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How Precisely Can Prostate Cancer Be Managed?

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Progress has been made in applying genetic information to disease management in the postgenomic era, and precision medicine is emerging in prostate cancer management. The prostate health index, the 4-kallikrein (4K) score, and the PCA3, TMPRSS2-ERG, and Prostarix tests have potential for refining prostate cancer screening in conjunction with traditional prostate-specific antigen testing. The Confirm MDx and PCA3 tests have shown promise in identifying men who need be rebiopsied after a primary negative biopsy. Oncotype DX, Prolaris, the biopsy-based Decipher prostate cancer test, and ProMark may improve predictive risk stratification in addition to the traditional Gleason score and tumor stage. Decipher and Prolaris may predict biochemical recurrence and metastasis after radical prostatectomy and possibly help identify patients who need adjuvant therapy. Androgen receptor splice variant 7 appears effective in guiding the selection of second hormonal manipulation with abiraterone or enzalutamide versus chemotherapy when treating metastatic castration-resistant prostate cancer.

Keywords: : Prostatic Neoplasms; Precision Medicine; Biomarkers; Receptors, Androgen

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INTRODUCTION

Precision medicine is an emerging approach for disease management that focuses on individual variability at the genomic, transcriptomic, proteomic, and metabolomic levels. Precision medicine has been used in cancer screening, stratification, guidance of treatment, and outcome prediction. Precision medicine has exciting and evolving applications in prostate cancer (PCa) management.

PCa is the most common cancer in United States (US) men and is the second leading cause of cancer mortality in men. In 2016, it is estimated that 180,890 men will be diagnosed with PCa, and 26,120 will die of PCa [1]. In 2016, the death rate in the US was found to have fallen to 50% of the peak rate. It is believed that early detection and improved treatment are important in decreasing cancer-related mortality [1]. Although the early detection and treatment of PCa improve survival, this must be balanced against overdiagnosis and overtreatment. In 2012, the United States Preventive Services Task Force recommended against prostate-specific antigen (PSA)-based screening for PCa (grade D recommendation), given concerns that the overdiagnosis and overtreatment of PCa may cause more harm than good [2]. However, this criticism was largely influenced by the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, a randomized clinical trial with high PSA screening contamination in the control arm [3]. Regardless, the grade D recommendation obviously challenges the current less-than-perfect PCa management. To improve the accuracy of diagnosis, the selection of necessary curative treatments, appropriate adjuvant therapy approaches, and the individualized

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treatment of metastatic disease, the development of precision medicine in PCa is as imperative as it is promising.

This review focuses on how currently available precision medicine tests are applied to common and challenging scenarios encountered in the management of PCa patients. We will discuss the following questions: (1) Who needs to be biopsied? (2) Who needs to be rebiopsied? (3) Who should be offered curative treatment or active surveillance? (4) Who needs adjuvant therapy after radical prostatectomy? (5) Who is a good candidate for secondary hormonal manipulation in castration resistant PCa?

WHO NEEDS TO BE BIOPSIED?

Although the benefit of PCa screening has been recently debated, many providers believe that PSA-based screening is still appropriate for early PCa detection. The 2016 National Comprehensive Cancer Network (NCCN) guidelines for the early detection of PCa recommended a PSA cutoff of 3 ng/mL in select populations to consider prostate biopsy. Patients with a PSA of 3–10 ng/mL are in a gray zone for prostate biopsy. Based on several studies [3,4], only 25%–35% of men with a PSA of 4–10 ng/mL who undergo prostate biopsy will be diagnosed with PCa, and most of those tumors will be low-grade. As recommended by NCCN guidelines, free PSA (fPSA), the 4 kallikrein (4K) and prostate health index (PHI) tests are recommended as options to detect more clinically significant PCa in addition to prostate biopsy or follow-up in 6–12 months with PSA testing and a digital rectal examination (DRE).

Free PSA

In contrast to total PSA (tPSA) in serum, %fPSA is the proportion of unbound protein. After the identification of fPSA [5], in 1998, the Food and Drug Administration (FDA) approved its use to improve PCa detection in men with total PSA levels of 4–10 ng/mL, largely based on the study by Catalona et al. [6]. This study showed that %fPSA can reduce unnecessary biopsies by 20% with a 95% detection rate in patients with a %fPSA ≤ 25%, a tPSA level of 4–10 ng/mL, and a normal DRE. The %fPSA significantly improved the predictive accuracy of PCa detection, with an area under the curve (AUC) of 0.72 vs. 0.53 for tPSA alone.

Although the above findings have been confirmed in other studies and reviews [7-9], %fPSA showed very little additional value in combination with the clinical application of tPSA for early detection in a prospective study [10]. This study included 246 consecutive men with prostate biopsies and showed that when the cutoff was set at 25%, the sensitivity for detecting cancer was 95%, but the specificity was only 20% for men with a PSA level between 4 and 10 ng/mL.

