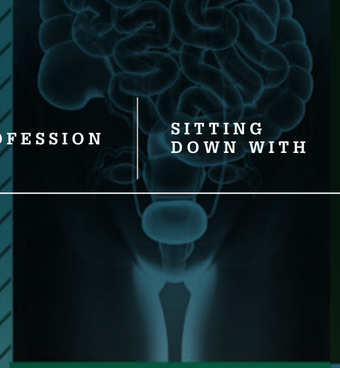
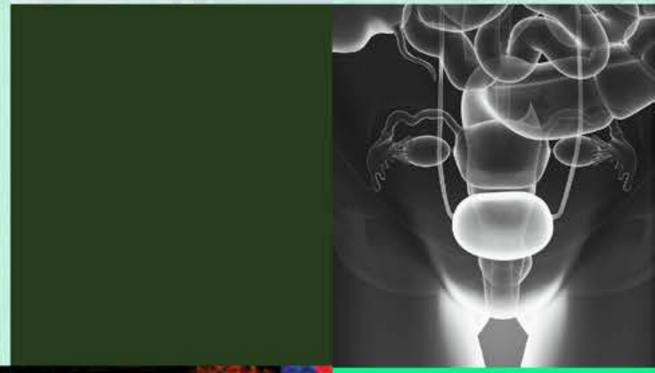
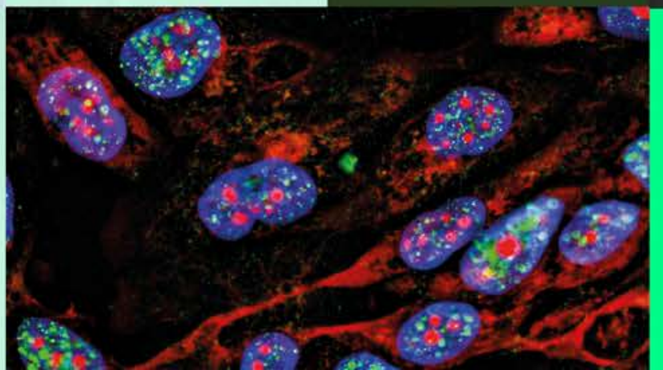






What's New in GU?

The Genitourinary Pathology Catch-Up

the Pathologist

Research Roundup: Optical Innovation, Volatile Algorithms, and Better Liquid Biopsies

What does the future of bladder cancer monitoring look like? Recent research offers some clues...

The Essence of Fluorescence

An at-home test kit, using fluorescence-based detection, identifies early-stage bladder cancer in unprocessed urine with 90 percent accuracy, according to a study published in Nature Biomedical Engineering.

The device, developed by a team in the Republic of Korea, detects bladder cancer biomarkers called urinary hyaluronidases as they pass through an organogel, causing enzymatic release of solvatochromic fluorophores. The change in fluorescence in the sample can then be detected via a smartphone app.

Because the biomarker particles are absorbed into the organic phase, there is no interference from blood proteins in the sample – overcoming a major limitation of most urine tests for early bladder cancer. This feature allows urine samples to be tested with no pretreatment.

The validation study tested urine samples from 105 participants – including patients with bladder cancer, other genitourinary conditions, and healthy volunteers. The system distinguished the cancerous samples, including those with early-stage bladder cancer, with 90 percent accuracy. By addressing the limitations of existing methods, such as low biomarker sensitivity and interference from hematuria, this innovation may facilitate non-invasive cancer diagnostics at the point of care.

Take Urine, Add AI

A new AI-powered urine test for the detection of bladder cancer has been granted FDA breakthrough device designation. The assay analyzes the molecular signatures of volatile organic compounds (VOCs) in urine via gas chromatography mass spectrometry, then applies an AI algorithm to determine a cancer risk score. Its design was inspired by a dog's ability to detect illness by sensing VOCs that the body releases when disease is present.

By assessing real-time changes in physiology and metabolism, the device has the potential to identify early patterns of disease before symptoms appear. It could reduce the number of costly and invasive cystoscopy examinations, which are routinely used to confirm or monitor bladder cancer. Sensitive enough to detect early-stage disease, it could help more patients receive treatment early, improving both outcomes and health economics for the disease.

FDA breakthrough device designation entitles developers to fasttracked approval reviews. In this case, the designation recognizes the potential to provide an accessible, non-invasive method of early cancer detection. The bladder cancer assay will now undergo rigorous validation testing to support its approval application.

Liquid Biopsy Feasibility Boost

Researchers from Weill Cornell Medicine and the New York Genome Center have developed a highly sensitive, error-corrected whole-genome sequencing method that enables the detection of trace amounts of tumor DNA in blood samples.

Leveraging a low-cost sequencing platform, the team achieved ultra-deep sequencing coverage, allowing them to identify circulating tumor DNA (ctDNA) at concentrations as low as parts per million. In their study, the researchers demonstrated that this approach – enhanced with a built-in error-correction method – accurately detects ctDNA without requiring prior access to tumor tissue. Their proof-of-concept involved patients with bladder cancer and melanoma, where mutational signatures previously studied by collaborating labs were incorporated to improve sensitivity. This allowed the detection of changes in ctDNA levels corresponding to cancer progression or therapeutic response.

As costs decrease and sensitivity improves, this study substantiates the promise of next-generation sequencing in clinical oncology. The findings point to a future in which routine blood tests could provide a noninvasive alternative to tissue biopsies for ongoing cancer monitoring.

Urothelial Methylation Marker

A prospective study conducted by researchers at Asan Medical Center evaluated the diagnostic utility of a urinary PENK methylation test in detecting urothelial carcinoma, including bladder cancer and upper tract urothelial carcinoma (UTUC). The study enrolled 183 patients with 13 cancer types and assessed the test's sensitivity and specificity in distinguishing urothelial cancers from others. The test demonstrated a high overall sensitivity of 94 percent – 88 percent for bladder cancer and 100 percent for UTUC – and a specificity of 96 percent, supporting its promise as a noninvasive diagnostic biomarker for urothelial malignancies.

While most non-urothelial cases tested negative, a few positive results were observed in cervical, colorectal, liver, esophageal, and kidney cancers. These findings suggest that although PENK methylation is strongly associated with urothelial carcinoma, background methylation in other cancers or benign conditions may contribute to occasional false positives. Nonetheless, the methylation signal was significantly stronger in patients with confirmed urothelial carcinoma, reinforcing its diagnostic relevance.

The authors note that the test could complement or reduce reliance on invasive procedures such as cystoscopy and ureteroscopy, which are currently standard for bladder and UTUC diagnosis. Given its noninvasive nature and diagnostic accuracy, the PENK methylation assay shows promise for use in screening and surveillance, particularly for UTUC, where diagnostic tools are limited.

Prostate Screening Stats Deliver Stark Warning

Men who skip prostate cancer screenings face significantly higher risk of death, study finds.

Consistently avoiding prostate cancer screening appointments increases the risk of dying from the disease, according to new research presented at the European Association of Urology (EAU) Congress in Madrid. The findings, based on long-term data from the world's largest prostate cancer screening study, shed new light on the impact of screening behavior on patient outcomes.

The analysis draws on 20 years of follow-up from the European Randomized Study of Screening for Prostate Cancer (ERSPC), which has tracked more than 160,000 men across seven European countries. Among the 72,460 men who were invited to regular prostate-specific antigen (PSA) screening tests, around one in six – over 12,400 men – never attended a single appointment. This group had a 45 percent higher risk of dying from prostate cancer compared with those who participated in screenings.

In contrast, men who attended screening appointments had a 23 percent lower risk of death compared with a control group who were never invited. Men who declined screening, however, faced a 39 percent higher risk of dying than the control group – suggesting that choosing not to participate may carry more risk than not being offered screening at all.

Lead researcher Renée Leenen said the findings identify a new high-risk group. "It may be that men who opted not to attend a screening appointment are care avoiders, meaning they're less likely to engage in healthy behaviours and preventative care in general," she said. "This is the opposite behavior of people who are perhaps more health conscious and are more likely to attend a screening appointment."

Prostate cancer is the most common cancer in men across more than 100 countries. Screening programs using PSA blood tests can lead to earlier diagnosis, less aggressive treatment, and improved survival. However, uptake remains a challenge.

Tobias Nordström of the Karolinska Institute, Sweden, added, "We need to better understand why these men might actively choose not to participate in screening, despite being invited to attend, and how this behavior is linked to worse outcomes when they get a diagnosis."

The full results of this sub-analysis will be published later this year, as part of ongoing efforts to guide evidence-based, risk-adapted screening programmes across Europe through the EAU-led PRAISE-U initiative.

Urine Biomarker Discovery for Prostate Cancer

A three-step approach to biomarker discovery indicates early-stage prostate cancer can be diagnosed from a simple urine sample

An international study has identified potential urine biomarkers for prostate cancer screening. By combining spatial transcriptomics, digital modelling of tumors, and machine learning, researchers identified a suite of biomarkers that indicate the presence and severity of prostate cancer with a high degree of precision.

In the study, published in Cancer Research, the researchers analyzed the micro RNA activity of all human genes in thousands of individual cells in prostate tumors using spatial transcriptomics. Knowing the position and degree of cancer of each cell, the team then constructed digital models of prostate cancer using a technique called pseudotime.

The models were analyzed with AI to identify proteins that could be used as biomarkers. Finally, the biomarkers were analyzed in the blood, prostate tissue, and urine of almost 2000 patients.

