# Interviews

EMJ is delighted to introduce two key opinion leaders, Axel Heidenreich from the University of Cologne, Germany, and Marcus Drake, Imperial College London, UK, who discuss two dynamic areas of urology. Axel Heidenreich unpacks the role of precision medicine in prostate cancer treatment, whilst Marcus Drake explores the complexities of neurological urology and the future of neuromodulation therapies.

**Axel Heidenreich**

Professor and Director,
Department of Urology,
University of Cologne, Germany

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**Q1** **After your medical studies at the Johannes Gutenberg University of Mainz, Germany, and the University of Texas Health Science Center, USA, was there a specific moment, or aspect of urology, that drew you to this field?**

Yes, definitely. It was before I did my last year of medical school in San Antonio, when I had already started a doctoral thesis in urology. At that time, it was an experimental thesis, so I had to do a lot of micro-surgical surgeries in rats to perform what we call a portocaval anastomosis. Due to this portocaval anastomosis, the animals developed renal stones, so my task was to develop a stone model, to create a model to treat patients with urolithiasis, and how to prevent urolithiasis.

I thought that if you're doing this type of doctoral thesis in urology, you have to go into this field to do some practical work in urology. I started at the Department of Urology in Mainz, Germany, which was at that time the largest urology department in Europe. You get exposed to numerous, very large, and complicated surgeries in oncology, reconstructive urology, and also paediatric urology. So, I thought, this is my field, this is what I want to go into. Then I started my last year in medical school in San Antonio, where I also rotated into Urology, and once I had finished medical school, I went into Urology.

**Q2** **Given the impressive sensitivity and specificity results of the AI tool in detecting prostate cancer in biopsy samples in the recent paper you co-authored entitled 'An international multi-institutional validation study of the algorithm for prostate cancer detection and Gleason grading', what do you think are the main challenges and potential implications on patient experience of integrating this AI classifier into routine clinical workflows?**

The challenge would be to validate this type of AI usage throughout all pathology departments, worldwide. Right now, it is essentially a single centre, single pathology study. The challenge is also to transfer this type of technology to other departments

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of urology and pathology, and to still obtain the same results with the same high specificity and sensitivity. I estimate that it will take maybe 1, 2, or 3 years to validate this type of process.

But then, if I have a look at some other types of AI we use, like radiomics in patients with testicular cancer, we have already validated this type of AI by external institutions, and we know that we can achieve this high sensitivity and specificity to predict significant cancer in those patient cohorts.

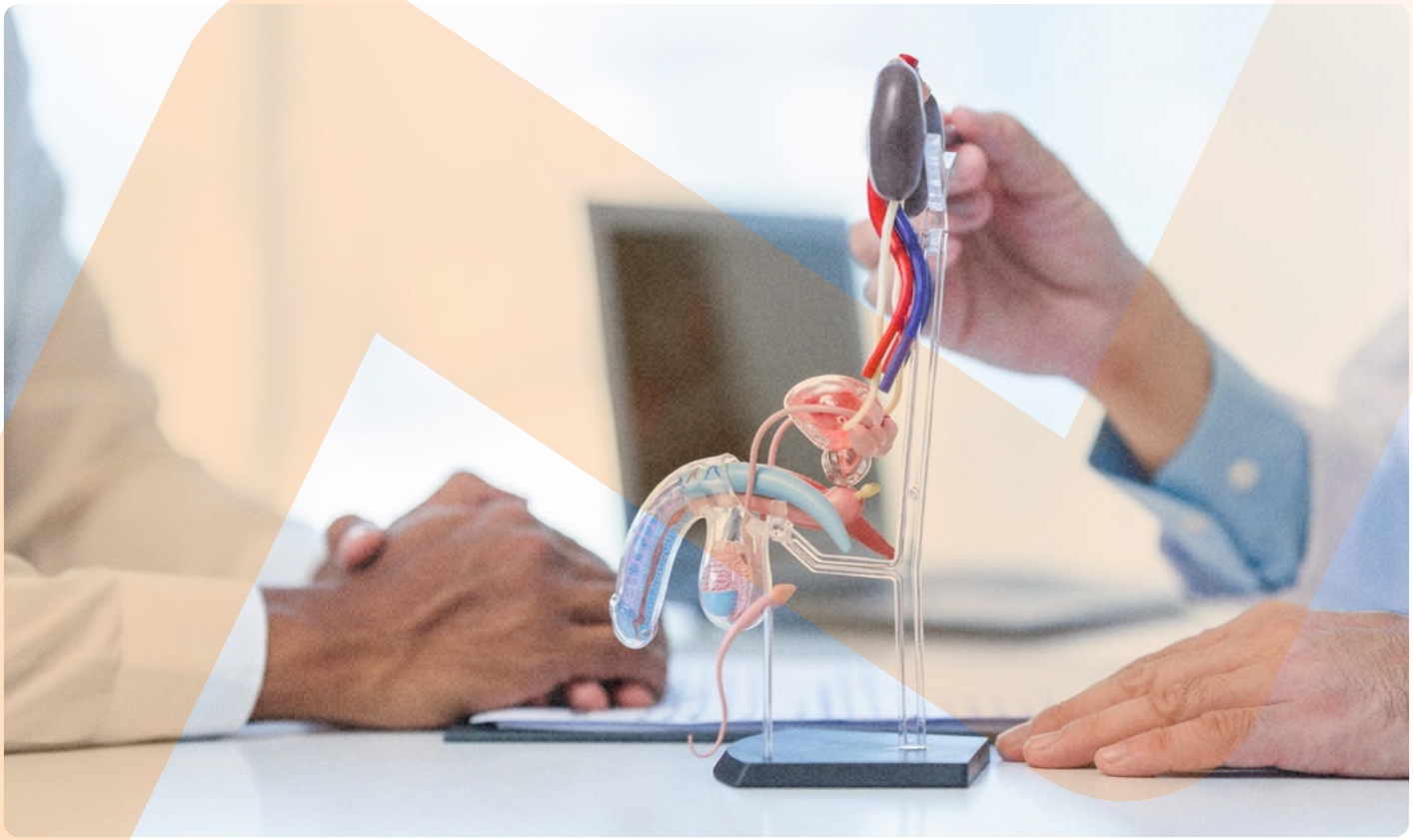
I think the same is true with prostate cancer, we will have or will achieve this widespread use within the next 2 or 3 years. For the patients, it will have significant implications because what we see is that whenever you have pathologists evaluating prostate biopsy samples, there is still a high number of variations in the correct diagnosis, meaning the correct Gleason score.

