Prostate cancer molecular and genetic biomarkers

Biomarkers, imaging, and risk assessment tools continue to impact decision-making strategies

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The EAU Section of Urologists in Office (ESUO) held its inaugural meeting last year during the 32nd Annual European Association of Urology Congress (EAU17) in London. Here in Copenhagen for EAU18, the ESOU Section Meeting has "All about prostate biopsy in an office urology and outpatient setting" as its theme.

The ESUO's second meeting once again demonstrated the growing need for an office urology perspective, in particular in the office management of the ever-prevalent prostate cancer.

ESUO addresses the core issues that impact the work and interests of urologists who provide comprehensive out-patient care in their own office environment. As opposed to a hospital's out-patient department, office urologists single-handedly manage the full breadth of urological conditions on a daily basis, while collaborating closely with clinics on the one hand, and general practitioners on the other. ESUO aims to provide support to office urologists, particularly with regards to scientific, clinical and professional information related to their specialty.

All about prostate biopsy in an office urology and outpatient setting
The ESUO Section Meeting focused on practical office topics of biopsy and re-biopsy indications, the growing prostate cancer biomarker field, patient biopsy preparation, biopsy procedure, management of biopsy complications, the roles of TRUS and MRI biopsy guidance, as well as TRUS-MRI fusion biopsy.

It is impossible to overstate the relevance of these topics. Prostate biopsy is one of the most commonly performed office procedures in urology. Of the estimated 1.1 million men globally who are diagnosed with prostate cancer each year, about 225,000 are Europeans.

The last decades have seen a dramatic increase in prostate cancer incidence due to widespread PSA testing, increased male life expectancy, and an increase in the total number of men undergoing prostate biopsy. Prostate biopsy that is triggered solely by prostate-specific antigen (PSA) and digital rectal exam (DRE), carries the inherent risk of false-negative findings and leads to over-diagnosis of clinically indolent prostate cancer.

PSA has a positive predictive value for prostate cancer detection in the range of 25-40%, while it's use to trigger prostate biopsy leads to negative biopsies in 65-70% of men presenting with a PSA in the range of 4-10ng/ml. Moreover, we have witnessed a shift away from the sensitivity to diagnose all cancers to more advanced diagnostic methods that improve the specificity to the discovery of the aggressive, high-grade prostate cancers.

During this period, the reputation of PSA was transformed from an initial "great" biomarker to "good" due to low-specificity, to "bad" as a trigger for over-diagnosis and over-treatment, to supposedly "harmful," prompting the controversial US Preventive Services Task Force (USPSTF) recommendation against PSA screening in 2012. Five years later the USPSTF "scraped the congealed egg from its face with a dull knife" (quoting Prof. Benjamin Davies) and revised its position.

The current 2017 USPSTF guidelines recommend individualized screening of men aged 55-69, while conceding that screening does offer a small potential benefit of reducing the chance of dying from prostate cancer. The EAU Guidelines state: "Do not subject men to PSA testing without counselling them on the potential risks and benefits" (Level of Evidence 3, Recommendation Grade B), as well as "offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least 10 to 15 years" (Level of Evidence 3, Recommendation Grade B). The topic of prostate cancer screening (particularly with PSA and DRE as triggers for prostate biopsy) remains one of the most controversial topics in urology.

Crucial implications
The dramatic implications of the low specificity of PSA for prostate cancer has led to an explosion of research into to the development and validation of tools to facilitate patient risk stratification and, particularly, to better guide prostate biopsy decision. The aim is, frankly, to identify those men who truly harbor clinically significant disease, while leaving at peace those with disease that will never impact their life-expectancy, keeping away the biopsy needle.

With that said, it is crucial to remember that the vast majority of actual PSA testing occurs by order of the general practitioners in most countries. This is the elephant in the room when urologists discuss PSA screening.

Novel tools that may aid the urologist include molecular and genetic biomarkers, which augment the specificity of prostate biopsy for clinically significant disease. Likewise, multiparametric prostate magnetic resonance imaging (mpMRI) has allowed for the non-invasive image-guided risk identification of clinically significant prostate cancer, as well as targeting.