Here, lead author Martin Smelik, of The Karolinska Institutet, Stockholm, outlines the key findings and their implications for prostate cancer diagnostics.

What are the unmet needs in prostate cancer diagnostics that inspired this study?

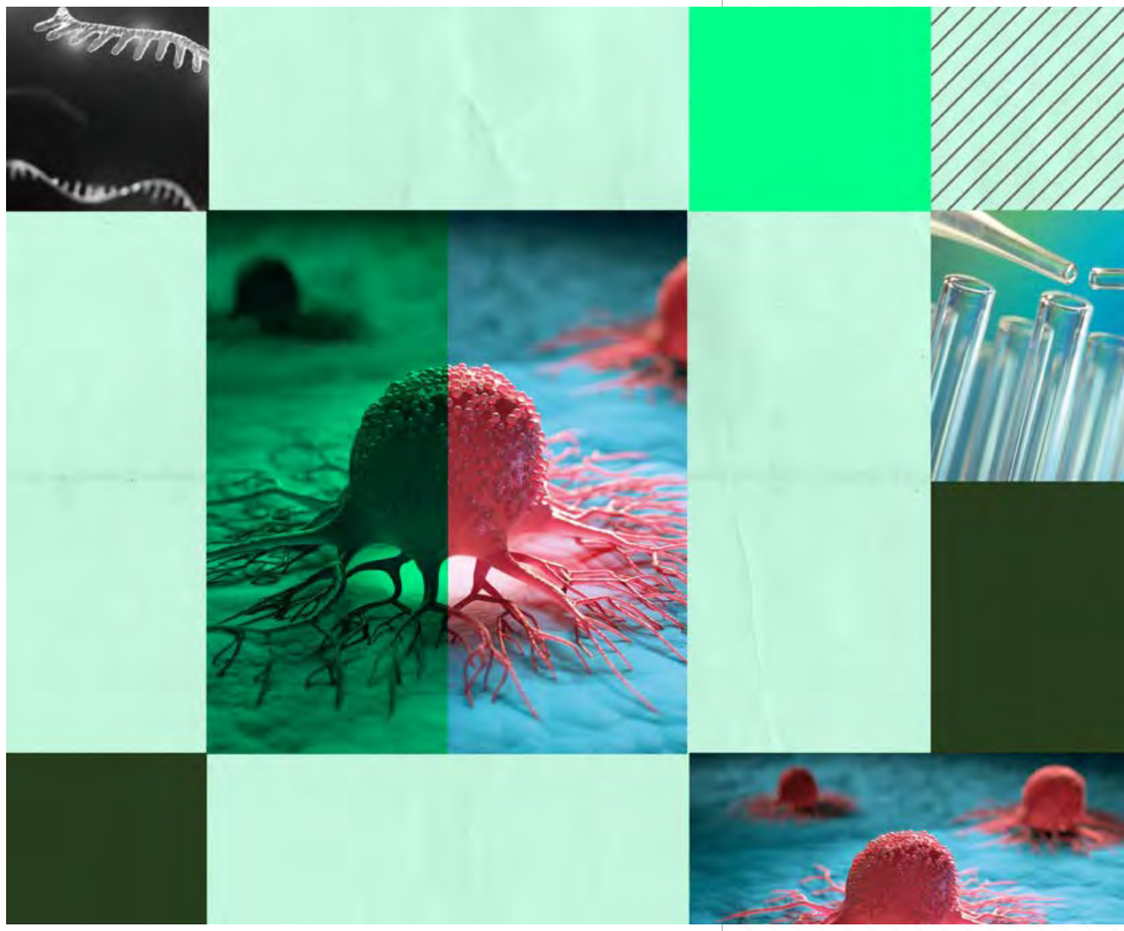
Currently, the most common test to diagnose prostate cancer is based on the blood level of PSA. While this is a great tool, it lacks specificity, which might result in many false positive cases – leading to unnecessary biopsies for patients. This limitation inspired us to identify new biomarkers which might be easily measured in urine.

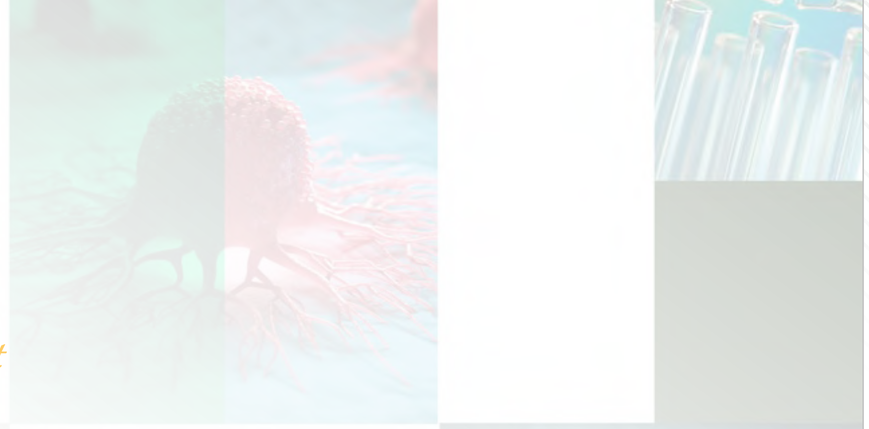
How did you integrate spatial transcriptomics, pseudotime analysis, and machine learning for biomarker discovery in prostate cancer?

Spatial transcriptomics is a new technology that allows us to study the prostate with great resolution. As we were interested in the development of the cancer, pseudotime comes as a natural choice of methodology.

Pseudotime is essentially a digital model of malignant transformation. In other words, we used pseudotime to model the development of the cancer and identified genes that were associated with this development.

We used machine learning approaches successfully in our previous





"The main implication of our study is that the screening tests might potentially be more precise if biomarkers are measured in urine, as opposed to blood, which is the current practice."

studies. For this study, our aim was to use this experience in a slightly different setting and find a way to effectively combine it with pseudotime and spatial transcriptomics.

How would you explain pseudotime modeling to the uninitiated, and how did it enhance your ability to identify reliable biomarkers for prostate cancer?

Pseudotime is essentially a digital model of malignant transformation. In other words, we used pseudotime to model the development of the cancer and identified genes that were associated with this development.

Of the 45 candidate biomarkers you identified, were there any that particularly stood out in terms of diagnostic performance or clinical relevance?

Indeed, there were several biomarkers that have been already studied in the context of prostate cancer. Some examples include TIMP1, which promotes proliferation of cancer cells in vivo, and S100A6, which is a calcium-binding protein implicated in a variety of biological functions as well as tumorigenesis.

Your study reports an AUC of 0.92 for urine-based biomarkers – significantly higher than that of serum PSA. What are the implications of this for non-invasive prostate cancer screening in clinical practice?

The main implication of our study is that the screening tests might potentially be more precise if biomarkers are measured in urine, as opposed to blood, which is the current practice.

Variability in biomarker expression between patients is a wellknown challenge. How did your approach address inter- and intra-patient heterogeneity?

We addressed the intra-patient heterogeneity by analyzing multiple prostate cancer samples from the same patients with a various level of cancer involvement. The inter-patient heterogeneity was addressed in the way we prioritized the biomarkers. Specifically, we selected those biomarkers that were consistently highly correlated with pseudotime across samples from multiple patients.

Looking ahead, how might this biomarker discovery pipeline be adapted to other cancers or therapeutic contexts?

We published all our codes to the online repositories where other researchers might access and re-use them. While we were focused specifically on prostate cancer, the methodology used in our study can be applied for other cancers which might potentially result in relevant biomarkers.

Biopsy to Bedside in a Week: A New Approach to Bladder Cancer Diagnostics

Can gene expression subtyping be used to guide treatment decisions for bladder cancer?

A clinical trial is underway in the UK to investigate whether treatment for muscle-invasive bladder cancer (MIBC) can be tailored to genetic subtypes of the disease.

The GUSTO study requires the laboratory team to deliver rapid gene expression subtype results to teams across twenty UK centers with a target turnaround of less than 7 days. To achieve this, the team has optimized new laboratory processes in collaboration with biomedical scientists, pathologists, National Health Service (NHS) laboratory management, and a commercial partner.