So, it's not only that you have to identify prostate cancer, but you also have to identify the biological aggressiveness of prostate cancer.

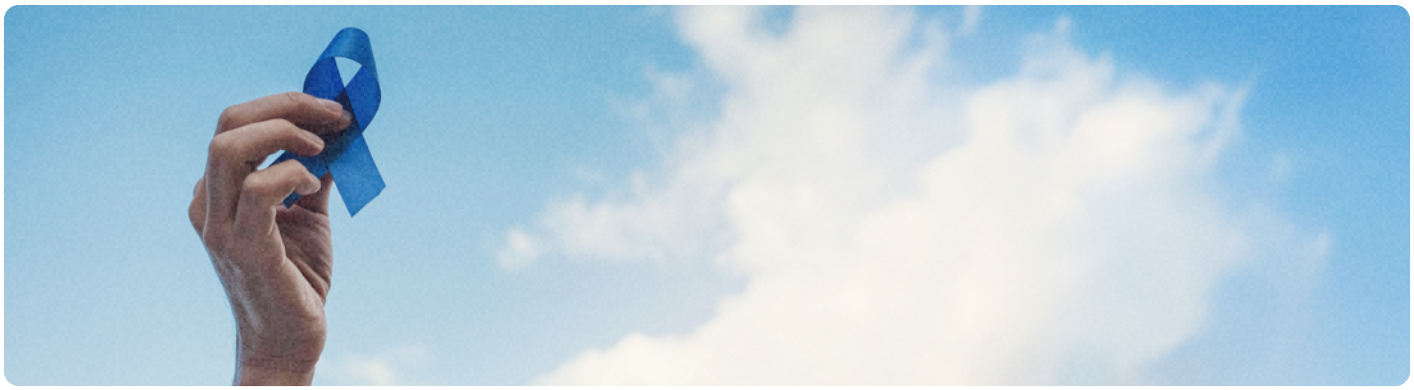
If a patient has low biological aggressiveness, they don't need any type of treatment, and they are followed by what we call active surveillance. If they have high-grade cancer, they need to undergo radical prostatectomy or radiation treatment with long-term hormonal therapy, and we see that there is a discordance between central pathology review and peripheral pathology diagnosis in about 30% of the patients. So, this type of AI probably makes it easier for the general pathologist to identify patients who have a high risk of progression and need active treatment, differentiating these patients from those who can just be followed by active surveillance.

