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INVITED REVIEW

Prostate Cancer

Risk calculators and updated tools to select and plan a repeat biopsy for prostate cancer detection

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Millions of men each year are faced with a clinical suspicion of prostate cancer (PCa) but the prostate biopsy fails to detect the disease. For the urologists, how to select the appropriate candidate for repeat biopsy is a significant clinical dilemma. Traditional risk-stratification tools in this setting such as prostate-specific antigen (PSA) related markers and histopathology findings have met with limited correlation with cancer diagnosis or with significant disease. Thus, an individualized approach using predictive models such as an online risk calculator (RC) or updated biomarkers is more suitable in counseling men about their risk of harboring clinically significant prostate cancer. This review will focus on the available risk-stratification tools in the population of men with prior negative biopsies and persistent suspicion of PCa. The underlying methodology and platforms of the available tools are reviewed to better understand the development and validation of these models. The index patient is then assessed with different RCs to determine the range of heterogeneity among various RCs. This should allow the urologists to better incorporate these various risk-stratification tools into their clinical practice and improve patient counseling.

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Keywords: biomarkers; prostate cancer; repeat biopsy; risk calculators

INTRODUCTION

Every year, millions of men undergo prostate biopsy procedures worldwide, most often due to elevated prostate-specific antigen (PSA) level, to discover prostate cancer (PCa) at an early stage. However, nearly 60%–70% of these biopsies fail to detect prostate cancer in men who were thought to harbor the disease.[1] The rate of false positive PSA level is further compounded by the prostate sampling error resulting in false negative biopsy rate of 10%–30%.[2] Thus, a major clinical dilemma regarding the need for repeat prostate biopsy arises in this situation where the initial intent was to detect prostate cancer, yet the diagnostic biopsy is negative.

Traditional risk-stratification approach relied on tools such as PSA level, PSA velocity (PSAV), PSA density (PSAD), % free-PSA (fPSA), presence of histological features such as high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP). The performance of these tools to detect PCa during subsequent biopsy has diminished over time as the general population has become more widely screened. Further, the traditional markers do not correlate well with PCa aggressiveness.[3] Newer risk-stratification tools like online PCa risk calculator (RC)[4–6] are available to determine the suitable candidates for repeat prostate biopsy and have been shown to outperform the PSA and related markers.[7] The performance of these RCs for repeat biopsy depends on the adequacy of the initial biopsy and the study population (e.g., heavily screened or early in the screening process).

Newer risk-stratification tools rely on biomarkers that may fit into the established online RCs or be used independently. These biomarkers may ultimately prove to be better indicators of aggressiveness compared to PSA. An understanding of how these risk-stratification models were developed is critical to the understanding of their variable performance in the clinical setting. As these newer risk assessment tools and biomarkers become available for clinical use, it is important to understand their validation methodologies, as well as their strengths and weaknesses, to better counsel our patients. This review will focus on the usefulness of available risk-stratification tools (**Figure 1**) in the population of men with prior negative biopsies and persistent suspicion of PCa.

RISK CALCULATORS

PCPT-based risk calculator

In 2006, the Prostate Cancer Prevention Trial (PCPT)-RC was made available online to facilitate the decision to re-biopsy. It requires data on six clinical risk factors: PSA, digital rectal examination (DRE), age, African American race, family history, and biopsy history.[4] The RC was based on 5519 men from the placebo arm of the (PCPT) which randomized healthy men 55 years or older with a normal DRE and PSA ≤3 ng ml^{-1} to either finasteride or placebo for 7 years.[8] Participants in the placebo group underwent a biopsy if their DRE became abnormal (for-cause) or PSA >4 ng ml^{-1}. At the end of the 7-year study, an end-of-study biopsy was requested of all participants regardless of PSA, digital rectal examination, or prior biopsy. Sextant biopsies (six samples) were most often performed during both the for-cause and the end-of-study biopsies. Only one biopsy per participant (the last biopsy of the study) was used to construct the RC.

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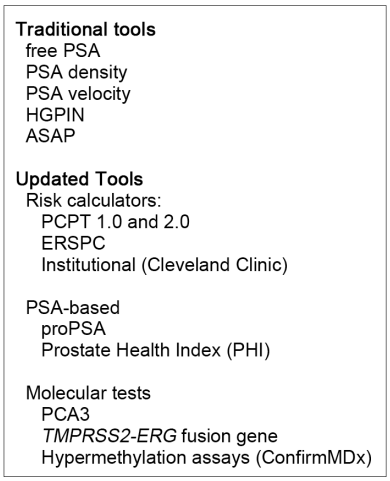

Figure 1: Traditional and updated tools available to plan a repeat prostate biopsy.