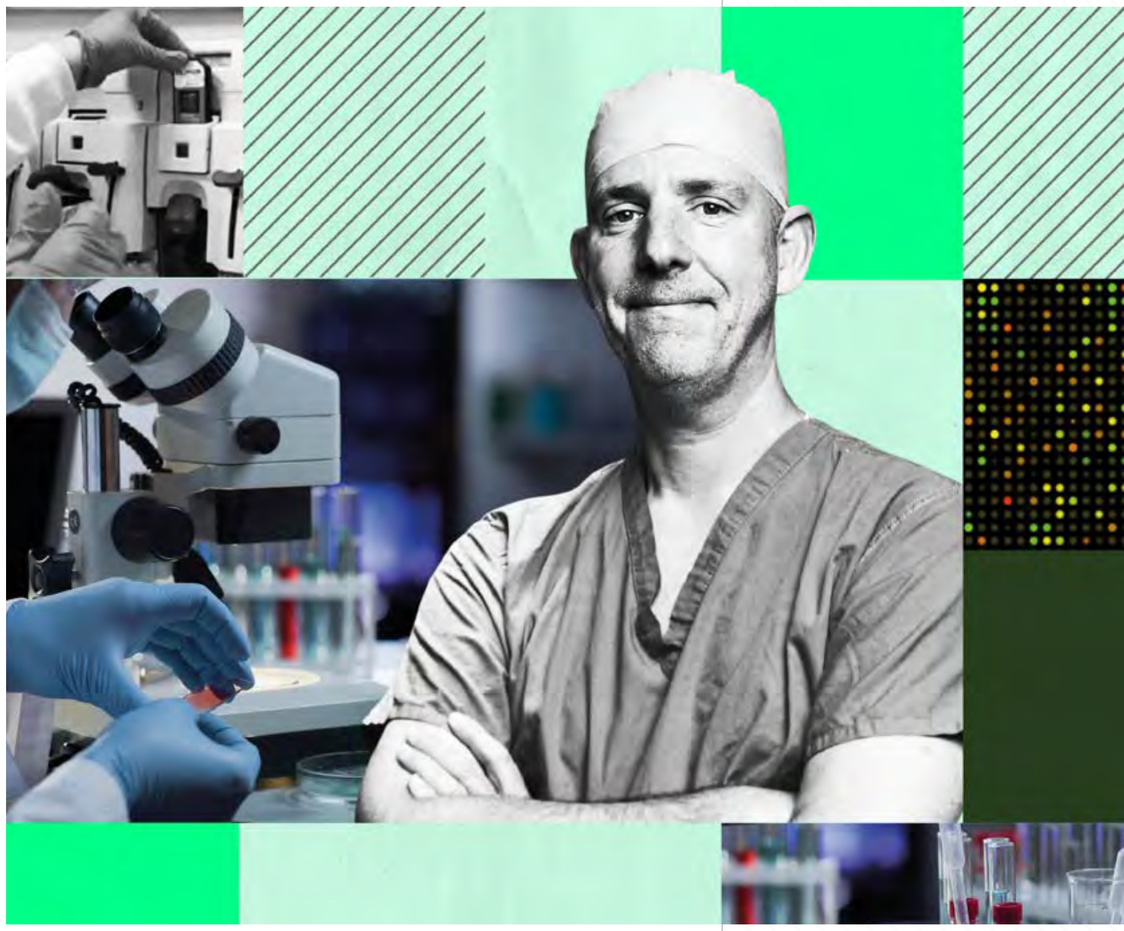
In recognition of its innovative approach, the GUSTO Trial Lab Team was recently honored by the Royal College of Pathologists, gaining one of its 2025 Achievement Awards.

We spoke with Jim Catto, Honorary Consultant Urological Surgeon at Sheffield Teaching Hospitals NHS Foundation Trust, Professor of Urology at the University of Sheffield, and Chief Investigator of GUSTO, to find out more about the study.

What inspired the GUSTO trial?

On a personal level, it is always individual patients who inspire our research. Some of our patients with MIBC achieved remarkable responses to chemotherapy, which led us to question whether removing the bladder was truly necessary in their cases. Others progressed during treatment, leaving us to wonder whether they might have been better served by immediate cystectomy instead.

We know that some patients with MIBC benefit from neoadjuvant chemotherapy given prior to radical cystectomy – but there are others who may not. Advances in molecular profiling have improved our understanding of genomic subtypes in bladder cancer, and several retrospective cohorts have suggested that responses to neoadjuvant therapy may differ depending on these molecular subtypes.



Who's involved, and what are the goals?

There is a huge team involved in GUSTO and all parts are equally vital. The Leeds Cancer Research UK Clinical Trials Unit, at the University of Leeds, runs the trial on a day-to-day basis. The sponsors (Sheffield Teaching Hospitals NHS Foundation Trust) and funders (NIHR and MRC) oversee safe implementation, patient safety, value of the trial, and delivery.

On the clinical side, we have the histopathology team in Sheffield that runs the pathological and genomics aspects, and a medical oncology team who developed the stratified care regimens and oversee safe delivery of the agents. There is also a surgical team of urologists that meets to discuss recruitment, standardize surgery, and review patient events.

Finally, we work closely with industry partners who supply the gene profiling tests and the study drugs.

How is gene expression subtyping used to guide treatment decisions in bladder cancer?

In the randomized controlled trial, the control arm receives neoadjuvant chemotherapy prior to radical cystectomy. The experimental arm is divided into three according to subtyping. Luminal papillary and luminal tumors have immediate cystectomy, without neoadjuvant treatment. Luminal infiltrated tumors receive neoadjuvant durvalumab and tremelumimab plus adjuvant durvalumab. Basal and neuronal subtypes receive neoadjuvant chemo and immunotherapy, and adjuvant durvalumab.

What were the key considerations for optimizing turnaround times for gene expression subtyping?

We need to deliver diagnoses within usual NHS timelines, so timing is key. We had to work out how to deliver samples of invasive cancers from consented patients to Sheffield, extract RNA, run profiling, and allocate subtypes – all before patients arrive at their oncology clinics to discuss treatments.

What are the implications of the GUSTO trial results for patients with bladder cancer?

This is a phase 2 trial and so the immediate implications from GUSTO will be about design of a phase 3 definitive trial. However, we have shown that you can deliver a genomic study in real-time NHS timelines.

Overall, we are seeing some exciting results suggesting the individualized care for patients with MIBC is possible. And, as new treatments are coming very quickly, GUSTO has set a paradigm for genomic stratification of patients.

Why are academic and clinical partnerships so important in advancing diagnostics?

As the GUSTO team membership reflects, trials like this would not be possible without strong and close academic and clinical partnerships. Both bring different aspects to the study and different strengths to deliver clinical improvements.

Are we Bypassing the Biomarker Experts?

Four genitourinary leaders discuss the critical role of pathologists in molecular cancer testing

As biomarker testing for genitourinary (GU) pathology plays catch up with the well-established, and well standardized, landscape in lung and breast pathology, we ask: what are the barriers to the ideal workflow? What happens when test manufacturers' marketing targets oncologists rather than pathologists? Why are tests being ordered and repeated unnecessarily? Why should pathologists be the stewards of all molecular testing?

These issues and more were addressed by our roundtable panel of four GU pathologists in the US. Here is what they told us…

Ming Zhou
Vice Chair for Oncological Pathology, Director of Urological Pathology Service and Fellowship Program, Mount Sinai Hospital and Icahn School of Medicine, New York

Fang-Ming Deng
Professor of Departments of Pathology and Urology, Director of Urologic Pathology, New York University Langone Health

Manju Aron
Professor of Clinical Pathology and Urology, Section Director, Urologic Pathology, Keck School of Medicine, University of Southern California

Anil Parwani
Chair of the Department of Pathology, Ohio State University

How has next-generation sequencing (NGS) impacted the diagnostic and prognostic landscape for GU cancers?

MZ: NGS has significantly improved our ability to characterize cancer at the genomic level. For both prostate and bladder cancers, we've started using NGS for prognostic stratification and to guide targeted therapies. For instance, in prostate cancer, NGS can identify actionable alterations – particularly those with therapeutic and prognostic significance.

We know that tumors with mutations in homologous recombination repair genes, for example, may respond well to PARP inhibitors. Similarly, tumors with microsatellite instability are often responsive to immune-oncology based therapies like immune checkpoint inhibitors. Because NGS can pinpoint those types of tumors, it has transformed the therapeutic landscape in prostate cancer. This is particularly relevant in advanced stages, such as castration-resistant prostate cancer, where tumor-based NGS is frequently ordered to help guide treatment decisions.

In some cases, we also pursue germline testing. If a patient carries a germline BRCA2 mutation, for example, there are important implications. Screening should begin earlier – around age 40 instead of 55 for the general population – and if such patients undergo local therapy, they may face a higher risk of disease progression and potentially lower overall survival.

These factors should be discussed with patients, especially if they are considering active surveillance.

