Revisiting Early Detection of Prostate Cancer

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LEADING experts gathered at the European Association of Urology (EAU) Congress 2025 to explore the rapidly evolving landscape of prostate cancer screening, calling for risk-adapted, evidence-based strategies amid rising global mortality. From updated EU recommendations to genetic profiling and MRI diagnostics, this important session showcased how 'smart' screening can improve early detection, reduce overtreatment, and address healthcare disparities.

NEW HORIZONS IN CANCER SCREENING

Opening the session, Harry de Koning, Erasmus University Medical Centre, Rotterdam, the Netherlands, cited the latest EU cancer screening recommendations from 2022,[1] which provide a key step towards improving early cancer detection throughout Europe. The goal was to increase participation in breast, cervical, and colorectal cancer screening programmes in those who qualify, and extend population-based screening programmes to lung and prostate cancer (PCa). He stressed that cancer screening is necessary to reduce socioeconomic health disparities.

In light of the surge in PCa mortality worldwide, Peter Albers, Heinrich-Heine-University, Düsseldorf, Germany, continued that "smart screening is the only way". Risk-adapted, organised screening for PCa, if started early, will likely detect all relevant cancers, and with personalised risk-stratified active surveillance, overtreatment can be avoided. Importantly, he added that baseline prostate-specific antigen (PSA) also works in low-income countries.

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GENETIC MARKERS FOR INITIAL RISK STRATIFICATION

Rosalind Eeles, Royal Marsden NHS Foundation Trust, London, UK, leader in the field of genetic susceptibility to PCa, reminded that audience that 20% of individuals in the general population will have a relative risk >2 for PCa. Genome-wide association studies have now identified a total of 451 single nucleotide polymorphisms (SNP) as genetic risk variants for PCa.[2] These common variants contribute to a large proportion of the genetic predisposition to prostate cancer (~44%), while rare germline variants, mostly found in DNA-repair genes, only account for 7%. The remaining 49% of genetic variation is still unknown: this is a significant pitfall for risk stratification.

On one hand, the National Comprehensive Cancer Network (NCCN) Guidelines recommend offering germline testing to men with high-risk localised PCa, metastatic PCa, or who met family history criteria. On the other hand, the European Society for Medical Oncology (ESMO) Guidelines recommend molecular testing for DNA-damage repair gene mutations in all patients with metastatic castration-resistant PCa, regardless of family history or disease burden. However, a negative result for somatic testing does not rule out germline variants, added Eeles. The European Guidelines for germline testing

in PCa recommend germline testing in men with multiple family members diagnosed with PCa <60 years of age or a family member who died from PCa. However, the UK National Testing Directory is slightly different, recommending germline testing for Ashkenazi Jewish ancestry or individuals with ≥1 grandparent from Whalsay, Shetland, as one in 43 have a *BRCA2* c.517-2A>G mutation.

