, cytopathologists will not be replaced by machines, so we need to focus on training to ensure an adequate number of well qualified and trusted experts.

EW: I just want to emphasize that cytology is the best possible specialty to get into. I am so grateful for the opportunities I've been afforded to specialize in this area.

We are medical doctors, and that's what this specialty reminds us every day. That's because, rather than staying behind a microscope, we are working at the patient's bedside, performing procedures, examining those patients, and talking to them. This gives us the perfect opportunity to show that we are physicians – and a truly integral part of the medical team. These days, no medical team can exist without us.

Cytology is not yet at its peak, but it is entering a golden era. We hope that there will be many more followers who will choose this amazing specialty.

SPONSORED FEATURE

Advancements in Liquid Biopsy Next-Generation Sequencing for Precision Oncology

Applications, challenges, and future directions of molecular testing for identifying targetable genetic alterations

By Gary Pestano, PhD, Chief Development Officer, Biodesix

Liquid biopsy next-generation sequencing (NGS) holds great promise in therapy selection for oncology, offering non-invasive and real-time insights into tumor genetics. While challenges remain, ongoing research and technological advancements are likely to significantly enhance the clinical utility and accessibility of liquid biopsy NGS, ultimately contributing to improved patient outcomes in cancer care.

The liquid biopsy landscape

Liquid biopsy testing can be used in the diagnosis of any cancer that secretes nucleic acid into the blood – both solid tumors and hematological cancers.

Saying that, it's important to remember that solid tumors, in particular, are very heterogenous and shedding rates vary greatly between different tumor types. Additionally, early-stage cancers do not shed to the same extent as late-stage tumors, meaning liquid biopsy, for reasons of sensitivity, is not always as effective in early-stage disease detection.

In the health care setting, clinical testing labs offer tests for guideline-approved biomarkers. Lung cancer has the largest array of actionable mutations, according to current knowledge, and therefore makes up the largest proportion of tests run.

In the clinical trial sector, however, biopharma investigates a much larger array of exploratory biomarkers using liquid biopsy testing. This includes PK–PD studies and other investigations beyond efficacy and therapy selection.

Late-stage disease applications

In late-stage cancer management, the main applications for liquid biopsy are in diagnostics and therapeutic monitoring. For both these applications, liquid biopsy is complementary to traditional tissue testing. Current guidelines require that negative liquid biopsies are always reflexed to a tissue-based assay for confirmation. That is because false negatives are more likely when interrogating circulating tumor DNA than when testing the tumor tissue directly. However, a positive liquid biopsy result can be acted on, and several tests are validated and approved for this use.

Early-stage disease applications

Liquid biopsy offers enormous potential in assessing molecular minimal residual disease, in both solid and liquid cancers, via analysis of circulating free DNA. There are several technologies already available in this space that may find utility in monitoring in the early-stage. Whilst initially focused on metastatic disease, these technologies are now being developed for the early-stage disease setting.

The challenge with the technologies in use today in late-stage is that sensitivity really needs to be optimized for assays in this space. Currently, a negative liquid biopsy in an early-stage cancer patient does not mean there is no cancer; it means more investigation is required as the tumor DNA may not be in circulation or at very low levels. It's also important to acknowledge that a false positive result can be devastating for the patient at the end of it.

The answer might be to develop liquid biopsies with a tumor-specificity in mind, for which we need more clinical evidence as well as technology research investments, and a reassessment of specimen collection and nucleic acid recovery methods in order to boost levels of ctDNA available for analysis.

Additionally, the reimbursement system also needs to catch up with the technology. If labs are not reimbursed to carry out early-stage disease testing, patients are going to miss out on that opportunity.

Advantages, limitations, and challenges

Tissue sections are a very scant resource, from which establishing the diagnosis is the first priority for pathologists, followed by molecular testing to establish genomic subtyping of a tumor. This is where the liquid biopsy is valuable – as often there is not enough tissue in a sample to support secondary testing. Overall, the benefit of the complementary tissue–liquid testing model is that of getting the patient on therapy sooner than with tissue biopsies alone, which, as oncology studies have proven, improves outcomes.

If this is the case, why don't we just adopt a model of concurrent liquid and tissue biopsies for every patient? Well, the testing technologies and practice behaviors are not yet well aligned enough to support this, with

tissue testing being largely based on immunohistochemistry, and liquid biopsies on molecular sequencing. Combining the techniques gives rise to a higher likelihood of confounding results than with single testing methods, which would introduce inefficiencies in the diagnostic process via retesting.

Liquid biopsy tests are relatively new to clinical diagnostics, and there is still a way to go to iron out the challenges. The way to address discordance between tissue and liquid test results for example, is through a good understanding of the cancer type being tested, as well as the technology types being used. With trust in the validation process of the assay, it becomes an investigative process to resolve the issue.

Establishing reliability and reproducibility of a liquid biopsy assay begins with establishing its goals. The next step is to set up verification and validation studies based on approved guidelines – of which plenty are now available from our learned organizations.

Then there are cost-effectiveness considerations. In the US, the reimbursement codes we use for our genomic tests are subject to regular revision, meaning the unit cost of tests is beyond our control. Pathologists, then, need to focus on the cost-effectives elements that are controllable, such as optimizing batch sizes or negotiating regional bulk discounts with technology suppliers.

Liquid biopsy techniques: rapid NGS versus digital PCR

Both technologies have their place in the liquid biopsy testing space.