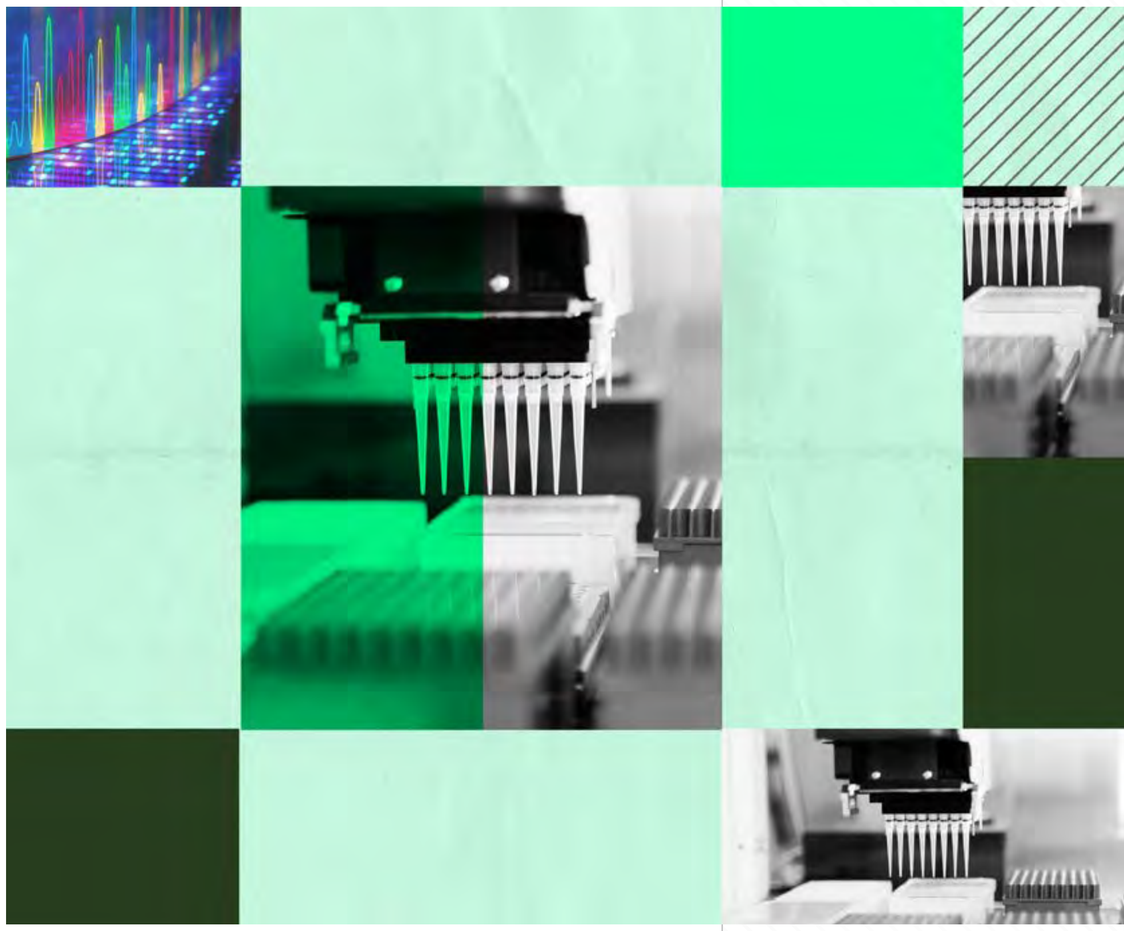
How are NGS tests typically ordered and implemented in GU pathology?

AP: In general, the tests we use are fairly generic – they're designed for a broad range of cancer types. We don't often have panels that are specific to GU cancers like prostate or bladder cancer. These are usually included as part of a broader solid tumor or pan-cancer panel, but not specifically highlighted or customized for GU applications.

There's also a recurring communication gap between GU oncologists, urologists, and pathologists. Often, oncologists attend national meetings like the American Society of Clinical Oncology (ASCO) or regional society conferences, hear about new tests, and then come back wanting to order them. But not many labs are set up to offer those tests, and pathologists aren't always looped in.

Some academic centers like ours do have in-house NGS capabilities, but many community pathologists rely on send-out testing. When that's the case, the ordering process can bypass the pathologist altogether. That's a concern.

MZ: Yes, I agree. Even at our hospital, most of these tests are still being sent out. We recently validated a 500-gene panel that was approved by the New York State Department of Health – but it's not yet in routine clinical use.



In practice, most NGS requests are still sent to large commercial laboratories. First, these tests are costly. Second, the turnaround time can be lengthy – at least two weeks. That can negatively impact patient care, because our clinicians are looking for results quickly to make timely treatment decisions.

F-MD: As Ming and Anil mentioned, most of the time we're using general-purpose panels. And for identifying prognostic markers or therapy targets, that's usually sufficient. But it can also add real value in challenging diagnostic cases. For example, when we're dealing with carcinoma of uncertain origin – where we're not sure about the exact cell lineage – NGS can sometimes provide additional clarity.

How well standardized are these tests across labs?

MZ: Since most of these tests are performed by centralized commercial labs, there's generally good consistency in how they're carried out. That centralization helps reduce variability across testing sites.

The challenge arises when we try to bring these tests in-house. Standardizing them internally is extremely complex and resource-intensive. That's where we face significant hurdles – in validation, quality control, reproducibility, and regulatory approval.

Does faster turnaround time come at the cost of consistency or quality?

MA: Yes, that's the trade-off. On the one hand, faster turnaround times are ideal for patient care. Some institutions – Memorial Sloan Kettering (MSK), for example – do have their own in-house molecular testing platforms, which I presume are well standardized and tightly integrated into clinical practice. But at most small and even mid-sized academic centers, like ours, oncologists tend to send specimens to large outside reference labs and then base clinical trials or therapy decisions on those results.

But as Anil mentioned earlier, most of these tests are being ordered by oncologists. And there's the issue of reimbursement – oncologists often order the tests directly and manage the billing and reimbursement process. They typically send specimens to large commercial labs, which offer validated, standardized platforms for clinical use. Based on those results, they can move forward with targeted therapies.

F-MD: Another issue – possibly more relevant to New York – is patient-driven test duplication. For example, the oncologist may send the tumor sample to the commercial lab. Then the urologist says, "Oh, we have our own 580-gene in-house panel," and orders another test. Then the patient visits MSK, and they run their own in-house platform again.

That kind of repeated testing adds unnecessary cost and effort. It can be a waste of both time and tissue.

MZ: That brings up a critical point – whether results across different platforms are actually comparable. And more importantly, what is the role of the pathologist in this process?

In many situations, clinicians bypass us completely. They send tissues directly to commercial labs without involving pathology. But our role is essential. As Manju mentioned, we need to ensure the tissue being submitted is representative of the tumor and that there's sufficient tumor content to yield reliable results.

And when results come back, I always emphasize that pathologists should be involved in interpreting them. We should integrate the molecular findings with the pathology report and the broader clinical context. That's key to ensuring results are meaningful and actionable.

To what extent are liquid biopsy tests being used in the detection and monitoring of GU cancers?

AP: In my experience, we're not seeing many liquid biopsy requests for GU cancers coming through pathology. The companies offering these assays market directly to oncologists, promising rapid turnaround times. From a pathology standpoint, it feels more like a clinical chemistry test – it doesn't offer any spatial perspectives on disease.

Right now, in my practice, there's little demand from urologists or oncologists for liquid biopsy testing. But I suspect that may change as adoption grows. There are potentially actionable applications, especially in bladder cancer, but I'll let my colleagues weigh in further.

MZ: Yes, I agree. At the moment, liquid biopsy testing – such as circulating tumor DNA (ctDNA) analysis – completely bypasses pathology. Blood samples are drawn in the clinic and sent directly to external testing labs without any involvement from the pathology department.

F-MD: That's exactly what we've observed. Like Anil said, we're not seeing many of these tests directly – but that doesn't mean they aren't happening. For example, in advanced bladder cancer, liquid biopsy is used before neoadjuvant therapy to assess disease burden. It's also commonly used for post-treatment monitoring and recurrence detection.

MA: And that's the real issue – it's happening, but we're not included in the process. These tests are ordered during routine clinical follow-up, often in outpatient settings. We only learn about them during multidisciplinary team meetings, when someone mentions ctDNA levels while discussing patient management.

MZ: Let me give you an example from when I was at Tufts in Boston. A patient with recurrent lung cancer had blood drawn for ctDNA testing, and the sample was sent directly to a third-party lab. The results were faxed to the ordering physician but never uploaded into EPIC. The physician didn't receive them, and when the results were needed, no one could locate them in the system.

We were asked to investigate, and we discovered the test had been ordered outside of our standard workflow. The pathology department had no record of the test ever being ordered or reported. Worse, we found out the testing lab wasn't even CLIA-certified. That's a serious concern. Without proper oversight, important results can fall through the cracks.

What are the barriers to using urine-based biomarker testing in monitoring GU cancers?

F-MD: I think urine-based testing has significant potential. There are already many commercially available tests – not necessarily in the US, but certainly in Europe, China, and India. The issue, though, is that there are so many options. Choosing the right one becomes a challenge.

More importantly, these tests need to be rigorously validated. At this stage, a lot of companies are pushing aggressively into the market, but the scientific and clinical validation is still catching up.

MZ: I completely agree with Fang-Ming. There's huge potential in using liquid biopsies – like ctDNA and urine-based tests – especially since these are considered noninvasive or minimally invasive techniques. That makes them attractive for both patients and providers.

However, as Fang-Ming mentioned, the problem is fragmentation. There are so many different tests, and most are only validated within limited patient cohorts. We don't yet have broad, cross-institutional validation studies. That makes it difficult to interpret and compare results across centers.

Another major barrier is reimbursement. Not all of these assays are covered by Medicare or commercial insurance, so financial feasibility becomes a concern. Plus, with so many options on the market, selecting the most appropriate test often depends on the individual urologist's experience and preference rather than standardized guidelines.

F-MD: Yes, and another important limitation is the size of the gene panels used in many of these assays. A lot of current urine-based tests are built on very narrow panels. That means sensitivity can vary widely depending on tumor type.

For example, some of the newer iterations claim improved sensitivity for bladder cancer. But for other GU malignancies, such as kidney or adrenal tumors, sensitivity remains relatively low.

Looking ahead, we'll likely need to expand these gene panels or incorporate additional biomarkers to improve test performance. Sensitivity, in particular, still poses a significant challenge.

Is the situation similar for epigenetic biomarker testing in GU pathology?

MA: It's definitely an evolving area. We're starting to see more

epigenetic markers identified – especially in bladder cancer – that appear to have predictive value. The field is growing, and I expect these assays to become more widely adopted in clinical practice.

In our institution, when oncologists request epigenetic or molecular testing, those orders typically come through pathology. As Ming mentioned earlier, we've set up a system to ensure appropriate tissue handling – verifying tumor content, confirming availability of adjacent normal tissue when required, and meeting all the pre-analytical criteria specific to each test.