Prostate Health Index

The PHI is a blood test using total PSA, fPSA, and [-2] proPSA, a PCa-associated isoform of fPSA [11]. This serum-based test was developed at Beckman Coulter (Brea, CA, USA) by putting the values of the above 3 PSA forms into an equation to obtain a PHI score. In multicenter studies, the PHI has been found to detect PCa with a greater specificity than total PSA and %fPSA [11-17], and showed a sensitivity nearly double that of %fPSA for cancer detection in men with a PSA between 2 and 10 ng/mL. In addition, the PHI showed more power in discriminating high-grade (Gleason score ≥ 7) cancer from low-grade cancer or prior negative biopsy (AUC of 0.815) [11,18]. The PHI is an FDA-approved test to refine the specificity of PCa detection in initial and repeat biopsies. The PHI is emerging as a more specific test to avoid unnecessary prostate biopsies, as approximately 36% of unnecessary biopsies would be avoided using the PHI, and only 2.5% of high-grade cancers would missed in patients with a tPSA range of 3–10 ng/mL.

4K Score

The 4K score is a serum based test of 4K markers: tPSA, fPSA, intact PSA, and human kallikrein 2. The test also takes the patient's age, prior biopsy results, and DRE into consideration to predict the prostate biopsy outcome. Several studies have confirmed its accuracy in the detection of clinically significant cancer (Gleason score ≥ 7) and its potential to reduce the number of unnecessary biopsies [19-21].

In a case-control study, 12,542 men were followed for > 15 years. A test model based on 4K scores significantly enhanced the prediction of metastasis compared with PSA levels alone [22]. In a prospective multicenter US trial of 1,012 patients, a high discrimination value was reported (AUC = 0.82). The study also showed that using 4K scores would avoid 58% of unnecessary biopsies while missing 4.7% of high-grade cancers [20].

Although the above 3 NCCN-recommended biomarkers are related to PSA derivatives, other markers may have potential to refine PCa detection in primary and secondary biopsies.

PCA3

PCA3 is a noncoding, prostate-specific RNA sequence that is overexpressed in PCa cells [23,24]. The *PCA3* gene was first identified by Bussemakers et al. [25] in 1999 and mapped to chromosome 9q21-22. The contemporary PCA3 test is a urinary assay measuring PCA3 mRNA normalized with PSA in prostate cells [26]. The PCA3 score is calculated as the ratio of PCA3 mRNA to PSA mRNA multiplied by 1,000.

Currently, a PCA3 score cutoff of 25 for repeat biopsy is well accepted [27-29]. When a PCA3 score >25 was used for the choice of performing a repeat biopsy, the biopsy sensitivity was 78% and specificity was 57%.

Although PCA3 is specifically overexpressed in PCa cells, the PCA3 test appears most informative in the repeat prostate biopsy setting. Its value in primary biopsy is limited by missing more high-risk (Gleason score>6) cancers in primary biopsies than in repeat biopsies [30-32]. For example, the Early Detection Research Network (EDRN) validation study in 895 men from 11 centers showed if the lower limit was set at <20, up to 13% of high-risk cancers would be missed in primary biopsies, but only 3% in repeat biopsies [30]. Although the NCCN and FDA do not suggest using PCA3 in the initial biopsy setting, the EDRN study demonstrated a positive predictive value of 80% if the PCA3 score cutoff was set at 60. This may make the PCA3 test valuable as a marker in patients prescreened by PSA for biopsy, especially combined with other clinical factors, such as age, PSA, DRE, prostate volume, or nomograms.

Prostarix

Prostarix is based on the metabolomics of PCa cells and was developed by Metabolon Inc. (Durham, NC, USA) as a post-DRE urine test. The test is based on the quantitative measurement of metabolites in the urine (sarcosine, alanine, glycine, and glutamate), which are combined in a logistic regression algorithm to generate a Prostarix risk score.

The test has been used for initial cancer evaluation to determine which men are candidates for prostate biopsy as well as for repeat biopsy decision-making for men with prior negative biopsies.

Sarcosine, a glycine metabolite, has also recently been identified as a mechanistic marker of PCa progression [33,34]. However, the specificity of sarcosine in the urine of PCa patients has been recently challenged. In a study evaluating amino acids as PCa biomarkers, 50 urine samples from PCa and benign prostatic hyperplasia patients were tested. Arginine, homoserine, and proline were more abundant in the urine samples of cancer patients. However, sarcosine was not a definitive indicator of PCa when analyzed in urine samples collected either before or after prostate massage [35].