Polymerase chain reaction (PCR)-based methods, being less expensive than NGS, are therefore far more accessible to many labs, but they can only provide limited variant information. Because of the lower cost and ease of use of PCR, it is most likely to be used for disease monitoring.

While NGS has relatively higher cost and complexity, it provides comprehensive biomarker information across hundreds of genes and is more likely to be used for baseline and landmark molecular tumor assessments and therapy guidance.

My experience with NGS technologies is in amplicon-based systems, which offer a comparable sensitivity to PCR testing. It also provides faster turnaround times than other NGS technologies due to its relatively low level of technical complexity in the test instrumentation – leading to a simplified workflow while retaining accurate and reliable results.

Hybrid capture technologies tend to have larger panels for more comprehensive screening, providing more molecular content than other technologies. In terms of informing treatment decisions, however, bigger isn't always better. As more hybrid capture-based larger panels are developed, it will be interesting to see the comparisons against smaller panels in various applications.

"In terms of informing treatment decisions, however, bigger isn't always better."

Future directions of liquid biopsy NGS testing technology

I anticipate that NGS technologies in this area will be developed on a cancer-by-cancer basis. In a recently published study, our research team collected real-world liquid biopsy data across multiple cancers. We found that it is still only really the "big four" cancers for which we have significant data. We must invest more on research for monitoring of all cancer types.

I also predict we will see more standardization of the technologies, the reporting, and the therapeutic choices. For early-stage cancers, we need to see a revolution in pre-analytics, reimbursement models, technologies, and bioinformatics in order to address the large unmet need in this space.

Currently, testing and treatment of metastatic cancers is working well. However, if we can drive down healthcare costs by reimbursing liquid biopsy testing in the earlier stages of cancer diagnostics, patient outcomes and quality of life will undoubtedly improve.

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DIGITAL PATHOLOGY

Doing What We Do Best – But Even Better

AI-augmented pathology brings remarkable advancements to the lab in support of cancer diagnosis and research

By Judith Sandbank

According to the American Cancer Society, 2024 will be the first year of its kind – hitting an estimated 2 million new cancer diagnoses in the US (1). However, labs are not sufficiently prepared to meet this demand head on. Pathology departments worldwide face various challenges with a decreasing workforce, while the increasing complexity of cancer demands a more nuanced approach to diagnosis.

In response, pathologists are becoming more receptive to using automated diagnostic tools developed with machine learning – serving as digital assistants to support quality diagnosis. These innovations mark a quantum leap in cancer diagnosis and bring remarkable advancements across the entire pathology workflow.

Case prioritization

When diagnosing biopsies, pathologists are tasked with systematically evaluating all possibilities and medical conditions. In addition to detecting cancer, they also need to consider if the patient has any premalignant conditions, malignancy simulators, or inflammatory conditions before reaching a final diagnostic decision. However, manual case review is a laborious and inefficient process, usually performed on a first come, first served basis.

However, AI-powered solutions are set to effectively streamline the diagnostic workflow. Operating much like a traffic light system, these solutions prioritize and triage cases with a higher likelihood of containing disease cells before passing it to a pathologist. This can help balance work more efficiently within the team according to sub-specialty and experience – alleviating the workload for pathologists while translating to faster turnaround times in the diagnostic process.

Enhancing diagnosis

Certain tasks, such as biomarker quantification and Gleason scoring, are subjective and can lead to varied interpretations based on individual experience and perspective. Automated decision-support tools now go beyond the already demonstrated accuracy and efficiency gains – reducing variability and improving consistency. AI can also enhance the skills of less experienced pathologists by allowing clinicians worldwide to tap into the expertise of specialists who help train the algorithms. This results in more informed and detailed cancer diagnosis. By incorporating expert insights, AI democratizes care – bridging gaps between high and low equality areas and ensuring all patients receive accurate and comprehensive diagnosis.

Optimizing lab workflows

The daily diagnostic routine provides critical components that influence treatment decisions. However, tasks such as mitotic counting, detecting lymph node metastases, biomarker quantification, and tumor sizing are traditionally time-consuming when performed manually. Deep learning automated systems can help expedite these tasks while improving accuracy, streamlining review, and assisting reporting.

Similarly, there's a possibility of improving efficiency in the immunohistochemistry workflow. Traditionally, ordering ancillary tests following an initial slide review introduces delays that impact turnaround time and increase review cycles for pathologists. Leveraging the 24/7 availability and speed of automated solutions, we can program algorithms that analyze cases prior to pathologist review and proactively trigger pre-ordering of additional stains.

The high accuracy of AI systems is also supportive in reporting clear benign cases, which may have otherwise required additional tests. Optimizing and streamlining the overall diagnostic process is also crucial to saving costs and reducing disruptions to the pathologists workflow – ultimately expediting patient diagnosis.

In an age of precision medicine and targeted treatment, accurate and early diagnosis has never been more crucial. If we want to overcome the headwinds of rising pathology caseloads and personnel shortages, we need to double down on the adoption of digital pathology and AI. Thankfully, the pathology community is responding positively to this call to action, with labs across the world changing century-old practices to improve diagnosis and transform cancer care forever.