Once results are received, they're routed back to us. We log them into our laboratory information system, append them as addenda to the original pathology report, and ensure they're integrated into the patient's electronic health record. That feedback loop is important – it helps us understand how these tests are being used and whether they're delivering value for patient care.

This applies not only to epigenetic markers, but also to NGS more broadly – for example, in urothelial tumors. These baseline assays are often done before patients begin neoadjuvant chemotherapy. Since the tissue is routed through us, we retain some level of oversight – unlike with liquid biopsy, which typically happens in outpatient clinics and bypasses pathology altogether.

That said, I don't have much direct experience with clinical epigenetic testing. We do have a strong research lab that works with methylation markers, but the clinical use in our setting is still limited. There are commercially available tests out there, but uptake is variable.

MZ: I recently had a question from a sales representative about orders of their assay – an epigenetic test used for patients with persistently elevated PSA but negative prostate biopsies. The idea is to help assess cancer risk in these ambiguous cases.

The rep emailed me asking why orders from our institution had dropped significantly. They wanted to know if we'd stopped using the test altogether. So I asked our urologists – and the answer was simple: they've started using other tests that they believe offer better performance or clinical value.

That really highlights the competitive and shifting landscape in this space. There are multiple assays available, and no one test has a permanent hold on the market. Clinicians will move on if they find alternatives they trust more, or that offer better validation, ease of use, or reimbursement.

So yes, epigenetic testing has potential, but its clinical adoption is shaped by many dynamic factors – including test performance, provider preference, and market competition.

How do you view the broader landscape of biomarker and NGS testing in GU cancers – and the role of pathologists within it?

F-MD: Unfortunately, pathologists are often left out of the process. But we have to advocate for a more central role – particularly in specimen selection and quality control.

Let me give an example: with a proprietary assay for prostate cancer, commercial labs may request specific blocks – often the one with the highest Gleason score. But if that area is very small – say, less than 0.5 mm – it may not be a good sample for molecular testing, especially if it comes from a targeted biopsy.

Even if there's another block with a larger volume of Gleason scoring tumor, the lab may insist on the highest-grade specimen. That often leads to test failures and repeated attempts. As pathologists, we understand which block is most appropriate. We're better positioned than commercial labs to select the right specimen – and that's where our expertise must be recognized.

AP: This is a global issue – not just a GU pathology problem. Biomarker and NGS testing are facing similar challenges across tumor types.

Imagine taking your car to the shop for a broken fuse, and the mechanic tells you the only solution is to replace the entire engine. That's what's happening right now in molecular testing. These broad panels are being marketed directly to oncologists, with minimal involvement from the pathology teams.

Companies are attending oncology meetings to promote these tests. They're even starting to show up at pathology conferences – but their marketing is still largely directed at oncologists.

Every test report comes back with 500 or 600 genes analyzed, and the result is a 30-page document. No one has time to fully interpret it. And often, the clinical question is very specific – say, FGFR3 mutation status. That's all the oncologist or urologist wants to know. But the report doesn't answer that in a straightforward way. Instead, it creates noise and redundancy.

Sometimes, the same broad panel is ordered again, for the same patient, at another institution. What we need is better collaboration between oncologists, urologists, and GU pathologists. This isn't just true for GU – it applies in GI pathology, lung pathology, and elsewhere.

The difference is that in lung cancer, melanoma, and colorectal cancer, there are clearer testing guidelines. GU feels like the "orphan child" of molecular testing. We lack both harmonized protocols and a coordinated multidisciplinary approach.

MA: I completely agree. As Anil pointed out, the fundamental issue in GU is that the field is still evolving. The data we have now are mostly from ongoing or early-phase clinical trials. It's not mature enough to draw firm conclusions.

That makes it hard to say, "This specific gene reliably predicts survival" or "This mutation correlates with recurrence-free survival." Until that evidence base matures, we can't identify the most clinically meaningful alterations the way we can in lung cancer, for example.

Bladder cancer adds another layer of complexity. Intertumoral heterogeneity is a major issue – different areas of the same tumor may have very different molecular profiles. And we also have multiple competing molecular classification systems. It's a very fragmented space.

So yes, it's all still in development. To move forward, we need two things: first, clearer data on which alterations truly affect outcomes like survival or recurrence; and second, testing strategies that are tailored to those validated targets. Until then, GU molecular pathology remains a moving target.

What needs to change in order to improve the molecular testing workflow?

MZ: We need more involvement from pathology. That's the starting point. But it's not just about individuals – it has to happen at the hospital policy and regulatory level as well.

Anil, as a department chair, will appreciate that institutions should have clear policies that designate pathologists as stewards of all tissue- and fluid-based molecular testing. Regardless of who orders the test, the process should require pathologist oversight.

That means before any specimen is sent to an outside lab for testing, it should go through pathology. And once the results come back, they should return to pathology, be incorporated into our laboratory information system LIS, and be integrated into the final pathology report. That kind of structured workflow ensures both accountability and clinical relevance.

AP: I completely agree. But the reality is – it's easier said than done. We already discussed the marketing strategies for commercial tests. These clinicians are being heavily influenced to order tests that may not even be clinically necessary or meaningful in the setting.

MZ: True – and we as pathologists also bear some responsibility.

In some cases, we've been hesitant to get involved because we feel we're not adequately trained. We say, "I wasn't trained to validate or interpret these tests," and so we step aside.

But I think that's a dangerous mindset. That reluctance creates a vacuum – and others step in to fill it.

AP: Exactly. This is just like what happened with earlier technologies – like PCR and even NGS itself. Initially, these methods weren't reimbursed. Mainstream pathology labs didn't want to invest in them. The infrastructure wasn't there, and the costs were high.

So what happened? Commercial entities moved in to fill that void. And now we're trying to reclaim the ground we gave up. Every time a new technology comes along – AI, NGS, liquid biopsy – you either take ownership of it, or someone else will. And if we don't, we can't really blame anyone but ourselves.

What can pathologists do to effect that change and ensure they have oversight of molecular testing?

AP: I think pathologists need to act on multiple fronts. It's not just about being involved in hospital-level test committees or engaging with C-suite leadership. We also need to be visible and active on the national stage – through our professional societies.

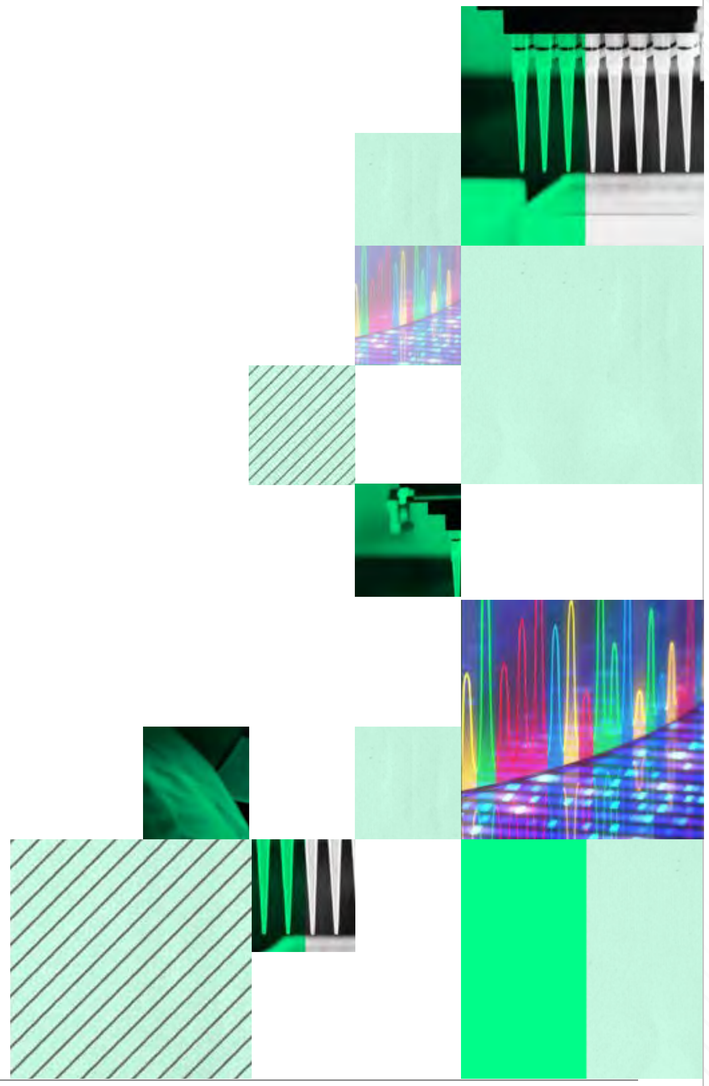
Within the GU pathology community, groups like the Genitourinary Pathology Society (GUPS), ISUP, CAP, and others should be issuing unified guidance. We need clear recommendations – best practices – for biomarker testing in GU cancers. Just as we've developed consensus guidelines for morphologic diagnosis, we now need to create structured frameworks for molecular testing.

If we don't step up, we'll continue to see a proliferation of companies offering redundant or unvalidated tests – like PTEN assays or FGFR3 panels – without any standardization. And once again, pathology will be sidelined.

This is an opportunity. We should be collaborating with our GU oncology colleagues and hospital stakeholders to ensure we're shaping the future of testing – not reacting to it. Every time I attend a tumor board or a biomarker advisory meeting, I advocate for this.