TMPRSS2-ERG

TMPRSS2-ERG is a urine-based post-DRE test. In 2005, the chromosomal rearrangement and fusion of the 5' region of the androgen-regulated gene *TMPRSS2* (transmembrane protease, serine 2) with *ERG* or *ETV1* (erythroblastosis virus E26 transformation-specific transcription factor family members) was found to occur in PCa [36].

As a result of this rearrangement, the overexpression of *TMPRSS2-ERG* fusion products was found to be close to 100% specific for the presence of PCa in tissue-based studies, and *TMPRSS2-ERG* gene fusion products were identified in approximately 50% of PSA-screened PCa samples [36]. Subsequently, reverse transcription-polymerase chain reaction (RT-PCR)-based assays were developed to detect TMPRSS2-ERG mRNA in urine [37,38]. As reported, the test has a sensitivity of 37% and a specificity of 93% in predicting PCa, with a positive predictive value of 94% [39].

TMPRSS2-ERG was also associated with clinically significant PCa found through biopsy and prostatectomy [40]. Measuring TMPRSS2-ERG fusion transcripts is encouraging and may represent a new method of improving accuracy in detecting clinically significant PCa.

WHO NEEDS TO BE REBIOPSIED?

More than one million prostate biopsies are performed every year in the US. Furthermore, 40% of men who have had an initial prostate biopsy will undergo a repeat prostate biopsy, and more than 700,000 repeat biopsies are performed in the US annually [41]. Multiparametric magnetic resonance imaging (MRI) followed by ultrasound-MRI fusion biopsy is emerging as a promising approach to identify more clinically significant cancers [42-44]. The previously discussed molecular markers, including %fPSA, the PHI, the 4K score, and PCA3, can also be used to guide repeat biopsies. Eventually, the use of markers to help determine which biopsies are truly negative is imperative to avoid unnecessary biopsies.

Confirm MDx

Confirm MDx, developed by MDx Health Inc. (Irvine, CA,

USA), is an epigenetic test that is used to predict the results of repeat prostate biopsy after an initial negative biopsy. A quantitative methylation-specific polymerase chain reaction assay is used to analyze methylation of the glutathione S-transferase p1 (*GSTP1*), adenomatous polyposis coli (*APC*), and Ras association domain family member 1 (*RASSF1*) genes from negative biopsy specimens. A negative result may help avoid unnecessary biopsies. The negative predictive value within 24 to 30 months of the initial biopsy was as high as 88%–90% [45,46].

WHO SHOULD BE OFFERED CURATIVE TREATMENT OR ACTIVE SURVEILLANCE?

After the diagnosis of PCa, the Gleason score is still the dominant factor in determining treatment. In the PSA era, most diagnosed cases of PCa (81%) involve organ-localized disease. However, given the heterogeneity of PCa in limited biopsy specimens, it is challenging to accurately predict the true risk level with biopsy specimens alone. Approximately 30% of low-risk PCa cases are upgraded or upstaged after radical prostatectomy [47-49]. Prospective studies have shown that curative management should be offered to patients with a good life expectancy and high-risk disease to maximize patients' survival while minimizing side effects [50,51].

According to the 2016 NCCN guidelines, curative treatment is recommended for any man with PCa with a Gleason score of 4 or 5. However, the role of active surveillance in very low-risk or low-risk patients (Gleason 3+3, PSA < 10, PSA density < 0.15, < 3 cores positive for PCa) can be challenging, as not all low-risk cases of PCa behave indolently. Identifying precise molecular markers to stratify potentially unappreciated high risk factors in seemingly low-risk cancers is imperative.

Oncotype DX

Oncotype DX introduced by Genomic Health Inc. (Redwood City, CA, USA), is a quantitative RT-PCR based test using small (1 mm) fixed paraffin-embedded tissue samples obtained by needle biopsy. This genomics-based test measures 12 cancer-related genes that represent 4 different biological pathways (androgen pathway, cellular organization, proliferation, and stromal response) and 5 reference genes, which are algorithmically combined to calculate the genomic prostate score (GPS) [52].

Together with the NCCN risk criteria, the GPS improves the risk discrimination of PCa by separating patients into very low, low, and modified-intermediate risk groups in order to help clinicians select appropriate candidates for active surveillance versus curative treatment [53,54].

Prolaris

The Prolaris test is a molecular test developed by Myriad Genetics Inc. (Salt Lake City, UT, USA). The test measures 31 cell cycle progression genes and 15 housekeeping genes selected for their correlation with PCa proliferation [55-58]. The test is performed in formalin-fixed paraffin-embedded tissue obtained by biopsy or prostatectomy. The results of the test are reported as 10-year PCa mortality, and stratify PCa patients into different risk categories. It is used to predict the level of risk in pretreatment PCa patients in order to choose between active surveillance versus curative treatment. It also may have a role in postprostatectomy patients with adverse pathological features (APFs) to guide the use of adjuvant treatment.