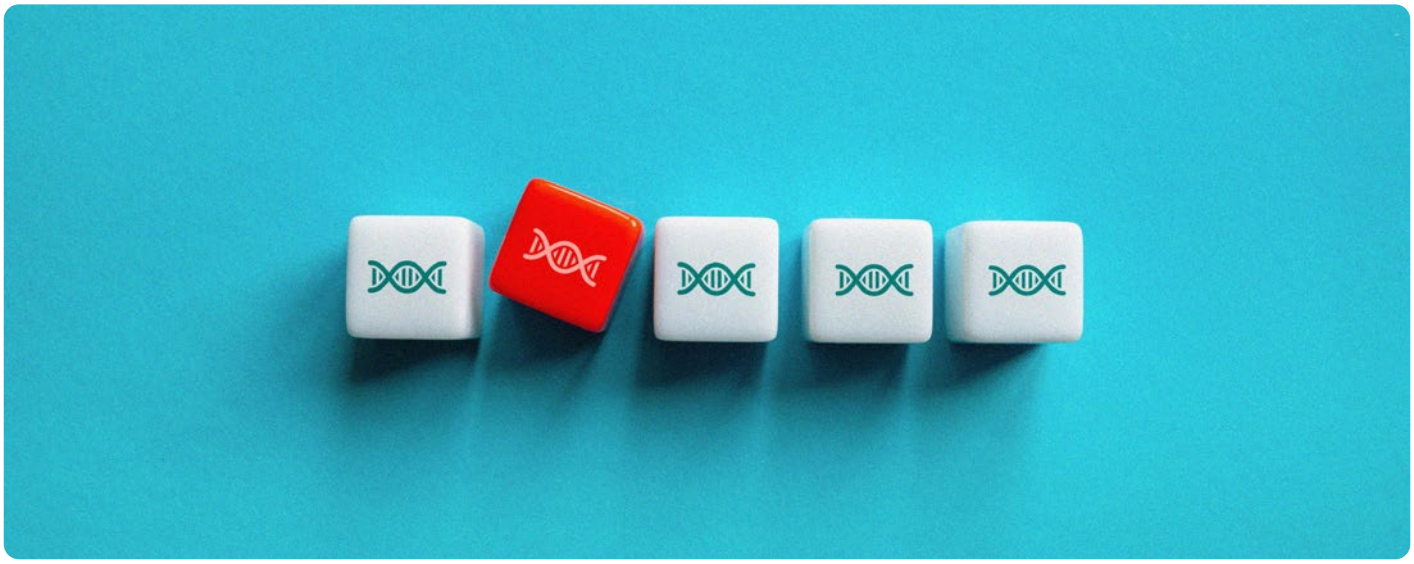
The difference in founder mutations across the world inevitably leads us to a second pitfall for risk stratification: guidelines may differ significantly depending on populations.

"So, which genes should we test for in a germline test?" asked Eeles. She recommended testing for 10 genes, with a blood test preferred over saliva test: DNA-repair genes *BRCA1, BRCA2, ATM, CHEK2,* and *PALB2*; mismatch repair genes *MSH2, MSH6, MLH1,* and *PMS2*; and the PCa-specific gene *HOXB13*, found at higher rates in Scandinavian populations. She added that not all mutations in the same gene are the same, and this is the next challenge. For instance, a truncation mutation in *ATM* has a higher odds ratio for PCa than a missense mutation, which also increases prostate cancer risk but to a lesser extent. Eeles added that another significant pitfall lies in variants of uncertain significance, which may be unrelated to the disease.

The IMPACT study,[3] spanning 65 centres and 20 countries, recently provided data on genetic markers for prostate cancer risk stratification. The study conducted annual targeted PSA screening for *BRCA 1/2* and Lynch syndrome mutation carriers, and findings led to the development of EAU guidelines for *BRCA2,* stating that annual PSA screening should be undertaken from age 40 years. Results also showed that certain gene mutations are associated with more aggressive disease, such as a 77% elevated risk in *BRCA2* carriers. Baseline data are currently being collected for Lynch syndrome mismatch repair genes *MSH2/6*. Eeles emphasised that targeted screening for individuals with monogenic higher-risk mutations is crucial to identify more PCa cases and target those with more aggressive disease.

With regards to common variants, the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL), a large global consortium, has looked at case-control studies of common PCa variations in over 200,000 individuals. Recent data shows that men of African ancestry have a two-fold greater lifetime risk for Pca compared to men of European ancestry, and reach this higher risk at an earlier age.[2] Eeles highlighted that more diversity is needed in PCa research to tailor risk profiles and screening strategies to different populations.

Moving on to implications for real-world screening, Eeles explained findings from the pivotal BARCODE 1 study,[4] which



assessed the feasibility of a community-based PCa screening programme based on polygenic risk scores (PRS). Saliva samples were collected from healthy males aged ≥55 years across 69 general practices in London, UK. PRS for PCa was calculated by genotyping 130 PCa risk SNPs, and men with PRS above the 90th percentile were invited for prostate MRI and biopsy. A total of 187 PCa cases were identified in this group, with a median age at diagnosis of 64 years, and median PSA at diagnosis of 2.1 ng/mL. A total of 55% of identified cancers had a Gleason score ≥3+4, and 21% needed radical treatment.[4] Eeles reinforced that genetic profiling is a valuable tool to risk-stratify populations, and BARCODE 1 suggests that PRS may be useful in population PCa screening programmes.