Judith Sandbank is Head of Pathology at Maccabi Healthcare Services and Chief Medical Officer at Ibex Medical Analytics

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DIGITAL PATHOLOGY

Tech to the Rescue

Is digital pathology the answer to burnout in pathology labs? Nathan Buchbinder shared his views

What do you believe is causing burnout among pathologists?

Pathology is plagued by an intensifying supply and demand challenge, which has been steadily worsening since the early 2000s. Between 2007 and 2017, the pathologist population decreased by 17.5 percent (1). Recent statistics show that the number of open roles for pathologists is near an all-time high (2); meanwhile, the global cancer burden continues to increase. The number of new cases per year in the United States is expected to cross 2 million for the first time in 2024 (3).

Unfortunately, burnout among pathologists isn't a new phenomenon. In 2021, 35 percent of pathologists reported feeling overworked (4), which increased to 41 percent in 2023 (5). It's undeniable that the supply and demand challenge will continue to take a toll on pathologists' work-life balance until it is addressed.

Advancements in precision medicine may also contribute to burnout. We're already seeing the impact from these developments in patient care and in enabling pathologists to practice at the top of their license. There's no doubt these advancements should continue to be introduced in the clinic, but we must also acknowledge the increased diagnostic complexity and added steps to the pathologist's workflow, such as running additional tests.

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What can department heads do to prevent/ease burnout?

It's time for department heads to transform their practices. If the answer lay in reorganizing existing resources and making slight modifications to current processes, we would have seen burnout start to ease by now. However, innovations like digital pathology, which are modernizing operations, have been proven to deliver many benefits that can combat burnout and set laboratories up for success.

What benefits does digital pathology bring to the lab and how can this help with burnout?

One of the most cited impacts of "going digital" is efficiency gains, which are crucial to overcoming the burnout burden. These largely result from overcoming the inefficiencies associated with glass slides. For example, pathologists can share images for collaboration and consultation in just a few clicks to quickly receive a second opinion, which could also help to improve diagnostic confidence – another commonly cited benefit of digital pathology – and give pathologists added peace of mind.

Digital pathology also provides flexibility to pathologists, allowing for remote working since they no longer need physical access to glass slides. By extension, going digital can help address staffing challenges. Laboratories can hire from further afield and attract the younger generation that often wants to work with the latest innovations.

How could recent advancements in AI-powered pathology ease pressure on individuals?

There are two broad categories of AI applications that we see in practice today, both of which are helping to reduce burnout.

Firstly, AI applications are unlocking insights that have gone unseen by the human eye. For example, companion diagnostics like PD-L1 quantification algorithms can consistently and accurately identify biomarkers to give pathologists information for delivering faster, high-quality diagnosis increasingly tied to precision therapies. With these applications, pathologists can free up time and gain peace of mind.

The second category of AI applications reduces time-consuming tasks, such as quality control (QC), to drive operational efficiencies. An AI-powered QC solution can complete the labor-intensive QC process up to six times faster than manual review alone – allowing pathologists to spend less time waiting for rescans and focus their attention on more complex elements of their role.

Are you hopeful that we will overcome burnout in pathology labs?

As real as the burnout situation is, I'm optimistic that it can improve. Digital pathology adoption is now being pushed at the national level in places like the UK, where the government recently agreed to recommendations to roll it out across the National Health System. In parallel, more laboratories are going digital. This momentum will generate added evidence on the impact of digital pathology on reducing burnout and overcoming the challenges that laboratories face more generally.

Nathan Buchbinder is Chief Strategy Officer at Proscia.

Credit: Proscia

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INFECTIOUS DISEASE

Contagious Math(s)

Epidemiology researchers showcase the benefits of mathematics in tackling infectious disease

Multidisciplinary collaboration is key in various aspects of scientific research – but the specific disciplines required in any given endeavor are not always obvious to everyone. For instance, mathematics plays a key role in helping us understand and predict epidemics that can spread through our communities, but kids (and the majority of the general public) are rarely exposed to exactly where math fits in the frontlines when battling infectious diseases. Enter the Millennium Maths Project based at the University of Cambridge (1).

Contagious Maths (2) is an initiative set up by the Millenium Maths Project to provide resources and open opportunities to students and the public so they can join researchers in the battle against infectious disease. The curriculum-linked resources provide teachers with full lesson plans backed by Cambridge research to provide students from the ages of 11 to 14 with interactive tools to give mathematical modeling a go.

To learn more about this exciting project, we spoke with Julia Gog, Professor at Cambridge's Department of Applied Mathematics and Theoretical Physics (DAMTP) and leader of the Contagious Maths initiative.

How did you become involved in epidemiology research?

I first became interested in using mathematics to understand epidemics when I was a fourth year university student. The idea that seemingly abstract mathematical systems could inform us on something as messy as an infectious disease outbreak really interested me – and still does to this day, more than 20 years later!

Credit: Queens' College, Cambridge

What inspired this project?

Large scale population dynamics, including epidemics, can only really be understood by looking at the numbers. All processes behind epidemics can be captured in relatively simple mathematics. Contagious Maths brings these ideas from a research environment to the classroom and public audiences.

How did you start?

Before the COVID-19 pandemic, I was lucky enough to be nominated for the Royal Society's Rosalind Franklin Award (3). I'd previously worked with the Millenium Mathematics Project for outreach and communications, which brought about conversations on how we could use this position to expand the mathematical horizons of secondary school girls. And from here, Contagious Maths was born.

How does the program work?