The PCPT-RC utilizes PSA as a continuous rather than a dichotomous variable as it is more reflective of the study population that incorporated men who underwent prostate biopsy across a range of PSA values. However, the RC went beyond just PSA by incorporating other significant variables found on multivariable logistic regression. From the original study, increasing log (PSA) ($P < 0.001$), positive family history of prostate cancer ($P = 0.002$), and abnormal DRE result ($P < 0.001$) were significantly associated with risk of prostate cancer. Having had one or more previous negative biopsies was associated with a decreased risk of prostate cancer ($P < 0.001$). Significant predictors of high-risk disease were similar except for the family history. African-Americans had a higher risk of high-grade disease than non-African-Americans ($P < 0.001$). Although age at biopsy was statistically significantly associated with an increased risk of high-grade disease, the odds ratio for each 1-year increase in age was only 1.03 (95% CI = 1.01–1.06, $P = 0.01$).

The RC is applicable to men who are at least 50-year-old, have no previous diagnosis of prostate cancer, and have DRE and PSA results that are <1-year-old. Following the entry of these variables, the RC reports 2 outcomes of prostate cancer: risk of prostate cancer and risk of high-grade cancer, with 95% CI. Furthermore, the RC has an ability to incorporate new biomarkers such as PCA3 and fPSA, which have been validated on external case-control cohorts.[9,10] Physicians may use the risk-stratification tool to better counsel patients on PCa risk to make a more informed decision on repeat biopsy. Moving toward more personalized medicine, the level of risk that triggers a biopsy is different in all men and the risk of high-grade PCa should be weighed against the risk of biopsy related complications including serious infections.[11]

Some significant criticisms of the PCPT-RC have been published after its inception. These have included overestimation of risk due to its modeling approach,[12] application to non-U.S. populations,[13,14] and use of 6-core biopsy schema.[15] Furthermore, most men currently presenting for prostate biopsy have an increased PSA level, abnormal DRE, and are younger than 55-year-old which may be quite different from the PCPT cohort used to develop the RC.[3] The outdated PCPT-RC has recently been replaced with the newer PCPT-RC 2.0. Both can be found at http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp.

PCPT-based risk calculator 2.0

The updated version of the PCPT-RC was subsequently developed to be clinically relevant in the dynamic world of prostate cancer. The PCPT-RC 2.0 included data from an additional 1145 biopsies added to the original 5519 biopsies in the PCPT placebo arm. It also included an expansion of the San Antonio Biomarkers of Risk (SABOR) case-control study for fPSA by 63 patients.[16] These additions were used to gain statistical significance in order to report 3 (rather than 2) outcomes which are negative, low-risk, and high-risk cancer.

The updated cohort of 6664 biopsies in PCPT revealed an average PSA level increase from 1.7, 2.1, and 3.1 ng ml^{-1} among the benign, low-grade and high-grade cases, respectively. On multivariable analysis, similar predictors of PCa that were incorporated in the first version of PCPT-RC were found. However, separating low-grade and high-grade cancer, prior biopsy and family history were statistically significant only for low-grade and not for high-grade detection. On the other hand, DRE and African American race were only useful for high-grade detection.

The SABOR cohort is derived from a clinical validation center of the Early Detection Research Network (EDRN) of the National Cancer Institute. It comprises a 3930 cohort of men from the San Antonio and South Texas area without a previous PCa diagnosis and 13 years of follow-up. Annual screening consisted of PSA and DRE, as well as a referral for biopsy (mostly 12-core) when PSA exceeded 2.5 ng ml^{-1}. The cohort of men found to have PCa had serum PSA measured within 2.5 years of diagnosis. There were ultimately 537 men in the SABOR biopsy cohort with on average decreasing fPSA moving from noncancer (32.0), to low-grade (22.3) to high-grade (18.2) cancer groups. The SABOR cohort with a different study population was used to incorporate fPSA into PCPT-RC 2.0 by a statistical technique that adjusted PCPT-RC risks by likelihood ratios of the markers in SABOR.