"We do have the technology, but the implementation needs cheaper tests and education about the promises and pitfalls of genetic markers," concluded Eeles. Trials incorporating genetic results will also be crucial for individualised care in PCa.

MRI: BEST PRACTICE FOR RISK STRATIFICATION

Veeru Kasivisvanathan, University College London, UK, reinforced the importance of MRI in the initial assessment of PCa. MRI can determine PCa risk and prognosis, guide biopsy decisions, direct targeted prostate biopsies, and determine treatment plans. The 2024 VISION study recently provided Level 1A evidence that a PCa diagnostic pathway with MRI is more favourable than one without.[5] "MRI signal through the PI-RADS score is one of the strongest predictors of significant cancer that we have today," said Kasivisvanathan.

He asked: "What do we do with a negative MRI: does this mean we can avoid a biopsy?" Data have shown that the negative predictive value of MRI in detecting clinically significant PCa is as high as 91%, meaning that it misses, on average, 9% of men with Gleason ≥3+4 PCa.[6] Furthermore, prostate volume obtained through MRI allows clinicians to calculate PSA density, and combining PI-RADS with PSA density can improve MRI performance, allowing men with negative MRI and low clinical risk to safely avoid biopsy. One of the most underappreciated aspects of MRI, continued Kasivisvanathan, is that it is a good predictor of the absence of significant cancer in the medium term, with 98–99% of patients free of Gleason ≥3+4 PCa within 3–5 years. He added that PSA surveillance in these patients is also recommended.

"What about a positive MRI: should we do a systematic biopsy?" continued Kasivisvanathan. He explained key findings from the multicentre MRI-FIRST study,[7] where men with clinical suspicion of PCa underwent an MRI. If the MRI was suspicious, they underwent targeted systematic biopsy; if it was not suspicious, they underwent a transrectal ultrasound biopsy. In this study, the addition of systematic biopsy increased the detection of Gleason ≥3+4 PCa by 5%, but showed no added benefit for the detection of higher-grade PCa (Gleason ≥4+3).[7] With perilesional biopsy gaining increased attention in the last 2 years, Kasivisvanathan cautioned that, while perilesional biopsy slightly increases detection of Gleason ≥3+4 PCa compared to targeted biopsy alone, taking more non-targeted biopsies also raises the risk of detecting more clinically insignificant cancer. He added that, for large PI-RADS 5 lesions, there is often limited value for additional biopsies.

EAU GUIDELINES ON PROSTATE CANCER: WHERE ARE WE GOING?

"We are aiming for timely detection of significant prostate cancer, while leaving insignificant prostate cancer undetected, and balancing diagnostic accuracy with the burden on an individual and healthcare provider," said Philip Cornford, Chair of EAU Prostate Cancer Guidelines Panel. However, is this achievable?

Current EAU guidelines on prostate cancer screening focus on stratified PSA testing, recommending the use of risk stratification

nomograms before considering MRI. For patients who benefit from MRI, MRI should then drive targeted, perilesional biopsies only, rather than systematic biopsies. PSA testing should always follow thorough counselling on its potential risk and benefits, and should be offered to all men at elevated risk of PCa: men >50 years, men >45 years with a family history of PCa and/or of African descent, and men >40 years carrying *BRCA2* mutations.

"We need to avoid the temptation to find all the cancer that is present," Cronford continued. Clinicians also need to be aware that MRI-targeted biopsies are associated with grade inflation. Citing recent data, he explained that post-screening radical prostatectomy was only associated with 0.2% mortality reduction at 15 years for patients with Grade Group 1 disease, and ≤5% mortality reduction for patients with Grade Group 2 with lower PSA and stage.[8] He reminded the audience that screening is important, but weighing patient benefits and risks should remain a priority to avoid overdiagnosis and overtreatment.

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