There are two different avenues or "routes" to explore in our Contagious Maths resources, which are tailored to different audiences. The NRICH classroom resources for schools are designed to be used as a sequence of lessons for ages 11 to 14. This route provides detailed teacher notes and learning outcomes mapped to the UK National Curriculum, all while providing students with the opportunity to apply their mathematics knowledge to avenues in infectious disease research.

The other route in Contagious Maths is the Plus Contagious Maths library. This avenue hosts a collection of multimedia resources aimed at general readers and older students. The articles, interactive media, and videos provided allow for an accessible introduction to disease modeling and enable exploration and learning at your own pace.

What are we missing from today's education system? Is there room for other initiatives like this to encourage students to join the field?

Absolutely! Our thinking with this initiative was to short circuit directly from my research world to mathematics education suitable for 11- to 14-year-olds, as well as making widely accessible resources for mainstream lessons. There are three underlying principles here that could be applied across STEM areas.

Firstly, we show students that what they study at their age has the potential to be applied in solving real world problems. Secondly, we bring models that are imperfect and under development into a classroom, demonstrating that mathematics isn't as black and white as it is portrayed in school. And finally, we introduce ourselves to students so they can see the real people behind the research – then maybe they can see themselves as future mathematicians and scientists.

What are your future plans for Contagious Maths?

We're looking forward to seeing how schools and the public use the resources we've created, and hopefully we can learn from the feedback to continue development. I'd love to see more projects making these connections from research to the classroom, especially in wider STEM fields and beyond.

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MOLECULAR PATHOLOGY

For Your Reference

The importance of standards in precision molecular oncology assays

By Gemma Halliday

Though next-generation sequencing (NGS) technologies have revolutionized cancer genomics by enabling comprehensive analysis of tumor genomes, the complexity of data interpretation poses a challenge for clinical practice. Clinicians, pharmaceutical companies, and companion diagnostics providers must navigate a vast array of genomic alterations, each with varying clinical significance. This work could include assessment of single genes (such as BRAF, EGFR or ALK), a composite genetic signature (such as mismatch repair or homologous recombination deficiency), or a comprehensive genome profiling (1).

What's more, such molecular assays lack value without validation. With this in mind, we look at recent innovations in molecular reference standards for both solid and liquid samples in oncology.

The role of reference standards

Reference standards serve as benchmarks for validating laboratory workflows and calibrating computational tools used for variant calling from patient samples. Scientists are able to compare identified variants in the reference standard with the known truth set. In this way, laboratories can assess their workflows' sensitivity, specificity, and reproducibility, ensuring reliable detection and interpretation of patient mutations.

In 2013, the Next-generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) workgroup recognized the use of reference standards as a key element of the implementation of NGS workflows (2). This conclusion directly led to the creation of "genome in a bottle" sample sets that are used by multiple laboratories around the world.

In oncology, no such reference standards exist. Recognizing this gap, a consortium led by the Medical Device Innovation Consortium (MDIC) started the Somatic Reference Samples (SRS) Initiative. One of its primary goals is to establish publicly available cell-line derived reference samples and a global genomic data resource library. These resources are expected to be instrumental across the entire life cycle of NGS-based diagnostics.

The impact of the SRS Initiative extends far beyond the development of reference samples. It's about transforming the entire ecosystem of NGS-based cancer diagnostics. From accelerating diagnostic development and regulatory approvals to enhancing reimbursement decisions and supporting precision medicine, SRSs are poised to make a profound difference in the lives of cancer patients.

A pilot project has started to create an initial set of 10 reference samples together with validated data sets. Work is ongoing by Revvity Mimix to engineer clinically relevant cancer variants individually into a well-characterized cell line HG002 (PGP/GIAB) background to be made commercially available in an FFPE format.

Liquid biopsy and minimal residual disease testing

With the introduction of liquid biopsy techniques, circulating tumor DNA (ctDNA) has recently gained popularity and has proved transformative in cancer diagnosis and treatment decisions. New NGS-based assays for liquid biopsy, especially those targeting minimal or molecular residual disease (MRD), require rigorous validation using appropriate reference materials. Like standard DNA assays, MRD testing requires the detection of very low quantities of tumor-derived ctDNA fragments – often orders of magnitude lower than typical detection limits.

For precise evaluation of assay performance including accuracy, analytical sensitivity, specificity, robustness and limit of detection of an assay, especially in the context of MRD detection, the development and use of "commutable" reference materials mimicking circulating tumor DNA (ctDNA) in real-world patient samples with extremely low variant allele frequencies are essential.

Precision medicine

The field of personalized medicine in oncology has witnessed significant growth, fueled by the increased use of NGS and molecular assays for cancer detection, research, and diagnosis. The growing number of instrument platforms, assays, and targeted drugs have made the field of oncology companion diagnostics a hotbed of innovation. All these innovations drive the need for accurate and well-qualified quality controls and reference materials for assay development and implementation.