We, as pathologists, must assert control over which tests are ordered, how they're interpreted, and how results are integrated into clinical care. No one understands the morphology and features of diseases like prostate and bladder cancer better than we do.

If we want a seat at the table, we can't just complain about being excluded – we need to step forward, show leadership, and claim our role as stewards of molecular diagnostics.



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From Tissue to Treatment

Optimizing biomarker testing in prostate cancer

By Lynda Corrigan and Stephen Finn

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Prostate cancer is the most commonly diagnosed cancer in men in Europe, and precision oncology in this field is evolving rapidly (1). Yet more can and must be done to fully realize its potential, particularly in the uptake and implementation of biomarker testing across healthcare systems. Progress to date has relied on large-scale multidisciplinary collaboration and active patient engagement, both of which will remain critical as the field continues to advance.

For decades, standard management of advanced prostate cancer primarily relied on androgen deprivation therapy (2). The landscape is steadily shifting as insights into the clinical relevance of homologous recombination repair (HRR) and DNA damage repair (DRR) alterations create new opportunities and highlight the growing importance of understanding the genetic drivers of every individual's disease. For example, we now know that up to one in four patients with metastatic prostate cancer harbor HRR alterations, including BRCA1/2 mutations, among others (3–5). Establishing mutational status at diagnosis enables personalized care, informs prognosis, and guides management for patients most likely to benefit from targeted therapies.

From zero to 100…

This new era of precision medicine brings both promise and challenges that must be addressed to ensure patients can benefit from the treatment most likely to derive an improved outcome, at the optimal point in their disease trajectory. While progress in precision medicine is advancing, it is comparatively less well established in prostate cancer than other biomarker-driven solid tumors such as lung or breast cancer. Clinical infrastructure, laboratory capacity, and physician education are evolving to keep pace with the growing demand for biomarker testing.

Fragmented access across Europe calls for a strong local process

Clinical guidelines increasingly support the integration of molecular diagnostic testing to guide treatment decisions (6). However, Europe's diverse healthcare infrastructures, funding mechanisms, and regulatory environments create a fragmented system in which the uptake and availability of biomarker testing vary considerably by country and institution (7). More important than striving for complete standardization in testing practices across Europe, however, is the need for each local institution to establish a high standard of testing and a clearly defined testing pathway integrated into routine clinical practice.

Similarly, practical improvements in workflow can also make a significant impact. Many centers rely on manual paperwork and physical sample transfers, which may create bottlenecks and result in delays along the testing pathway. Digital test-ordering, streamlined test requesting, and standardized reporting systems can improve turnaround times from sample acquisition through to reporting of results, while also reducing administrative burden.

Rethinking timing and workflow

Perhaps the greatest technical barrier is tissue quality. Research shows failure rates of approximately 30 to 40 percent on tumor tissue testing in patients with metastatic castration resistant prostate cancer (8). This is mainly due to limited tissue availability after diagnostic histology, insufficient tumor content, and DNA degradation or poor DNA yield (9).

Improving outcomes requires rethinking not only how but also when testing is performed. Testing at the onset of metastatic disease rather than castrate resistance may provide higher-quality samples and reduce reliance on suboptimal archival tissue for those with de novo disease. This is more challenging for patients with recurrent disease, although earlier molecular testing in high-risk localized prostate cancer patients, such as those with Gleason 8 or higher-grade tumors, may become an area of interest.

A complete approach to biomarker testing also requires integration of both somatic and germline analyses, particularly for BRCA1/2 mutations where patients tend to have particularly poor outcomes (10). Effective precision medicine necessitates coordination between tumor molecular pathology and cancer genetics to ensure comprehensive patient management.

A further opportunity lies in how cases are discussed across multidisciplinary forums. In many cases, patients are presented at multidisciplinary team (MDT) meetings after test results have returned, but earlier discussion could optimize the pathway. For example, if pathologists and oncologists evaluate upfront whether available tissue is adequate for molecular analysis, they can anticipate challenges and plan alternative strategies before delays occur.

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"Every pathologist, regardless of subspecialty, must increasingly act as a molecular pathologist to some extent."

Similarly, molecular tumor boards (MTBs) play an increasingly important role in ensuring precision medicine delivers value in practice. Beyond interpreting complex genomic findings, MTBs can also systematically review failed tests, identify reasons for failure and recommend process improvements. Embedding a culture of continuous audit and feedback within these forums helps to optimize testing pathways, minimize repeat failures, and ultimately shorten the time to clinically actionable results.

These meetings, and proactive, open communication among all stakeholders in the care pathway are critical to institutional process enhancements that will benefit patients.

Pathologists at the center of precision oncology

In this often complex and evolving landscape, the role of the pathologist is more critical than ever. Every pathologist, regardless of subspecialty, must increasingly act as a molecular pathologist to some extent. This means understanding the requirements and limitations of molecular testing, the adequacy of tissue samples, and the impact of their initial diagnostic decisions on downstream analyses.

Greater education and training around molecular techniques, tissue selection, and sample preservation are essential. A biopsy that is adequate for histological diagnosis may not always meet the needs of genomic testing. By embedding molecular considerations into routine diagnostic workflows, pathologists can help ensure that patients are not disadvantaged later in the pathway by insufficient or degraded material.

Emerging approaches and future directions

Liquid biopsy, specifically analysis of circulating tumor DNA (ctDNA), is poised to play an increasingly important role in the prostate cancer clinical pathway, offering a minimally invasive method to capture tumor genetic information (11). Concurrently, genomic classifier scores, such as the Decipher Prostate Test, and artificial intelligence platforms that integrate histopathology with clinical factors are beginning to refine prognostic assessment and further guide personalized treatment strategies (12,13). While promising, these approaches have their own limitations and require validation and considered integration into clinical workflows to ensure reliability and utility.

If we aim for precision medicine to truly benefit people living with prostate cancer, it is our responsibility as clinicians to better understand the underlying tumor biology and effectively integrate biomarker testing seamlessly into routine care. We must call for continued learning and education, clearly defined institutional processes and pathways, a commitment to timely turnaround and multidisciplinary alignment. We should also support informed patient decision-making, by providing information around targeted treatment options and associated biomarker testing.

As medical practitioners, we will always face hurdles or barriers, but we must continue to proactively advocate for and drive the change necessary to ensure that every patient has access to the right treatment. Only then can patients across diverse healthcare settings fully benefit from this new era of precision oncology innovation.

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Harnessing the Power of Urine Biomarkers

DNA methylation testing could address unmet needs in bladder cancer surveillance

By João Lobo

Bladder cancer currently represents the second most common urological malignancy after prostate cancer, and incidence is expected to increase in the coming decades. While a subset of patients already presents with advanced muscle-invasive bladder cancer, the vast majority are diagnosed with non-muscle-invasive bladder cancer (NMIBC).

The natural history of NMIBC, with frequent recurrences over a long period of time, typically requires repeated follow-up visits for cystoscopic assessment, making bladder cancer one of the most expensive cancers to treat.

The approach to surveillance of NMIBC, in particular, is quite challenging. For many decades, diagnosis and monitoring has relied on two major pillars: cystoscopy and urine cytology.

Unmet needs

Despite technological improvements cystoscopy still misses or misinterprets a significant number of urothelial lesions. Moreover, as an invasive procedure it adds to patient morbidity.

As for urine cytology, and notwithstanding high specificity for detecting high-grade urothelial cancers, its sensitivity is relatively low, missing a significant number of clinically-relevant tumors. Moreover, the reporting system is focused on identifying high-grade cancers and does not reliably detect low-grade lesions, which may still require treatment.

Interobserver agreement also remains a concern, and the use of grey zone categories such as "atypical urothelial cells" is challenging to translate into clinical action, since it may represent a vast array of histology results – from benign lesions to high grade urothelial cancer.

Finally, urothelial carcinoma has a tendency for multifocality, and diagnosing an upper tract lesion in voided urine samples can be challenging, since cells are more often degenerated.

Given the limitations of both cystoscopy and cytology, there is an urgent need for more accurate means of diagnosing and monitoring NMIBC patients. Less invasive, more personalized, and more cost-effective tests are required, ultimately leading to better risk stratification, optimal treatment selection, and improved patient outcomes.

Urine: the promising biofluid

Taking advantage of its intimate contact with the urothelium lining of the bladder (and upper urinary tract), urine represents a logical and promising biofluid, carrying valuable diagnostic information about each patient's bladder cancer at a specific time

point. This makes urine the most useful source of liquid biopsy biomarkers for diagnosing and monitoring NMIBC patients. Among the several analytes within a liquid biopsy sample, aberrations in DNA methylation of tumor DNA – including circulating tumor DNA – are particularly attractive. Silencing of gene expression (namely of tumor suppressor genes) through promoter methylation is part of the epigenetic mechanisms facilitating tumor initiation and progression. Such epigenetic changes occur early, frequently preceding morphological changes that draw clinical attention. This places DNA methylation-based tests as optimal candidates for screening or early diagnosis of cancer, as well as for non-invasive detection of minimal residual disease during follow-up.

One PCR-based assay – that detects aberrations in the DNA methylation pattern of a panel of 15 biomarkers – has a CE-IVD mark and is approved for clinical use by the FDA for non-invasive monitoring of NMIBC patients. The test is convenient and non-invasive (using voided urine samples), requiring a low amount of DNA. Strengths of the workflow include same-day results, standardization of protocol and workflow, and automatic software analysis.