The PCPT-RC 2.0 was externally validated, with and without fPSA, on the EDRN and the Prostate Biopsy Collaborative Group (PBCG) data sets, respectively. The risk-stratification tool performed well in both data sets. The inclusion of fPSA significantly improved prediction for high-grade prostate cancer versus no cancer but did not improve high-grade versus low-grade cancer.

Not surprisingly, the major criticism of the PCPT-RC 2.0 is the heterogeneity of the SABOR and PCPT cohorts.[17] The SABOR cohort was comprised mainly of patients undergoing 12-core biopsies and had higher rates of detection of both low-grade and high-grade PCa. Still, the majority of the PCPT-RC 2.0 is based on the PCPT cohort who mainly underwent 6-core biopsies. The authors contend that modern 12-core biopsy schemes only marginally improved the original PCPT-RC in an independent validation[18] and, therefore, the RC is still relevant. External validation of the new PCPT-RC 2.0 is needed to determine its usefulness as a risk-stratification tool.

ERSPC-based risk calculator

The European Randomized Study of Screening for Prostate Cancer (ERSPC) RC was developed from data obtained from the Rotterdam section from 1993 to 1999.[5,19] Initially, 19 970 men aged 55–74 underwent a first time screening with serum PSA, DRE, and transrectal ultrasonography (TRUS). Triggers for sextant biopsy included abnormal DRE, TRUS (hypoechoic lesion), or PSA ≥4.0 ng ml^{-1}. After May 1997, PSA ≥3.0 ng ml^{-1} was the sole biopsy indication. A repeat PSA-based screening algorithm was then undertaken in men who were initially screened without PCa detection and who were 55–70 years old at the time of screening. Various clinical data points from these cohorts were then used for different multivariable logistic regression models.

The ERSPC-RC is categorized for use by nonmedical and medical personnel. For nonmedical use, there are two different RC to determine

the risk of PCa from 6288 men at initial screening using age, family history, and urinary complaints or the PSA value alone. For medical use, there are currently four different RC available.[20,21]

The ERSPC-RC 4 is designed to determine the likelihood of cancer in the repeat biopsy. RC 4 was developed from a cohort of 2896 men undergoing sextant biopsies after subsequent rounds of repeat screening PSA testing. In these men, RC 4 reports the risk of PCa on biopsy as well as the risk of high-grade disease using the standard variables, with the addition of prior biopsy results. The repeat screening cohort included 987 men who had a previous negative prostate biopsy. A total of 547 (55.4%) PCa cases were detected, of which 131 (23.9%) were considered high-grade (Gleason score ≥7 or T2b). Mean PSA value for this cohort was 4.8 ng ml^{-1}.

The ERSPC-RC 5 is only used to determine the risk of indolent cancer by using positive biopsy core information. RC 6 is the latest in the series and determines future risk by age, PSA, DRE, family history, DRE volume, and prior biopsy results. Its outcomes are similar to PCPT-RC 2.0 by determining the risk of no-cancer, low-grade, and high-grade PCa.

Similar to PCPT-RC, the ERSPC-RC is limited by the use of sextant biopsies and application to other population. ERSPC-RC also uses information from TRUS and DRE volume estimates which can be inaccurate and are not routinely used by general practitioners.[22,23] The RC has tested but not yet incorporated PCA3 and fPSA into the online RC, which they found to be of some value in increasing predictive value.[24] The RC is available at http://www.prostatecancer-riskcalculator.com.

Prostate cancer risk assessment (Cleveland clinic calculator)

Several institutions have also developed risk calculators based on their own cohorts. One of the more popular ones is the Cleveland Clinic-Risk Calculator (CC-RC). The CC-RC may be used for both counseling patients undergoing initial or repeat prostate biopsy. However, for the purposes of our study, we focused on the development of the RC for repeat biopsy.[6] This was developed based on an initial set of 408 patients from the Cleveland Clinic undergoing repeat biopsy after an initial negative biopsy between 1999 and 2008. Extended biopsy scheme (10–12 cores) was used in 91% of the initial negative biopsies, and the institution began using saturation biopsy (≥20 cores) in the majority of repeat biopsies after 2003. The indications for repeat biopsy were not uniform and may have included elevated PSA, abnormal DRE, and/or the presence of HGPIN or ASAP on initial biopsy. A validation set of 470 patients between 2001 and 2009 was also used to develop the RC.