Gemma Halliday is Technical Business Manager, Revvity Mimix. Anup Chugani is Senior Product Manager for Diagnostic Reference Standards, Revvity. Ephrem Chin is Head of Global OMIC Services & Molecular Reference Standards, Revvity

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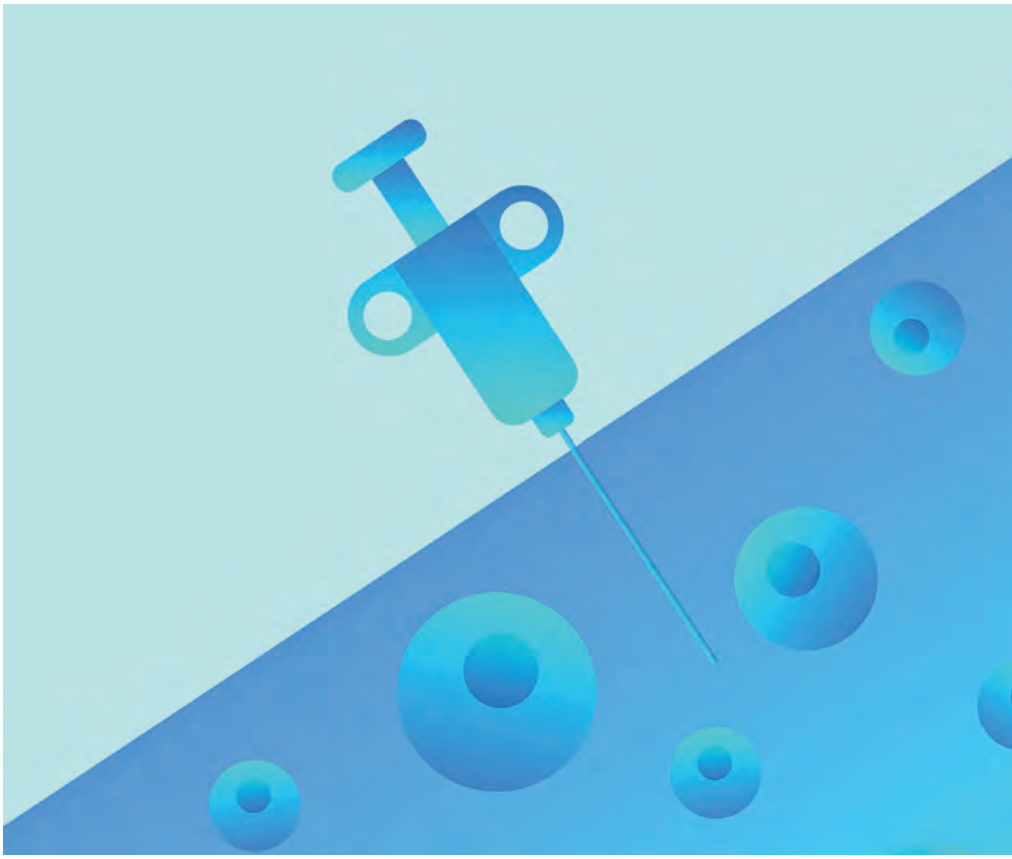
IN PRACTICE

Cell Wash

Mining the precious genomic reserves of core needle biopsies

By Han Wei



The core needle biopsy is today's standard procedure for the laboratory testing of tissue samples when malignancy is suspected. Sampling in this manner continues to provide invaluable insights into the morphological features of mass lesions in the body. Through morphological analysis, pathologists can discern whether the mass is benign or cancerous and – if the latter – gather insights into its stage, level of aggressiveness, and metastatic potential.

However, there resides in these core needle biopsy specimens much more potential than the delivery of conventional morphology. Herein is presented a simple method that opens the doors for pathology labs to improve upon the recovery and uncovering of the secrets behind the microscopic image.

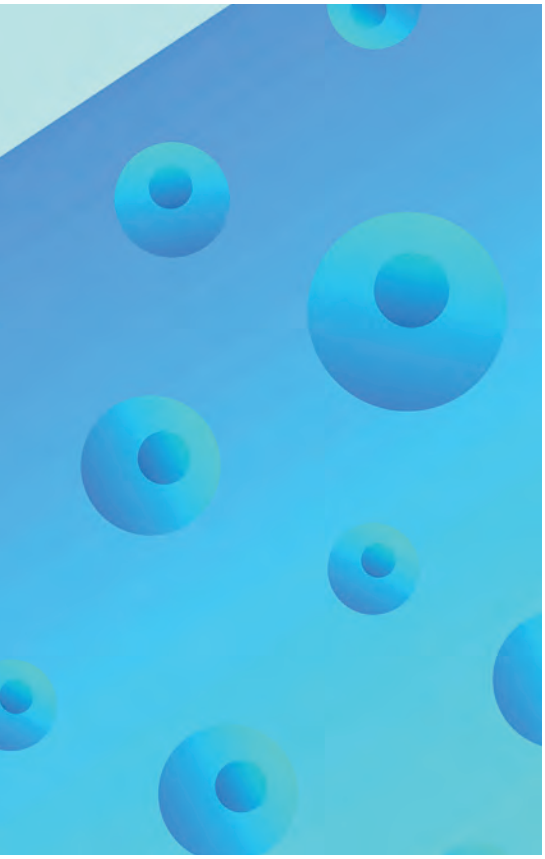
Formalin-fixation: a double-edged sword?

The handling of core needle biopsies is critical to the reliability and reproducibility of results. At many facilities, the collected sample has to be transferred to the pathology laboratory, which demands formalin fixation. The resulting formalin-fixed, paraffin-embedded tissues are stained and analyzed with immunohistochemistry or immunofluorescence methods. Thus, formalin fixation enables morphological analysis by allowing phenotypic evaluation, visualization between normal and cancerous cells and protein detection by immunohistochemistry.