**Q3 In the Phase II TRITON study, patients with *BRCA* and *PALB2* mutations showed strong responses to rucaparib, but responses were limited in those with particular mutations. Could you elaborate on why PARP inhibition is more effective for certain DNA damage repair gene alterations than others, and what the results of this trial suggest about the future of precision medicine in treating metastatic castration-resistant prostate cancer?**

That's very difficult because right now we don't have good evidence to explain why different mutations result in different responses to these types of PARP inhibitors. However, we know that, for example, we have several PARP inhibitors like rucaparib, olaparib, and niraparib, and they act differently depending on the type of mutations we see in these *HRD* genes.





It is not clear why there is a difference, but the TRITON study, as well as some of the other prospective randomised clinical studies, give us the evidence that we have to perform a whole mutational analysis of all *HRD* genes which are available on a molecular basis. Then, depending on the specific type of this mutation in DNA damage repair genes, you select the specific drug which will then give the most optimal treatment response to your patient. The drawback of the TRITON study is that rucaparib will only work in *BRCA1* and *2* mutations and the *PALB* mutations.

We have other studies on talazoparib, which also work in *ATM* mutations, for example. The bottom line is that we have to do a whole genomic sequence of all DNA damage repair genes. The other option is to include an analysis called an HRD score, which is the relative frequency of *HRD* mutations on the number of HRD genes that have been evaluated. If this score is above 50%, these patients will respond to PARP inhibitors.

This is a type of analysis already used for ovarian cancer. PARP inhibitors have been approved by the FDA and by the European authorities to be used in patients without a specific DNA-damage repair mutation but who have a high HRD score, and this is what we also use in clinical practice right now.

**Q4 In light of the findings from your real-world data study on 177Lu PSMA therapy, which identified prostate-specific antigen decrease after the first two cycles and ALP levels as potential predictive biomarkers, what do you see as the next steps for validating these markers in clinical practice to aid in treatment decision-making for patients with metastatic castration-resistant prostate cancer?**

What we already know, which has already been integrated into daily clinical routine, is that patients typically receive just two cycles, or if a patient is started on radioligand therapy, then it is six cycles, which is according to the VISION trial as well as other prospective randomised trials. However, it's important to note that not every single patient needs six cycles in a row, because some of them respond after two or three cycles, and some of them don't respond at all.

Evaluating patients after two cycles of treatment will give you the direction of further treatment. If a patient shows minimal PSA reduction after two cycles, it indicates that they are unlikely to respond to subsequent cycles, whether it's the third, fourth, or even the sixth. In such cases, you can stop radioligand treatment, and start thinking about other treatment options, like PARP inhibitors, second-line chemotherapy, and personalised treatment based on specific mutations. If a patient, however, responds very well after two cycles, for example, by PSA level decreasing by at least 80% or by demonstrating a significant objective response based on a PSMA PET CT scan, you could stop treatment after two cycles. You follow the patient and reintroduce another course of radioligand treatment in case of PSA or metastatic disease progression.

Having these two cycles as a threshold number of cycles to be delivered will give you the optimal strategy on who should continue, who could be interrupted, and in whom radioligand treatment should be stopped.

**Q5 In the COTRIMS trial, nerve-sparing retroperitoneal lymph node dissection (nsRPLND) showed high oncological efficacy with minimal morbidity for low-volume metastatic seminoma. Given these promising results, how do you see nsRPLND fitting into the standard treatment landscape for clinical Stage IIA/B seminoma?**

I think it will change the treatment landscape. Currently, most of the guidelines still recommend either chemotherapy or a combination of radiation therapy plus chemotherapy in patients who have clinical Stage IIA/B disease.

The problem is that chemotherapy and radiation treatment are highly effective, the cure rate in Stage 2A is in the range of about 95% and the cure rate in Stage 2B is in the range of 82–90%; however, the problem is that both of these established treatment options result in significant long-term toxicity.

Long-term toxicity means side effects that develop 30–40 years after treatment, and these could be cardiovascular disease, heart attacks, an apoplectic insult, metabolic disease, or secondary malignancies. We see that about 80% of patients who die after the treatment of testicular cancer, about 30–40 years after discontinuation of chemotherapy, have died not due to cancer but due to these long-term side effects.

Surgical therapy like RPLND, in our case, has a relapse rate of only about 10–15%, so 85–90% of patients are cured by surgery alone. This means that they will not develop long-term toxicity and that only about 10–15% of patients will need chemotherapy. So far, the American Urological Association and the National Comprehensive Cancer Network (NCCN) guidelines have integrated RPLND for Stage 2A and B disease with a maximum lymph node diameter of 3 cm as the current treatment approach of choice within the European guidelines. We are still discussing this approach, but most probably it will be integrated in 2025 as one of the standard options for the treatment of those patients.