In the initial data set, the overall prostate cancer detection rate was 31.6%, among which 69.8% and 30.2% were classified as low- and high-grade cancers, respectively. The validation set's overall cancer detection rate was 34.5%, among which 68% and 32% were classified as low- and high-grade cancers, respectively. On multivariable analysis, the most significant predictors of positive repeat biopsy were PSA, cumulative number of negative cores, history of HGPIN or ASAP, prostate volume, and family history of prostate cancer.

The current CC-RC for repeat biopsy requires the patient to enter PSA, DRE, age, family history, prior biopsy information (HGPIN or ASAP), and body mass index (BMI). It is the only risk calculator to incorporate BMI as the authors believe the documented inverse relationship between obesity and PSA level is important. It computes the % risk of the positive biopsy and high-grade disease. The CC-RC can be found at http://www.clevelandclinic.org/lp/prostate-cancer-risk-assessment/index.html.

Comparing the risk calculators

Several studies have been performed to externally validate both the PCPT-RC and ERSPC-RC on men who have undergone prior biopsy. There are currently no studies comparing the PCPT-RC 2.0 and CC-RC. Since different screening cohorts comprise the PCPT and ERSPC, it is of no surprise that the risk calculations can be quite different even when identical patient variables are entered. Furthermore, studies on whole population have produced inconsistent results on the performance of both RC. Trottier *et al.*[14] compared the performance of both RCs on a Canadian cohort of 982 men. Prior negative biopsy was found in 29% of men and PCa was detected in 46.2%, of which 22.9% was high-grade (Gleason ≥4). While the PCPT-RC had better overall calibration, ERSPC-RC was found to be superior to PCPT-RC on area under the curve (AUC) for both detection of PCa (0.71 *vs* 0.63, respectively) and high-grade disease (0.78 *vs* 0.68, respectively). The better performance of the ERSPC-RC may be attributed to similar biopsy indications, incorporation of TRUS findings, and prostate volume measurements. Furthermore, age and family history had either no or very little association in this Canadian cohort, which PCPT-RC incorporates into its formula.

Oliveira *et al.*[15] compared the diagnostic accuracy of the PCPT-RC and ERSPC-RC on a contemporary screened cohort from Portugal. Among the 390 patients included in the analysis, 31% had a history of a previous negative biopsy and 39.7% were diagnosed with PCa. The ERSPC-RC (AUC 0.779) had a statistically significant 7.96% increase in the predictive accuracy compared to the PCPT-RC (AUC 0.699). Similar to Trottier *et al*., the authors attribute the superior performance of the ERSPC-RC to TRUS hypoechoic lesions and prostate volume for better discrimination.

Zhu *et al.*[13] externally validated the PCPT-RC and ERSPC-RC on a cohort of Chinese men (n = 495) with very low rates of family history of PCa. Prior biopsies were done on 18.8%, and PCa was detected in 28.7%. The median PSA level of 10.2 was much greater than the PSA level in both RC. The AUC values for the prediction of PCa were 0.783 and 0.831 for the PCPT-RC and ERSPC-RC, respectively. For high-grade cancer, the respective AUC values were 0.813 and 0.852. The superior performance of ERSPC-RC may be attributed to the median PSA levels of the ERSPC cohort being much higher than PCPT. Furthermore, the PCPT incorporates family history in its calculation, of which this Chinese cohort only had three men with positive family history. Overall, both RC overestimated the probability of biopsy outcome by approximately 20%.

The major limitation of the comparative studies of the performance of these RCs after prior negative biopsy lies in the heterogeneity of the control and the study groups. All the three studies[13–15] that reported the superior performance of ERSPC-RC analyzed men with prior negative biopsies, as well as those with no history of biopsy. Another important and intuitive, but often overlooked, feature is the intensity of PSA screening within that population. The performance of any risk assessment tools may be quite different if the study population is at the beginning of its screening program as opposed to a population where widespread screening has culled out most of the prevalent cancers over the years. It is, therefore, difficult to make any conclusions regarding the superiority of one RC over the other. It is fairly well-established that RCs are superior to using clinical judgment or PSA or other clinical variables alone. In clinical practice, we feel it is best to use more than one of the available RCs, especially when counseling highly anxious patients, to arrive at an informed decision about a repeat biopsy.