Despite these benefits, core needle biopsies have limitations that make further sample analysis cumbersome. In today's era of precision medicine, there exists a strong demand for molecular analysis on this fixed material, as the underlying genomic content in these cancer cells can reveal critical mutations that contribute to specific altered pathways. Such information is instrumental in biomarker discovery and drug development, with rapidly emerging critical implications for patient treatment.

Nevertheless, the nature of the core needle biopsy specimen, and the subsequent tissue fixation it routinely undergoes, are in direct conflict with molecular analysis. To begin with, the tissue obtained via core needles is quantitatively minute, thus limiting the ability to perform multiple modality testing on the same sample. More importantly, formalin is a chemical that creates crosslinks between macromolecules, making it a challenging proposition to collect high-quality genetic content for biochemical applications, such as PCR and next-generation sequencing, both vitally important tools in today's burgeoning field of precision medicine.

"The key to a comprehensive sample analysis lies in the ability to extract sufficient amounts of cells and use a fraction solely for molecular testing."



Cell harvest for molecular analysis

The key to a comprehensive sample analysis lies in the ability to extract sufficient amounts of cells and use a fraction solely for molecular testing. This can be achieved by an additional washing step during sample preparation. When a core needle is used for collecting a tissue sample, a number of cells are dislodged and adhere to the inner wall of the cylinder. These residual cells can be recovered and retained for molecular testing by submerging the needle in a phosphate buffer saline (PBS) solution. The non-toxic and isotonic nature of the PBS buffer allows these dislodged cells to go into solution and be recoverable while protecting the cells' integrity and preventing the loss of their precious genetic content. With this minor modification step in specimen processing, the pathologist gains access to two samples, one for morphological analysis and the other for molecular testing.

The role of DNA recovery in taking full advantage of cell washing cannot be overstated. The primary objective is to recover sufficient amounts of high-quality DNA from these dislodged cells that originated from the already diminutive core needle biopsy tissue specimen. The phrase "high quality" here refers to DNA integrity and purity – crucial features for reliable biochemistry assay outputs. To that end, the solid phase reversible immobilization (SPRI) technique has repeatedly shown value in genomic DNA purification. Through manipulation with a magnetic field, SPRI paramagnetic beads enable seamless isolation of genomic DNA by reversibly binding nucleic acids and separating them from the rest of the cell lysate solution.

Wilfrido D. Mojica, Chief of Pathology at the Niagara Falls Memorial Medical Center, developed a cell wash method to harvest these dislodged cells that concurrently enables tissue recovery. Mojica's lab demonstrated the applicability of the method using a variety of biopsy specimens. "The recovery of these cells and the rapid stabilization of their nucleic acids helped us freeze and preserve the DNA, giving us flexibility as to when to perform the molecular testing," Mojica explains. "We successfully obtained high-quality DNA with the desired purity and integrity for demanding molecular testing applications. More importantly, integrating a commercially available reagent kit into the workflow significantly accelerated DNA recovery by allowing rapid separation and high-throughput implementation, as these kits are often amenable to automated liquid handling."

Future implications of cell washing and DNA recovery

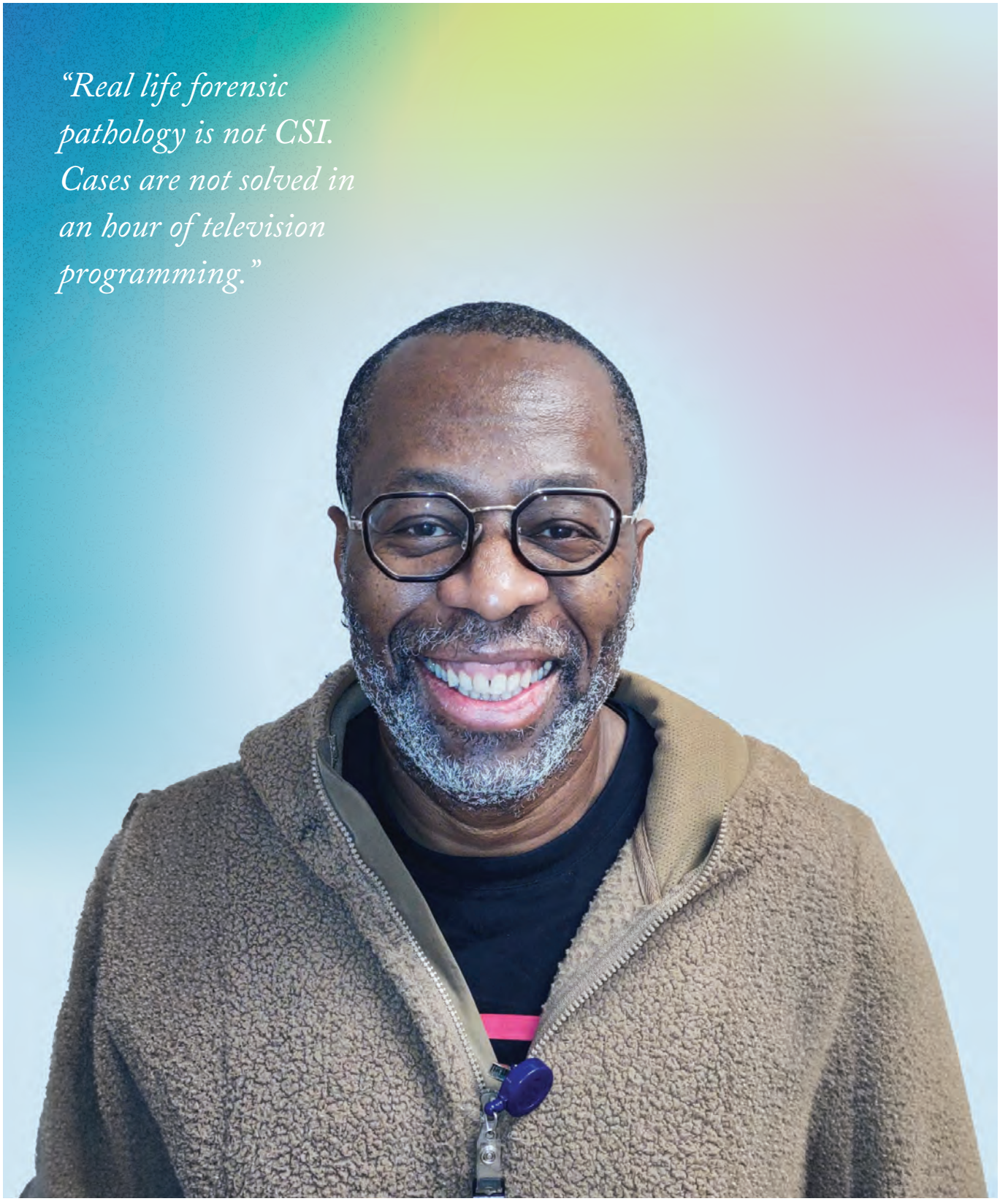
Cell wash with DNA recovery is gaining more recognition as an easy and valuable addition to core needle biopsies. Unlike extracting nucleic acids from fixed tissue, this process is easy to adopt without high-end instrumentation or advanced expertise, making it highly accessible to pathology labs with limited resources. In addition, it broadens the scope of research applications for diagnostics by enabling morphological and molecular analysis simultaneously from the same tissue sample. Even in the event that immediate molecular analysis is not desired, the liquid aliquot containing the dislodged diagnostic tumor cells can be preserved should testing be sought at a later timepoint.

