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How PSMA PET is refining risk calculators in the primary prostate diagnostic pathway.

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The PSMA PET imaging train has steamrolled through the staging and restaging of prostate cancer (PC) and, the selection of patients for theranostic therapy, and has now arrived in the early detection space (1). Prospective trials such as PRIMARY have demonstrated the superior diagnostic capability of primary diagnosis pathways that include PSMA PET when compared to more traditional algorithms (1).

Given the recent introduction and variable access to this imaging modality, however, it is yet to be implemented globally as a standard of care in the primary diagnosis of PC, let alone risk calculators (RC).

RC play an important role in informing the decision-making process for whether to proceed to biopsy by considering the key risk factors for the presence of significant cancer. Since the introduction of PSA, RC have been used by some clinicians as part of the risk stratification for decision-making on further investigation for primary PCa. As RCs have evolved, they have integrated patient risk factors and the outcomes of imaging tests. The utility of RC lies in harnessing the different tools in the diagnostic pathway to provide a well-informed risk of a patient harbouring clinically significant cancer.

In 2006, the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) was one of the first freely available RCs utilising PSA and patient risk factors. The RC was developed based on the 5519 men in the placebo group of the PCPTRC(2). This resulted in an AUC of 0.64 for csPC (2). In 2012, PCPT 2.0 was introduced, advertising the ability to better discriminate low grade (Gleason 3+3) and higher grade (3+4) by utilising similar data from the PCPT whilst

including multiple negative biopsy results, rather than one single result. The new model improved the PCPTRC to an AUC of 0.69 for csPC.

The PCPT highlighted several key roles for RC that are still pertinent in 2023. Those being; disproving the notion of a 'healthy' PSA range(2), assisting in the decision-making to proceed to biopsy for identifying csPC cancer, highlighting other risk factors and assisting patients in evaluating the decision of surveillance vs. biopsy as they age(2).

In the same year as PCPT, numerous RC's were developed based on the Dutch cohort of the European Randomized Study of Screening for Prostate Cancer (ERSPC). It was developed using data from PSA-driven trans-rectal biopsies. ERSPC RC has been externally validated amongst numerous European, Asian, African, American and Australian cohorts and has therefore produced a range of AUC's. Typically, ERSPC R3 (biopsy naïve) and R4 (repeat biopsy) which were designed for clinicians, yielded an AUC for csPC of 0.76 and 0.74 respectively when externally validated in a 2016 study.

The practice changed leading to a superior diagnostic yield after the PRECISION trial identified that mpMRI prior to prostate biopsy could identify targetable lesions leading to a higher proportion of men diagnosed with csPC, and a lower incidence of clinically insignificant disease. Therefore, the next progression of PCa RC's evolution was the addition of mpMRI performed by Leeuwen et al in 2017. They created three diagnostic models, a base model including PSA only, a multivariable model including PSA, DRE, age, prostate volume and information on previous biopsy and an advanced model adding the PIRADS score from mpMRI to the multivariable model. By adding the components of the

multivariable model to the base model the AUC improved from 0.598 to 0.797. When mpMRI was added to the multivariable model, the AUC increased to 0.883.

The next advancement in the primary localisation of prostate cancer was the introduction of PSMA PET. In its infancy, PSMA PET was primarily used for PC staging, however numerous studies also noted the accuracy of this modality in assessing the primary prostate lesion. Consequently, this led to Emmett et al creating the first prospective phase II trial (PRIMARY) that evaluated the performance of PSMA PET in the primary diagnosis of prostate cancer.