Multiparametric prostate MRI, alongside biomarkers, has an EAU Guidelines designated role in the post-negative biopsy setting, while the National Comprehensive Cancer Network (NCCN) guidelines have gone further – providing a recommendation for biomarker and mpMRI use in the pre-biopsy setting. Early use of biomarkers and mpMRI is inevitably the direction we are moving in.

During the ESUO meeting it was a privilege to discuss the dynamic topic of molecular and genetic biomarkers in the primary and secondary biopsy decision-making setting. At the dawn of the PSA-era, we are in the age of a growing need for liquid-biopsy biomarkers and risk stratification tools, for the non-invasive risk assessment of prostate-bearing men. By this time, we as urologists really need to know and use the available tools to avoid the pitfalls of PSA testing. At the same time, with so many options to choose from – high-quality clinical validation is key, although often scarce.

What's new and relevant in PCa biomarkers?
The EAU Guidelines recommendations have been well-defined and are readily available.

Blood-based biomarkers such as the 4K Score Test and prostate health index (PHI) have been recognized as the best studied. 4K Score has been shown to predict biopsy outcome more accurately than PSA and age alone, and with the addition of clinical information in the algorithm to have a solid diagnostic performance (AUC 0.82) in predicting clinically significant prostate cancer (Gleason Group Grade 4 and above) upon biopsy.

The past year has seen the publication of a large meta-analysis which has shown evidence of 4K Score superiority over PHI in 11 of 12 clinical validation studies comprising of a total of 11,134 men as well as an interesting publication demonstrating near-equal clinical validity of 4K Score with or without DRE. Another multi-center prospective trial was also concluded demonstrating validity in a population with a large proportion of African-American men, bringing the total number of men involved in the 4K Score validation to an impressive >22,000.

Prostate Cancer Gene 3 (PCA3) is the other established EAU Guidelines recommended (post-DRE urine-based) prostate cancer biomarker. However, results of studies on the role of PCA3 in predicting clinical-pathological features of prostate cancer (Gleason Score, tumour volume, stage, extraprostatic extension) have been disappointingly contradictory. The three-gene urinary-panel (HOXC6, DLX1, TDRD1) developed at the same Nijmegen (NL) laboratory as PCA3 forms the basis of SelectMDx, which also includes clinical data, and can be used accurately to identify patients with clinically significant prostate cancer (AUC 0.78).

SelectMDx and mpMRI
In the face of scarce head-to-head comparative biomarker studies, an interesting paper recently matched SelectMDx and mpMRI showing promising results regarding the correlation between the SelectMDx result and mpMRI standardized assessment. SelectMDx outperformed PSA and PCA3 to predict mpMRI outcome (AUA ROC 0.83 vs. 0.66 and 0.65, respectively), with SelectMDx scores being significantly higher in men with PI-RADS 4-5 lesions on mpMRI.

Unfortunately, promising tests such as the STHLM3 Model (Stockholm 3 model) and MiPS have availability limited in Europe and the USA, respectively. Their validation is also limited (as of this writing). Interestingly, STHLM3 is an example of a still evolving prostate cancer biomarker, the algorithm was recently updated by taking intact PSA out of the formula and including HOXB13 instead - contributing to an improvement of AUC from 0.74 from 0.75. At the same time, it continues to be studied within an exceptionally homogenous Northern European population of men.

ExoDx Prostate (Intelliscore) is unique in that it has opened a new category of urine-based biomarker tests – which need not be preceded by a conscientious DRE (as do PCA3 and SelectMDx). It is an exosome-based test – which means that the testing is performed on the protein and RNA content of cellular exosomes physiologically secreted from cells. The exosome content originating from cells of clinically significant prostate cancer is highly representative of their source. A negative predictive value (NPV) of 97.5% should put this new test in the scope of interest of urologists seeking tools to decide whether it is justified to take a biopsy needle out of its sterile pouch.

When you and your patient do make the informed decision to perform a prostate biopsy, make sure the quality of the sampling is maximal and in accordance with EAU Guidelines (Photo: S. Czarniecki)

Prostate cancer biomarkers, imaging, and risk assessment tools will continue to transform the way we urologists deal with prostate cancer detection at the dawn of the PSA era.

Saturday 17 March
10.15-14.00: Meeting of the EAU Section of Urologists in Office (ESUO)
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