Alongside a quantitative score, the test offers a qualitative result denoting high or low probability of bladder cancer, facilitating clinical decision making. Validation studies show an overall sensitivity and specificity of 74 percent and 84 percent, respectively, or 91 percent and 81 percent for high grade urothelial cancers. What's more, recent reports have also demonstrated the test's ability to detect upper tract urothelial cancers.

Follow-up testing

Although cystoscopy cannot be completely replaced, the high negative predictive value – 98 percent for high grade urothelial cancers – of the DNA methylation test makes it a useful complement to the follow-up of bladder cancer patients, working as a "rule-out test". Results in several centers have validated the strategy of alternating cystoscopy with DNA methylation testing, which led to a decrease in the frequency of cystoscopies, thereby reducing patient burden and boosting cost-effectiveness.

Moreover, studies have shown that patients with positive DNA methylation results have a higher risk of recurrence during follow-up, even before a cystoscopic change can be detected. This anticipatory positive result can help guide the selection of patients for more intense follow-up regimens. Further studies are required to assess the performance of the test in additional indications and diverse populations.

DNA methylation testing in practice

In conclusion, DNA methylation testing constitutes a promising route to precision medicine for NMIBC. And what about the role of pathologists in this odyssey? Pathologists are at the core of precision medicine, having a critical role in the implementation and reporting of any biomarker test. The laboratory's input to liquid biopsy processing, pre-analytical variables, laboratory workflow, biobanking, and quality control is crucial.

At our Department of Pathology of the Portuguese Oncology Institute of Porto, we have implemented NMIBC DNA methylation testing since January 2025. The pipeline is entirely performed at the Molecular Pathology lab, which received certification for performing this test. This requires a multidisciplinary team of fully trained professionals, careful planning and organization, and constant communication with the urology clinic.

Liquid biopsy biomarker tests are moving towards clinical implementation and changing the paradigm – offering the power of precision oncology information in a non-invasive way. The field of bladder cancer is no exception, where harnessing the power of urine biomarkers may make the difference in personalized patient management.

Precision Prostate Cancer Management

Gene fusion rearrangements point to emerging biomarkers and therapeutic opportunities

By Nallasivam Palanisamy

Prostate cancer is a highly heterogeneous disease, with some tumors growing slowly and others progressing rapidly to metastatic, castration-resistant stages. This presents an urgent need for continued stratification of prostate cancers into biologically and clinically relevant subgroups that can inform prognosis and treatment strategies.

The identification of gene fusions formed due to chromosome rearrangements has provided critical insights into prostate cancer biology and helped shape molecular subclassifications. The most common of these are the ETS family of gene fusions, occurring in approximately 50 percent of cases.

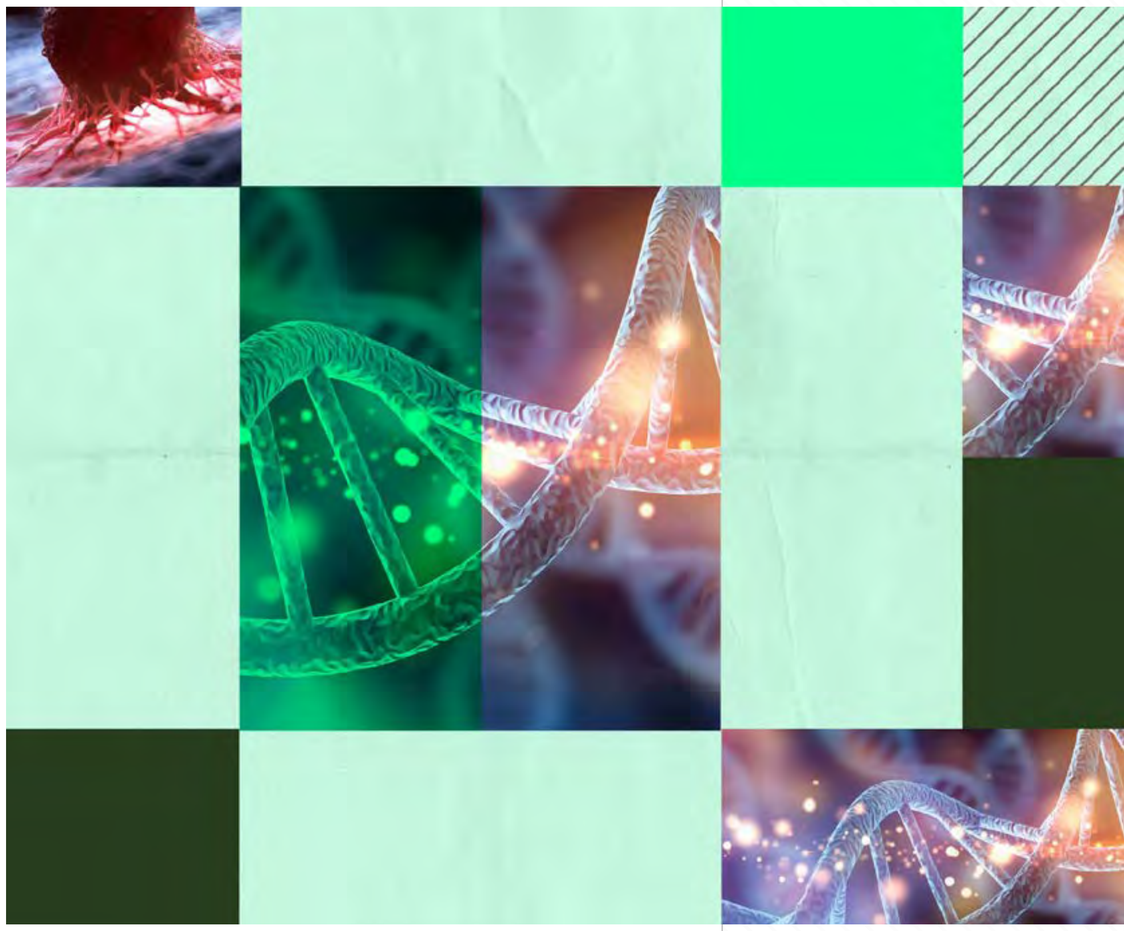
More recently, advances in high-throughput sequencing have uncovered rare but targetable non-ETS gene fusions, including those involving RAF kinases and pseudogenes. In particular, the discovery of fusions such as SLC45A3-BRAF, ESRP1-RAF1, and KLK4-KLKP1 has expanded the spectrum of oncogenic drivers and illuminated novel opportunities for precision medicine in prostate cancer.

In parallel with these discoveries, the Cancer Genome Atlas and other large-scale sequencing efforts have led to the development of a comprehensive molecular taxonomy for prostate cancer. This classification is primarily based on genomic alterations and includes ETS-positive and ETS-negative subtypes.

Let's take a closer look at the targetable non-ETS gene fusions and their potential as prostate cancer biomarkers.

RAF kinase fusions as therapeutic targets

Researchers investigating transcriptome sequencing of ETS-negative prostate tumors identified two novel gene fusions involving RAF kinases: SLC45A3-BRAF and ESRP1-RAF1. While RAF kinases are well known as drivers of other malignancies, these particular fusions represent a paradigm shift in our understanding of oncogenic drivers in prostate cancer.



Studies show that expression of these particular fusions in prostate cells leads to malignant transformation, increased cell proliferation and survival, and sensitivity to RAF and MEK (MAP2K1) inhibitors. Hence, these results point to the oncogenic potential of RAF pathway activation in prostate cancer and suggest there may be a subset of patients who could benefit from targeted therapies.

Though rare – implicated in less than one percent of prostate cancers – RAF fusions are more prevalent in advanced or therapy-resistant tumors. Their identification supports a broader trend seen in other cancers, such as melanoma and gastric cancer, where RAF fusions both drive disease and predict response to targeted inhibitors.

The pseudogene-associated fusion with biomarker potential

KLK4-KLKP1 is a fusion between the protein-coding KLK4 gene and the non-coding pseudogene KLKP1 – both members of the kallikrein family. This fusion was discovered via transcriptome screening using next-generation sequencing of over 650 prostate cancer samples.

This aberration may be detected in around 32 percent of prostate cancer patients. In a US study, it occurred more frequently in Caucasian than African American patients. In vitro and in vivo studies show that KLK4-KLKP1 enhances cell proliferation, invasion, and migration, as well as intravasation and tumorigenesis.

Importantly, this gene fusion is detectable in urine samples, indicating its potential as a non-invasive biomarker. Given its association with lower PSA levels and younger age at diagnosis – typically less than 50 years of age – it may serve as a screening and early detection tool, especially in ETS-positive patients.

Implications for precision oncology

The identification of rare but actionable gene fusions in prostate cancer demonstrates the importance of comprehensive molecular profiling. These findings have profound implications for the future of precision oncology:

- Diagnostic stratification: KLK4-KLKP1 and RAF fusions can help refine molecular subtypes and predict clinical outcomes
- Therapeutic targeting: RAF fusion–positive tumors may benefit from MEK or RAF inhibitors, expanding treatment options beyond androgen deprivation.
- Noninvasive monitoring: Urine-based detection of KLK4-KLKP1 provides a promising avenue for screening and monitoring disease recurrence.

Looking forward, integration of transcriptomic data into clinical workflows will be essential for identifying patients who can benefit from personalized therapies and for uncovering new therapeutic targets in molecular disease subtypes.