**Q6 Do you think there is a possibility that nsRPLND could potentially replace or complement traditional chemotherapy or radiotherapy approaches, especially considering the goal of reducing long-term toxicities?**

My idea would be that nsRPLND could replace chemotherapy or radiation therapy in specific patients who have to be marker-negative, meaning that tumour markers in the serum have to be negative or only very, very slightly elevated. Patients should only undergo this type of surgery by an experienced surgeon, as relapse rates are likely to increase if the procedure is conducted by someone who performs only a few RPLNDs annually.

These types of surgeries need to be centralised. In Germany, for example, we perform about 100 procedures annually, which is half of all RPLNDs nationwide. Similarly, we also see that in some centres in the USA, such as those in Los Angeles, Indianapolis, and New York, about one-third of all RPLNDs are done in highly specialised centres. Relapse rates after RPLNDs in those specialised centres are around 10%, as we have published, compared to about 30–40% in not-so-experienced centres. So, this is a prerequisite, a good surgeon, good indication, marker negative, and then RPLND could replace chemotherapy or radiation therapy.

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**Q7 Looking to the future, what would you say are the most crucial areas for further research and clinical development to improve outcomes for patients with metastatic prostate and testicular cancers?**

When it comes to testicular cancer, we have two goals. What we do currently is de-intensify the treatment by the use of active surveillance in clinical Stage I disease, primary RPLND in marker negative clinical Stage IIA/B disease. We also have patients who already have widespread metastatic disease at the time of diagnosis, and we separate those patients, depending on the localisation of their metastatic disease and the concentration of the tumour markers in the serum, into those who have a good, intermediate, or poor prognosis. Right now, the treatment of choice in patients with good prognosis is with three cycles of the cytotoxic PEB-regime (cisplatin, etoposide, and bleomycin).

Most recent studies show that there is a proportion of patients with a good prognosis who will have a very high cure rate with three cycles of PEB. However, we also know that there are some patients who have highly elevated lactate dehydrogenase (LDH) levels in their blood and will need four cycles of treatment. We are just in the process of setting up a prospective randomised trial in those patients based on clinical and molecular markers. So, personalised treatment with very easily available markers like LDH or the biomarker miR371 in the serum would be the next goal. This approach aims to identify the high-risk population of patients with testicular cancer, those who will have a poor prognosis, and to intensify treatment, and de-intensify treatment in the rest of the patients whose prognosis and long-term outcome will be good.

We also have a cohort of patients who have chemorefractory testicular cancer, who have undergone one or two rounds of chemotherapy but continue to experience disease progression and develop new metastatic sites. We don't have very good treatment options for such cases. Currently what we do is perform complete next-generation sequencing, a very intensive molecular analysis of progressing metastatic sites to identify druggable mutations, similar to the approach used with PARP inhibitors in prostate cancer. These are the three areas in testicular cancer where I would expect most of the development within the next years.

With regard to prostate cancer, it is still very important to focus on early detection. It is necessary to develop a type of individualised screening strategy and to omit the unnecessary annual screening visits, and one approach involves assessing baseline PSA levels. Ideally, men should have their first PSA test around the age of 50 years, and if this PSA level is below 1.0 ng/mL, the probability of this specific person developing clinically significant prostate cancer within the next 20 years is minimal. So, in such cases, men should only need to visit a urologist every 4–8 years. However, we know if the PSA level is above 1.0 ng/mL, even if it's only 1.2 ng/mL, the risk of developing locally advanced disease, or metastatic disease, is increased 25-fold compared to those men with a PSA level less than 1.0 ng/mL. These patients need to undergo regular follow-ups every 1–2 years.

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depending on the multiparametric MRI to identify those patients who will need a so-called MRI fusion biopsy and those who can be followed independently of the PSA level. When it comes to treatment, we still treat too many patients who have been diagnosed with organ-confined disease. In Germany, we have a very high percentage of patients who have organ-confined disease, with prostate cancer of a very low biological aggressiveness. Most of these patients could be followed by active surveillance, as their 15-year overall and cancer-specific survival rates are 98%, even without treatment. This survival rate remains 98% with radical prostatectomy or radiation therapy, meaning most of these men will just be exposed to side effects, but not to an oncological benefit. Therefore, it’s crucial to educate urologists on the importance of adopting active surveillance for these patients.

On the other hand, you have patients with locally advanced disease, and we need to develop multi-modality treatments to increase the cure rate. This may involve not just radical prostatectomy or radiation therapy but a combination of specific treatment options to enhance the outcome of patients. When it comes to metastatic disease, it is more focused on the development of personalised, individual treatment decisions or treatment strategies depending on the molecular profile of patients with prostate cancer.