Cell washing of core needle biopsies is in its infancy, performed mainly for research use in small-scale laboratories, but has the potential to grow in popularity as laboratories continue to examine new methods and see the benefits firsthand. As envisioned by Mojica, "It is the wise and prescient pathologist who begins to optimally process these specimens to take full advantage of this unrealized – but clinically valuable asset – so as to improve upon not only small tissue biopsy management but also patient care."

Han Wei, Global Product Manager Genomics, Beckman Coulter Life Sciences

Credit: Beckman Coulter Life Sciences

"Real life forensic pathology is not CSI. Cases are not solved in an hour of television programming."



Real-Life Forensic Pathology Is Not CSI

Sitting Down With… Ken Obenson, Forensic Pathologist at The Saint John Regional Hospital, New Brunswick, Canada

How did you get into the field of forensic pathology?
My interest in forensic pathology developed early in my career because of my experiences as a specialist pathologist in Montego Bay Jamaica with the United Nations Volunteers. I wanted to gain credentials that would be appreciated by my peers, legal colleagues, and employers.

How do you approach cases – and what factors influence the decision-making process during an autopsy?
For the most part, I approach a case the same way a clinician approaches a live patient: gain a history (and/or the circumstances of death from the investigating authorities), examine the body and document findings, take samples for testing, review all the results, and put together a report – in this case, a cause of death determination. Obviously some cases are easier than others. For example, a simple external examination may be appropriate for one case while another would require more complex dissection and a far greater investment of time and thought.

What motivated you to create the New Brunswick Pathology Forum? How do you think it has benefited the community?
Local gatherings tend to foster local connections and cross pollination. I think the death investigative staff have a better understanding on why we insist on certain protocols. Now, we are all able to put names to faces and, by making informal introductions, it is much easier to pick up the phone and call when we need each other's assistance.

What specific methods do you use to improve the quality of forensic pathology?
Apart from the usual discussion of cases before and after autopsies, we have robust (though not infallible!) peer review processes, which include near 100 percent review of all reports. Certain cases (suspicious deaths or homicides) are mandatorily reviewed before they are signed out. "Administrative review" is a phrase we use to describe a review by a non-pathologist who hopefully brings the perspective of how a lay person could misunderstand the report. We are also tightening up protocols to have consistent random peer review of court testimony.

How has the adoption of advanced radiologic imaging techniques benefited forensic autopsies?
These new techniques facilitate the production of "sanitized" evidence for juries – minimizing the risk of undue prejudice and aligning with the standard of care in infant death cases. They are also really useful in complex gunshot wound cases where determining wound direction can be difficult. Finally, they provide a permanent internal archive in cases where the next of kin object to an internal exam (in our institution it is usually infant death cases).

Improving pediatric death scene investigation is a focus for you. Could you discuss some challenges that are unique to this area?
The challenge is always gathering as much data at the death scene before the start of the autopsy. I admire the UK model in which a pediatrician has a chat with the family to tease out additional details. We are not quite there yet, but a few of our retired pediatricians might be persuaded to make virtual house calls. We already have a strong Child Death Review committee, which I also sit on. It is interesting to observe how we can all look at the same data yet interpret certain things differently. I appreciate the diversity of professional opinion.