We should expect future research to continue to focus on comprehensive transcriptomic analyses, particularly in ETS-negative and treatment-resistant tumors, to uncover additional rare drivers. These efforts will be critical in ushering in an era of personalized therapy for prostate cancer patients, guided by the unique molecular fingerprint of their disease.

Careers Uncovered: Genitourinary Pathology

Swati Bhardwaj, Genitourinary Pathologist at the Johns Hopkins Hospital, Baltimore, Maryland, details her lengthy pathology training and the importance of continued education

Tell us about your career path so far

I'm an international medical graduate from India. After completing medical school in Delhi, I then did a three-year pathology residency there. It was similar to a combined anatomic and clinical pathology program in the US, but with a stronger focus on anatomic pathology.

Toward the end of my residency, I started reading international research papers and realized how much more could be done with better resources. That inspired me to pursue further training

in the US. After completing my step exams, I started over and completed an anatomic and clinical pathology residency at the Icahn School of Medicine at Mount Sinai in New York.

Having prior residency experience gave me a head start and allowed me to get more involved with the pathology community. I served as chief resident, chaired the College of American Pathologists (CAP) Residents Forum, and am now the immediate past chair. I'm also active on a few CAP committees and had the opportunity to serve on the CAP Board.

I was always interested in surgical pathology, but during residency, I became especially passionate about genitourinary and gynecologic pathology. I worked closely with excellent mentors and collaborated with urologists, which gave me a broader clinical perspective.

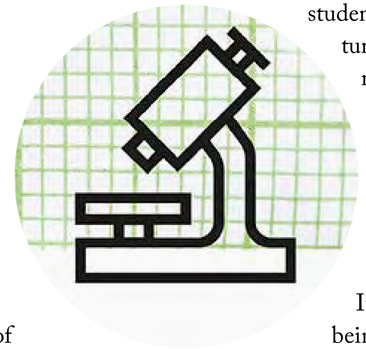
I'm currently a PGY-5 fellow in genitourinary pathology at Johns Hopkins and will be completing a gynecologic pathology fellowship next year. Although doing two fellowships is less common today, I genuinely love both fields. There's overlap between genitourinary and gynecologic pathology, and growing interest in molecular pathology in both, which gives me exciting opportunities to explore further.

What's your favorite aspect of your work?

One of my favorite parts of being a pathologist is that it combines both science and medicine. It's not just about diagnosing diseases – it also gives me the opportunity to contribute to patient care, conduct research, and teach. Education is something I really enjoy.

It's exciting to be able to teach the next generation, even while still learning during residency. As they say, knowledge is the only thing that grows when you share it.

What's the hardest part about what you do?



Recently, a friend of mine – also in medicine – joked that it was a rare change when a pathologist gave a benign diagnosis. That really stayed with me, because one of the hardest parts of my work is dealing with bad news.

Even though we don't deliver diagnoses directly to patients, it's still difficult knowing that most of the genitourinary and gynecologic specimens I handle involve cancer. It can be heartbreaking to see how widespread disease can be.

However, the positive side is that our work gives us opportunities to study these diseases more deeply, discover new biomarkers, and potentially identify new targets for treatment.

Tell us about a memorable experience in your career so far.

One moment that stands out is from when I was a medical student choosing pathology as a career. I attended a tumor board meeting with oncologists, surgeons, radiologists, and a pathologist. During the meeting, they discussed a case of carcinoma of unknown primary – no one knew what was going on. Then the pathologist spoke up, identified the primary site, and recommended a treatment option based on a specific marker.

It was incredibly impressive. I often describe it as being like a general directing an army in the fight against cancer – knowing exactly where and how to strike. That moment helped solidify my decision to pursue pathology.

On a day-to-day basis, one case I'll never forget involved a kidney tumor in a man in his 50s or 60s. Based on the tumor's appearance, we suspected Birt-Hogg-Dubé syndrome. Further testing confirmed it, and because of that diagnosis, we were able to inform the family and recommend genetic screening.

That experience reminded me how a single pathology case can impact not just one patient, but an entire family – and sometimes even broader patient populations. It motivates me to approach every case with the bigger picture in mind.

What's one thing you'd like people to know about what you do?

I want people to understand that pathologists aren't just reading books or slides. Diagnosing is complex and challenging, and our work requires deep clinical involvement. We play a critical role in patient care, and our impact is much greater than people often realize.

How would you describe pathology in five words or less?

The backbone of medicine.

Navigating the Morphology, Biology, and Clinical Impact Triangle

Sitting Down With… Arno van Leenders, Professor of Urological Pathology, Erasmus MC, Rotterdamn

How did you find your way to pathology?

At school I was interested in sciences that challenged analytical thinking – mathematics, physics, chemistry, and astronomy. I also liked biology, but as an analytical tool to understand how the human body works, what can go wrong, and what we can infer about disease from that knowledge.

When it came to higher education, I initially considered mathematics. But, uncertain where that path could take me, I eventually opted for medicine because the career options were better defined.

It was not until my second year of studies that I was introduced to pathology. I was immediately fascinated by the beauty of the colors, structures, and patterns I saw under the microscope. My analytical brain immediately began looking for the differences between normal and abnormal tissue.

Later in my studies I took the opportunity of a three-month pathology placement at the University of Budapest. That confirmed my interest and, after graduating, I went on to do a Phd in prostate cancer that combined pathology, urology, and basic science.

Even now, when I look into the microscope, I compare it to walking through the Louvre or a flower garden – and I'm actually paid to do it!

How would you summarize your contribution to the field of genitourinary pathology?

My research on prostate cancer has focused on understanding the tumor on the basis of what we can see under the microscope combined with what we can determine about its molecular biology, and what that means for the patient. It's that triangle of morphology, biology, and clinical impact that really fascinates me.

Some people have the perception that pathologists have no direct impact on clinical care. But, personally, I don't agree with that at all. The work of my group has resulted in changes to the guidelines for treatment thresholds in patients. Because of our research, a population of men with prostate cancer, who previously would have been automatically operated on, are now put on active surveillance instead. That has a major impact on their quality of life.

How did your role as director of the pathology residency program at Erasmus MC shape your views on medical education?

I found it fascinating, and really quite inspiring, to work with young people at the start of their careers. And I saw that a lecturer's own enthusiasm and passion for their subject is crucial in inspiring the next generation of practitioners. I find pathology fascinating, and I love talking about it, so I hope I was a good role model.

But I also learned that, to be a good role model, it's important for your students to understand that your way of doing things is only one way, and is not necessarily the gold standard; somebody else might do it differently. In that way, students can look at processes or research more critically and learn to think, "How would I do it better?"

Nowadays, my involvement in education is in organizing training events such as workshops, courses, and consensus meetings for international societies. The challenge now is to really understand my audience and their needs. Two presentations with the same title, delivered to audiences of pathologists or urologists, would look completely different and have very different key messages. I really enjoy putting them together.

What have you learnt from working with the Erasmus MC Tissue Bank?

Whilst we are very lucky to have access to an incredible tissue bank here, I would like to see it do more than just store paraffin blocks or frozen sections. The real value will come when we can connect the tissues with the patients, to show the patient information, the clinical follow-up, maybe even the molecular analysis that was performed, and what it showed.

It will be quite challenging to capture all these data together, but, when we do, the bank will become a goldmine. It will allow pathologists and oncologists to start connecting things we might never have thought of.

What is the most interesting thing you've learned in your career?

That came about in the last few years with the advent of spatial imaging. Until then, I had only ever seen cancer in two dimensions, on a glass slide. But these new imaging techniques have allowed us to see the three-dimensional structures of normal prostate glands, compare them to cancerous glands, and examine the growth patterns.

Finally seeing the three-dimensional background of this disease I've been studying for over 20 years was one of the most fascinating learnings of my career.

What are the biggest challenges currently facing pathology, in your opinion?

Detailed knowledge of one area is so important for prognostic work and a deep understanding of the treatment options. It's demanded by clinicians and patients, and is very impactful in terms of patient outcomes. Since the number of pathologists is limited, the challenge will be balancing in-depth knowledge with guaranteed coverage of all subspecialties.

What innovations in diagnostics are you most excited about?

Genitourinary cancer is behind lung and breast cancer in terms of precision medicine. I'm excited about seeing an acceleration of companion diagnostics for bladder and prostate cancer in the next few years, as more and more molecular therapeutic targets are discovered.

The problem is that molecular tests are very expensive. But the more we can connect molecular aberrations with tumor morphology, the more likely we will be able to predict a patient's likelihood of having a particular oncogenic driver mutation from the biopsy, and reduce the number of molecular tests required.

What advice would you give to someone starting out on their pathology career?

Mainly just to enjoy it – enjoy looking at the fascinating colors and structures and solving the puzzles.

And try to forge your experience across the whole broad field of pathology in those early years. You will have plenty of time to specialize later on, if you choose.

Precision Medicine is Key to the Future of Sustainable Healthcare

Unlocking better outcomes through collaboration and biomarker-driven precision medicine.

Precision Medicine has the power to change the lives of those affected by cancer. Collaboration is critical to evolve biomarker-driven approaches and enable timely, accurate identification of those who may benefit from a targeted treatment.

Hear more from Eva Comperat, MD, PhD, Professor, Chair of Uropathology at the Medical University of Vienna , who shared her perspective at the European Congress of Pathology: [Link to Eva's Video]

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