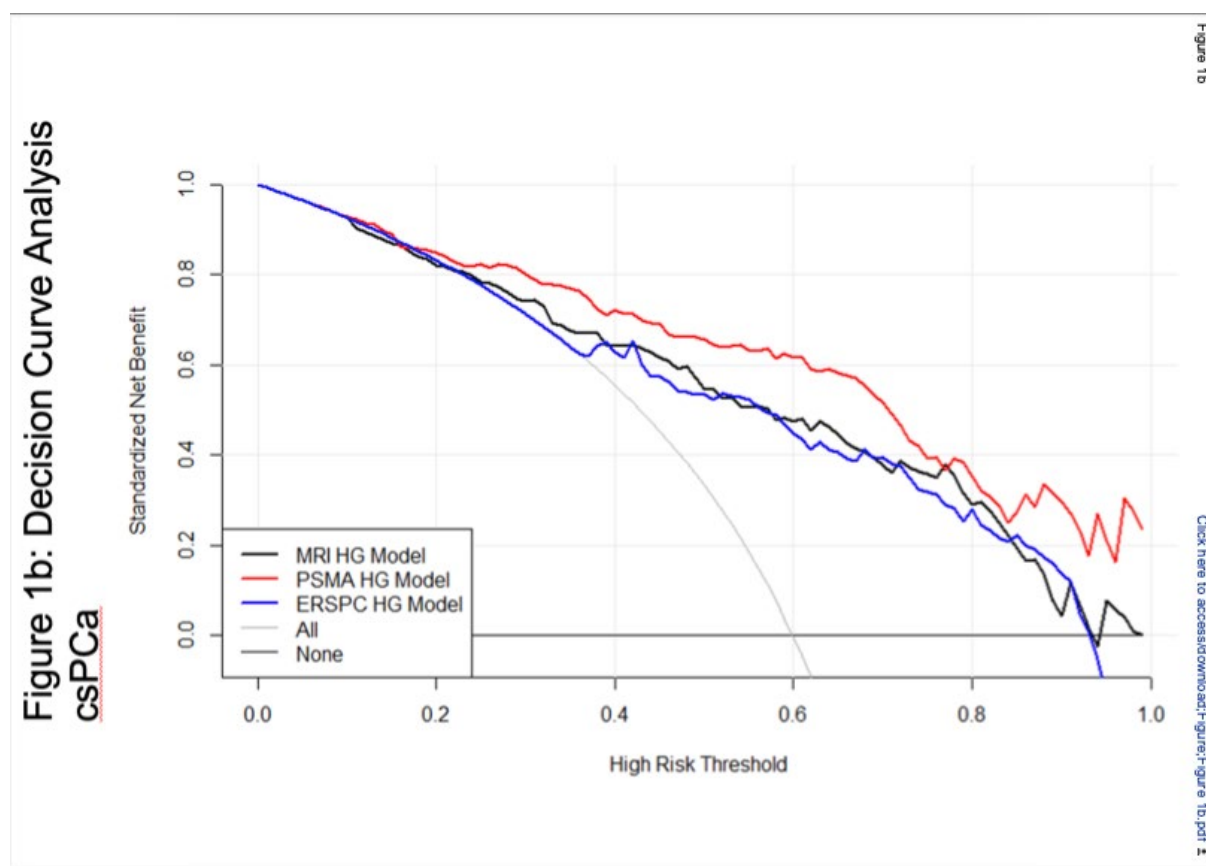
The PRIMARY trial investigated whether pelvic-only PSMA PET in addition to MRI could improve the detection of clinically significant prostate cancer in men with suspected PC(1). It was found that PSMA PET intensity was associated with the Prostate Imaging Reporting and Data system (PI-RADS) and biopsy grade. Adding PSMA PET to MRI improved sensitivity and negative predictive value for the detection of clinically significant prostate cancer.

Consequently, Kelly et al published the first RC that has incorporated PSMA PET & mpMRI based on the PRIMARY dataset(5). This novel RC was the first published RC incorporating pre-biopsy mpMRI and pre-biopsy PSMA PET. To test the additive value of PSMA PET, Kelly et al designed an MRI-only RC with the PRIMARY data. The MRI-PSMA RC for identifying patients at risk of having csPCa had an AUC of 0.876, compared to 0.812 for the MRI-only RC (Figure 1). Kelly et al demonstrated that the addition of PSMA to MRI-only RC in a population who had undergone both studies improves the AUC.

Although Kelly et al have proved the addition of PSMA PET strengthens RC in the diagnosis of csPCa, their RC is yet to be externally validated. Their patient cohort was extrapolated from the novel PRIMARY cohort, for which at present, there is no equivalent prospective patient cohort. Uncertainty exists relating to incorporating PSMA PET internationally given the cost. However, this model was built to ascertain the most efficacious diagnostic algorithm in a unique Australian (where PSMA is more accessible) cohort. Additional limitations of PSMA have been demonstrated in a recent Systematic Review by Ptasznik et al highlighting little consensus on how to perform and/or report PSMA in the primary localisation of prostate cancer. Thereby compelling PSMA to strive for the reproducibility of PI-RADS before it can be responsibly incorporated into clinical practice.

As diagnostic modalities are improving, such as TP biopsy, targeted biopsy and pre-biopsy mpMRI, the addition of pre-biopsy PSMA PET has the potential to risk stratify men who may harbour csPCa. The use of risk calculators in daily practice which include information from these novel technologies should be encouraged as they will continue to assist in shared decision-making with our patients.

Figure 1:



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Figure 1: Was published in European Urology Open Science. Publication Title: Prostate Cancer, Vol number 53, Author(s) Kelly et al, Title of article: A Novel Risk Calculator Incorporating Clinical Parameters, Multiparametric Magnetic Resonance Imaging, and Prostate-Specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Risk Stratification Before Transperineal Prostate Biopsy, Page Nos: 90-97, Copyright Elsevier (2023)."

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