We evaluated the performance of different RCs listed in **Table 1** using a hypothetical index patient who was 55-year-old Caucasian

Table 1: Characteristics of the various online prostate cancer RC

RC	*Study population*	*PCa detected (%)*	*HG PCa (%)*	*Variables*	*Outcomes reported*
PCPT-RC	USA, PCPT (*n*=5519 men from placebo arm)	21.9	4.7	PSA, DRE, age, race, family history, biopsy history	Risk of positive biopsy Risk of HG cancer
PCPT-RC 2.0	USA, PCPT (*n*=6664 men from placebo arm; *n*=537 men from SABOR)	PCPT - 21.9 SABOR - 53.4	PCPT - 3.8 SABOR - 16.8	PSA, DRE, age, race, family history, biopsy history, ±%fPSA	No cancer Low-risk cancer High-risk cancer
ERSPC-RC4	Rotterdam (*n*=2896 from ERSPC)	18.9	4.5	PSA, DRE, TRUS, prostate volume, biopsy history	Risk of positive biopsy Risk of HG cancer
CC-RC	Cleveland Clinic (*n*=408 in initial set, *n*=470 in validation set)	Initial=31.6 Validation=34.4	Initial=9.5 Validation=11.1	PSA, DRE, BMI, age, family history, biopsy history	Risk of positive biopsy Risk of HG cancer

RC: risk calculator; CC-RC: cleveland clinic-risk calculator; ERSPC-RC4: european randomized study of screening for prostate cancer-risk calculator 4; PCPT-RC: prostate cancer prevention trial-risk calculator; SABOR: san antonio biomarkers of risk; PCa: prostate cancer; HG: high-grade; PSA: prostate-specific antigen; DRE: digital rectal examination; fPSA: free-prostate-specific antigen; TRUS: transrectal ultrasonography; BMI: body mass index

male, no family history of prostate cancer, normal DRE and BMI, PSA 8 ng ml^{-1}, estimated prostate volume of 25 ml with a negative prior biopsy. As evident from the **Figure 2**, there is significant heterogeneity in the cancer detection rates reported by different RCs. The PCPT-RC overestimated both the risk of detection of PCa and high-grade disease. The ERSPC-RC performed similar to PCPT-RC 2.0 with slightly lower risks given for overall detection in the latter RC. However, when increasing the estimation of prostate volume on DRE, the ERSPC-RC will report the lowest risks of both detection of PCa and high-grade disease. The CC-RC reported the lowest rates of any cancer and high-grade cancers which is likely a product of the single-institution cohort used to develop their RC.

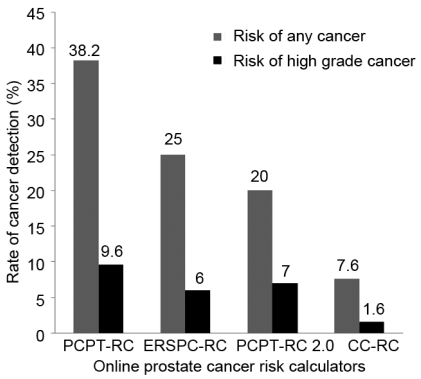

Figure 2: Cancer detection rates as predicted by various risk calculators using an index patient: 55-year-old Caucasian male, no family history of prostate cancer, normal DRE and BMI, PSA 8 ng ml^{-1}, estimated prostate volume of 25 ml with a negative prior biopsy.

UPDATED BIOMARKERS

Prostate cancer antigen 3 (PCA3)

The Progensa PCA3 test was approved by the US Food and Drug Administration (FDA) in 2012. It is intended to aid in the decision-making on performing biopsy when there is still suspicion of PCa after previous negative biopsy and/or elevated PSA and/or abnormal DRE. The test measures the concentration of PCA3 and PSA RNA molecules in urine specimens after DRE. A PCA3 score is then calculated using the ratio of PCA3 RNA to PSA RNA. A PCA3 score <25 usually decrease the likelihood of PCa, and even lower cutoffs reduce false positive rates.[25–27] A multi-institutional review on PCA3 looking at patients after negative biopsy determined average sensitivity of 52.6%, average specificity of 71.6%, and an overall accuracy of 66%.[25]

Auprich *et al.*[27] compared the performance of PCA3 and other biomarkers such as total PSA (tPSA), fPSA, and PSAV on a cohort of men (n = 127) with multiple repeat biopsies. Overall PCa detection was 34.6%. PCA3 was found to be most useful on the first repeat biopsy with AUC of 0.80 to predict PCa. At second and ≥ third repeat biopsy, fPSA had the highest accuracy with AUC of 082 and 0.70, respectively. Although limited by a small sample size, the study provides some basis for counseling patients being considered for multiple repeat biopsies.