What's your biggest career highlight to date?
Becoming the first Black Canadian to be certified in Forensic Pathology by the Royal College of Physicians and Surgeons of Canada.

How can social media contribute to the broader dissemination of forensic pathology knowledge and public awareness?
Social media breaks down the mysticism behind what we do. Death investigation services are under constant threat of budgetary cuts (since the dead do not vote – though their next of kin do). If the lay public understands that funding provides qualified staff and equipment, they may be more disposed to advocate on behalf of the death investigation service.

An educated public – and hence jury pool – is more likely to provide an objective assessment of evidence when it is properly placed before them. It is important that they are able to understand the limits of what forensic science and pathology can do. Real life forensic pathology is not CSI. Cases are not solved in an hour of television programming.

What advice would you give to young pathologists who are keen to enter the forensic pathology field?
Find a mentor and get as much exposure as you can in training. Attend national meetings and, if possible, collaborate on a research project. There will always be a forensic pathologist willing to go out of their way to convince you to join the specialty. Most importantly, salaries are going up so you no longer have to take a vow of poverty!

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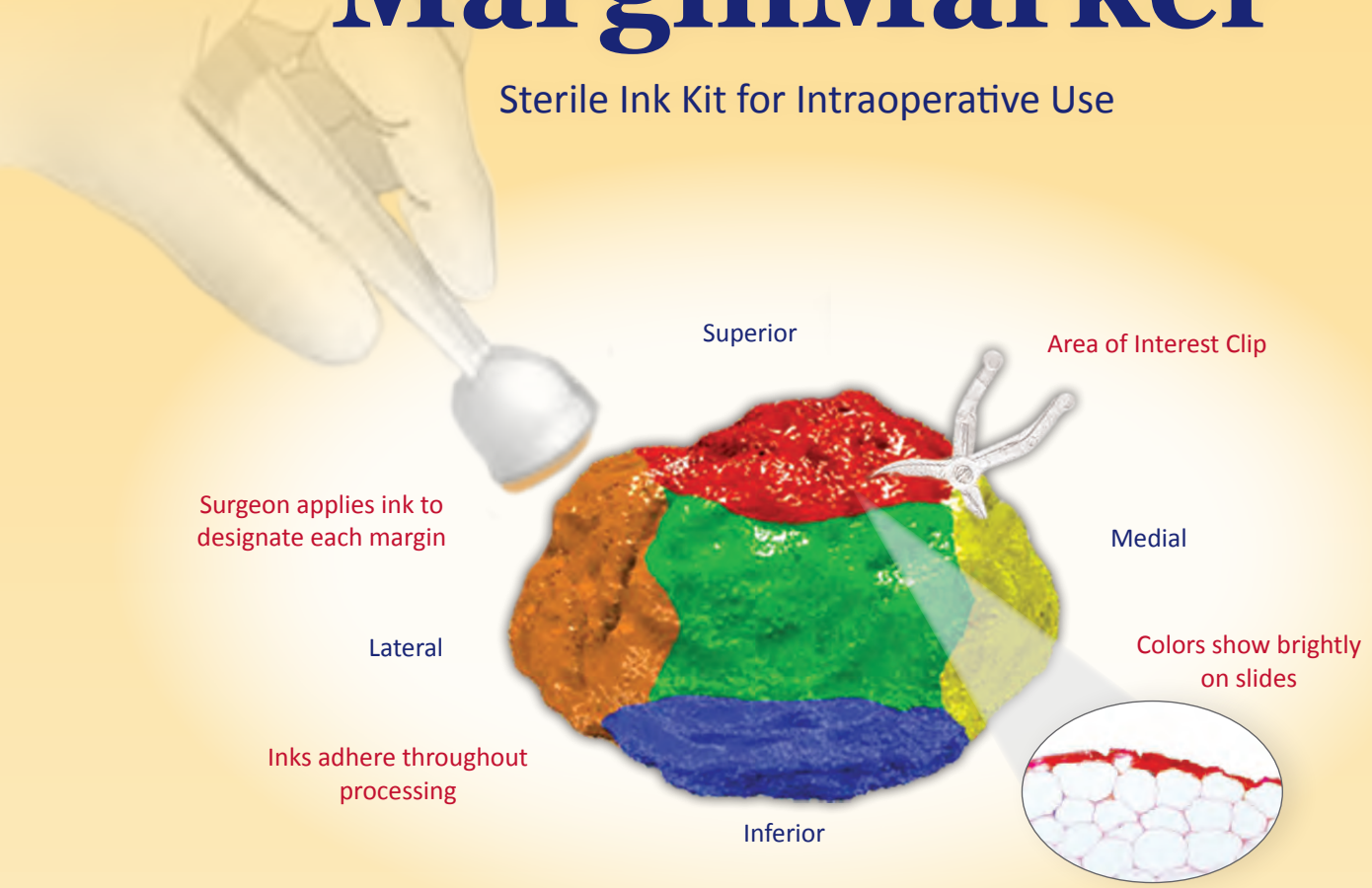

Pathology Receives Specimens With Margins Clearly Marked by the Surgeon

In cancer surgery, the single most important predictor of local recurrence is the tissue margins.[1] Research shows discordance rates as high as 52% in the identification of specimen margins.[2,3] Re-excision rates exceed 20% in breast surgery.[4] Use of Vector Surgical's MarginMarker can result in:

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