Prostate cancer risk stratification: to biopsy or not to biopsy?

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The application of the ERSPC risk calculator to the clinical setting has been demonstrated to be acceptable for both patients and Urologists (7), with 83% of patients and clinicians complying with the recommendation of the ERSPC calculator in the decision for prostate biopsy. Those who decided not to comply were generally patients with a PCa was defined as ISUP grade 1 or 2 without invasive cribriform growth pattern and intraductal carcinoma. High-risk PCa was defined as ISUP grade 2 with a cribriform pattern or intraductal carcinoma and PCa with ISUP grade ≥3.

The updated ERSPC risk calculator demonstrated a similar AUC to that of the previous model in predicting any PCa, however there was a significantly higher discriminative ability for the prediction of High-risk PCa (0.91 versus 0.84; P<0.001). The application of the updated risk calculator to this patient cohort on internal validation demonstrated a 34% reduction in unnecessary biopsies, while missing 2% of High-risk PCa cases.

This research offers a promising approach to the work-up of patients under investigation for PCa. This tool can prove useful to the urologist in risk stratifying patients for prostate biopsy, in risk stratifying patients for pre-biopsy MRI, or indeed in the primary care setting to decide on the need for referral. As stated in the article, this updated risk calculator requires external validation before it can be trusted in clinical practice, however it has the potential to become a useful clinical decision aid in the PCa management paradigm.

In a recent paper published in European Urology, Roobol et al. have examined the potential impact of updating the outcome measure that is being predicted by the ERSPC step 3 risk calculator (5). This new definition incorporates the new International Society of Urological Pathology (ISUP) grading system for PCa as shown in Table 2 (6). Low-risk
low risk who still wished to have a biopsy, or those patients with a low risk and a Prostate-Specific Antigen (PSA) >3 ng/mL, who underwent biopsy on the advice of their clinician. The best method to bring a PCa risk calculator into clinical practice may be to incorporate the model into a smartphone app, as has been performed for the ERSPC risk calculator (8).

Attempts to improve the decision for biopsy is a fundamental area within PCa research. The main avenues towards this improvement are to improve the individual risk factors with the calculator; for example novel biomarkers, pre-biopsy imaging studies such as MRI and a systematic approach to family history.

The current ERSPC model under investigation in this paper still relies on PSA as the biomarker of choice. However, PSA has proven to be an inefficient biomarker for PCa risk prediction. Therefore “the search for and the integration of additional diagnostic factors, including the development of improved prediction models, remain integral parts of scientific research and clinical practice” (9). The Prostate Health Index (phi) and 4K biomarker panels are two leading examples of this. In order to best predict the outcome of prostate biopsy and ensure the best decisions are made to improve patient care and patient outcomes, future PCa research must focus not only on the discovery of novel biomarkers of disease, but also it is imperative that the currently available tests and novel biomarkers are independently validated so that informed decisions regarding their use can be made. Future studies should also focus on the relationship between these tests and whether there is value in their incorporation. The performance of the phi score and 4K test have been compared and have demonstrated equal efficacy (10), however it is the author’s belief that the fundamental strategy which will improve PCa diagnosis is the integration of biomarkers rather than their use alone. The ERSPC risk calculators can also incorporate the phi score and demonstrate improved predictive ability over the use of PSA (11,12).

The use of MRI in patients prior to prostate biopsy is a growing trend, and so one may ask where risk calculators will fit into the PCa management paradigm. Risk calculators may become an important decision tool, not just for biopsy, but to risk stratify patients for prostate MRI. PCa is still one of the few malignancies to undergo a random biopsy

d| Traditional Gleason score | New ISUP score |
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ISUP, International Society of Urological Pathology.
approach. However convincing evidence for targeted MRI-guided biopsy is emerging (13), including its ability to avoid the overdiagnosis of insignificant disease.

To make the best use of the basic clinical information, efforts should be made to carefully record each patient’s family history and specifically the age at PCa diagnosis and the aggressiveness of the PCa diagnosed. A father who died from metastatic PCa is likely a greater risk factor than a father diagnosed with Gleason 6 disease who died from another cause. Grill et al. have demonstrated in a recent paper that family history adjusted for age at diagnosis is a significant independent risk factor for PCa (14) and so, improved recording of family history has the potential to improve the predictive ability of PCa risk calculation.

There remains the question as to whether or not this risk calculator can be applied in clinical practice with a focus on “High-risk disease”. This is because a transrectal ultrasound (TRUS) biopsy has an inherent element of inaccuracy and is associated with a risk of Gleason upgrading at radical prostatectomy. In other words, TRUS biopsy can underestimate the aggressiveness of a patient’s PCa. The largest study to date identified that 43.1% of all Gleason 6’s at biopsy were upgraded to Gleason 7 at radical prostatectomy and that a further 1.6% were upgraded to Gleason ≥8 (15); while Epstein et al. quoted a 36.3% upgrade risk if Gleason 6 was found on biopsy (16). At the moment, to advocate the use of the High-risk calculator alone has the potential to miss many significant PCa’s that represent prostate tissue missed on TRUS biopsy. There is also the risk of false negatives associated with TRUS biopsy. This risk has been reported in the literature to be as high as 24% (17).

The patient cohort in the ERSPC trial, from whom the ERSPC risk calculator is derived, are a group of men who underwent PSA screening. Worldwide, there exists much debate over whether PSA screening should be carried out (18). Which begs the question as to whether these risk calculators should be applied to all men, or only those undergoing PSA screening? And indeed, where does the symptomatic patient fit in to this risk stratification process?

**Conclusions**

The decision for prostate biopsy in men under investigation for PCa can be aided through the use of PCa risk calculators. These tools provide a logical and systematic approach to the use of patient information and can facilitate patient risk stratification. PCa risk calculators are not without fault, and there are many areas of potential improvement. Roobol et al. have investigated one such area of potential improvement and demonstrated an increased efficacy in the prediction of High-risk patients. The ERSPC risk calculators allow for an individualised approach to PCa diagnosis, they can be used to aid in the decision for prostate biopsy, and should be utilized in routine clinical practice.

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**Footnote**

*Conflicts of Interest:* The author has no conflicts of interest to declare.

**References**


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