A first catch urine sample of at least 2.5 ml after applying pressure on each lobe of the prostate is collected for the PCA3 test.[28] The sample can be transported right after collection or kept frozen for 5 days before analysis. The PCA3 test has not been validated on men who were on 5α-reductase inhibitors (5ARI) or anti-androgen therapy and, therefore, should not be used in these patients.

Prostate health index (phi)

The phi was developed by Beckman Coulter in partnership with EDRN and was approved by the FDA in 2012.[29] It combines (-2) proPSA (p2PSA), a molecular isoform of fPSA identified as the most prevalent in tumor extracts, as well as fPSA and total PSA into one mathematical formula. The phi is designed for prostate cancer detection in men aged 50 years and older with total PSA levels between 2 ng ml^{-1} and 10 ng ml^{-1} and DRE findings that are not suspicious for cancer.[30] The phi score is suggested to be divided into three categories by the manufacturer using World Health Organization (WHO) calibration: 0–20.9 (low-risk); 21–39.9 (moderate risk); 40 and above (high-risk). The manufacturer states that estimates of the risk of cancer being detected in biopsy are 8.7% for men in the low-risk category, 20.6% in the moderate risk category, and 43.8% in the high-risk category.[28]

A recent study by Lazzeri *et al.*[31] evaluated %p2PSA (p2PSA/fPSA) and phi on a prospective cohort (n = 222) of men with a negative first biopsy who underwent repeat biopsy because of persistent suspicion of PCa. Prostate cancer was found in 77 of 222 (31.9%) men undergoing a repeat biopsy. Furthermore, %p2PSA and phi were significantly higher in men with PCa at repeat biopsy and were the most accurate predictors of disease. The phi outperformed total PSA and p2PSA, but not fPSA. %p2PSA outperformed total PSA, fPSA, p2PSA, but not phi. The authors concluded that the combination of both tests can improve the selection of candidates for repeat biopsy and aid in counseling.

Both phi and PCA3 were recently compared to multiparametric magnetic resonance imaging (mp-MRI), which is becoming a very popular tool in the repeat biopsy setting.[32] The study looked at 170 patients with initial negative biopsies and persistent suspicion of PCa either by elevated PSA or abnormal DRE. Overall, median phi and PCA3 scores were higher for patients with positive repeat biopsies compared to negative biopsies (43.9 and 43 *vs* 36.3 and 20, respectively). Multiparametric MRI only missed 9.6% of positive biopsies while PCA3 missed 42.3%, and phi missed 57.7%. In the multivariable logistic regression analysis, only mp-MRI was a significant independent predictor of PCa on repeat biopsy (P < 0.001). The addition of phi

to mp-MRI was only slightly better than the addition of PCA3 to mp-MRI (OR 103.5 *vs* 94.5, respectively). In the absence of MRI, PCA3 was a better predictor than phi. Although detailed analysis of new imaging for detection of prostate cancer on repeat biopsy is beyond the scope of this review, it is important to consider this evolving technology in this setting with or without the addition of new biomarkers.

The phi specimen should be assayed on Beckman Coulter Access instruments.[28] The blood specimen should be centrifuged within 3 h or the p2PSA concentration may increase significantly. Similar to PCA3, phi has not been tested on patients using 5ARI and, therefore, should not be used in these patients.

TMPRSS2:ERG fusion gene

The transmembrane protease serine 2 (TIMPRSS2) to v-ets erythroblastosis virus E26 oncogene homolog (ERG) fusion is a common finding in PCa.[33] It is a urine-based assay similar to PCA3. Alone, the gene fusion was found to have a low sensitivity of 37% but a high specificity of 93%. However, when combined with PCA3, the sensitivity increased to 73% without compromising specificity.[34] Another study found even higher rates of the sensitivity of 80% and specificity of 90% when both markers were combined.[35] The increased sensitivity of both biomarkers is likely due to the heterogeneity of PCa. Both TMPRSS2:ERG and PCA3 rely on a urine sample post-DRE and because some subtypes of PCa have less of a tendency to invade into the ductal system, this may increase the false-negative rates as less cells are shed into the urine.[36]

A multi-center study by Stephan *et al.*[37] was the first to look at TMPRSS2:ERG, PCA3, and phi in a cohort of 246 men of which 110 (45%) had ≥1 prior negative biopsies. The overall PCa detection rate was found to be 45%. TMPRS22:ERG was found to have slightly better performance than PSA or fPSA, but this was not statistically significant. Furthermore, combining TMPRS22:ERG with the other biomarkers did not improve their performance in multivariable models. PCA3 was found to outperform TMPRSS2:ERG and phi in the repeat biopsy cohort with a 90% sensitivity. In this study, TMPRSS2:ERG accuracy for predicting repeat biopsy outcome was lower than that observed in prior studies that used the same research assay.[38,39]

DNA hypermethylation assays

Hypermethylation of CpG islands in the promoter regions of cancer-associated genes (GSTP1, APC, and RASSF1) is linked to PCa.[40–42] ConfirmMDx, offered by MDxHealth (Irvine, California), detects an epigenetic field effect based on DNA methylation with up to a 90% negative predictive value (NPV).[43,44] The initial study was performed on 498 European men undergoing repeat prostate biopsy showing an NPV of 90% and later validated on 350 U.S. PSA screened patients with an NPV of 88%. MDx uses prostate core specimens collected during a 12-core biopsy. MDx is able to diagnose PCa in specimens that are otherwise histologically benign because of a "halo effect" that a cancerous lesion can have.[45] To date, Hypermethylation assays have not been compared to any other biomarkers discussed in this review. The cost of the test remains a significant barrier to its utilization in most markets.

CONCLUSION

The counseling to our patients on the need to undergo repeat prostate biopsy after a negative biopsy should incorporate new risk-stratification tools such as online RCs and biomarkers. There is a wide range of reporting variability among different RCs even when entering the same patient information, so one must exercise caution and utilize more than one calculator. Combining the information from the RCs with PCA3, phi, TMPRSS2:ERG, or hypermethylation assays may help to make a more informed decision. Multiparametric MRI is proving to be extremely useful in predicting repeat positive biopsy and may be incorporated into the dynamic RCs in the future. The individualized approach to repeat a prostate biopsy when there is high suspicion of PCa should be the standard of care.

EDITORIAL COMMENT – (BY DR. JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

For men evaluated for an abnormal PSA level and/or digital rectal examination, a subsequent prostate biopsy certainly leads to more information than simply looking at PSA metrics or change in physical examination. In simplistic terms, the biopsy will show cancer that will be managed a certain way, or does not show cancer and is monitored as such. For negative biopsies, as a personal aside, the phrase "unnecessary biopsy" is an unfortunate part of nomenclature often utilized when calculating the number of biopsies that might be avoided when using a novel marker or PSA metrics. A negative biopsy is not really unnecessary – the test significantly reduces the odds of a patient having any cancer and/or any high-grade cancer. Yet we all certainly recognize that performing a biopsy carries risk of pain, bleeding, and sepsis. Unfortunately, negative biopsies are not always correct due to sampling error. As Sorokin and Mian expertly review, risk calculators are available to improve decision-making, as are novel biomarkers that are heavily validated in the prior negative biopsy/rising PSA dilemma. Together, such new information can improve detection of remaining cancers that somehow avoided detection at primary biopsy.

A constant problem with this dilemma is that there is no professional opinion or guideline as to what threshold of cancer detection is correct, and patients may have their own ideas on the threshold. Many novel biomarkers suggest a new test threshold for biopsy that would avoid a certain number of (don't say unnecessary) negative biopsies and only miss a small number of cancers normally detected – the latter figure remaining an undefined acceptable amount. Nevertheless, we do have significant help now. In my clinical experience working with risk calculators, there are two main contributions: (1) the visual representation of possible results from the PCPT calculator into negative biopsy, low-grade, and high-grade, and (2) allowing the thresholds of biopsy out of concern for any cancer versus high-grade cancer to be discerned. The end produce is a more individualized choice for the patient.

AUTHOR CONTRIBUTIONS

IS and BMM both conceived of the study and each participated to draft the manuscript. Both authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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