Decipher PCa Test

Decipher (GenomeDx Biosciences, San Diego, CA, USA) uses the expression of 22 selected RNA markers to predict cancer control outcomes in postradical prostatectomy tissue. In addition, several studies have recently shown that Decipher can be used in prostate biopsy specimens to predict the risk of cancer progression events, such as metastasis at 10 years, pelvic lymph node invasion, and APFs in the pretreatment setting.

Although biopsies yield a limited amount of tissue, the transcriptomic features detected in biopsy and prostatectomy tissues are highly correlated ($r = 0.96$) [59]. The concordance between Decipher scores in prostatectomy tissue and biopsy tissue was reported to be as high as 86% in a recent study. This high concordance may allow the Decipher score in biopsy tissue to accurately predict pelvic lymph node invasion (0.78) and seminal vesical invasion (0.7) in prostatectomy tissues [60]. Biopsy-based Decipher scores have also been reported as an independent predictor of adverse pathology at surgery (c-index, 0.71) and clinical metastasis after surgery (c-index, 0.80) at 10 years, compared with 0.75 by NCCN risk stratification [61].

Based on the above studies, biopsy-based Decipher scores may represent another genomic tool to stratify biopsy-proven PCa patients to inform the choice of active surveillance versus curative treatment. It may also improve operative planning by indicating patients who require pelvic lymph node dissection or neoadjuvant therapy.

ProMark

ProMark (Metamark Genetics Inc., Waltham, MA, USA) is a proteomic PCa prognostic test using biopsy tissues [62]. Eight protein biomarkers (CUL2, DERL1, FUS, HSPA9, PDSS2, pS6, SMAD4, and YBX1) are measured with a fully automated immunofluorescent imaging platform. The 8 biomarkers represent PCa aggressiveness and lethality and were selected from 160 candidate proteomic markers using a quantitative proteomic approach [63]. This test aims to stratify the aggressiveness of PCa in Gleason 3+3 and 3+4 biopsy specimens to guide treatment choices.

In an initial study [62], the risk score for favorable and unfavorable pathology was defined in a sample of 381 patient biopsies with matched prostatectomy pathology. At a risk score ≤0.33, the predictive values for favorable pathology in very low-risk and low-risk NCCN groups and low-risk D'Amico groups were 95%, 81.5%, and 87.2%, respectively, higher than for these current risk classification groups themselves (80.3%, 63.8%, and 70.6%, respectively). At a risk score >0.8, the predictive value for unfavorable pathology was 76.9% across all risk groups.

The ProMark assay may provide better individualized and independent prognostic information than current clinicopathology-based risk stratification systems, improving the precision of clinical decision-making following prostate biopsy in patients with Gleason score 3+3 or 3+4 disease.

WHO NEEDS ADJUVANT THERAPY AFTER RADICAL PROSTATECTOMY?

Radical prostatectomy is an effective curative treatment for intermediate and high-risk PCa in patients with a life expectancy of more than 10 years [50]. However, some patients have APFs, such as positive margins, extracapsular extension, and seminal vesicle or bladder neck involvement. Although biochemical recurrence rates are high for men with APFs at radical prostatectomy (up to 60% at 10 years following surgery), it remains unclear whether it is beneficial for all men to undergo adjuvant treatment immediately following surgery [64].

The natural history of metastasis was studied in 3,089 patients who underwent radical prostatectomy in the PSA era at Johns Hopkins [65]. Forty-three individuals (n=1,327) within the cohort had APFs at the time of radical prostatectomy. In the group with APFs, the metastasis rate was 7.5% at 10 years, while the cumulative incidence of metastasis was 6% at 10 years for all patients. Thus, treating all patients with AFPs after radical prostatectomy would result in overtreatment in more than 90% of patients.

Despite the available level I evidence favoring the treatment of APFs with adjuvant radiation therapy (aRT), the use of aRT in patients is still limited [66,67]. Surgeons are cautious to recommend aRT due to concerns of morbidity and overtreatment. Even without adjuvant treatment, almost 50% of patients with APFs do not develop biochemical recurrence [68-71].

Utilizing the genomic features of prostate tissue may offer more precise decision-making in response to the above concerns regarding postprostatectomy APFs.

Decipher

Decipher is a genomic test that serves as a prognostic marker to predict cancer control outcomes in postradical prostatectomy patients that has shown a very high discrimination in predicting clinical metastasis (0.75–0.83) and cancer-specific mortality (0.78) in external validation studies, outperforming all routinely available clinicopathologic characteristics [72-75]. In a large single institutional study with 260 patients, of whom 99 experienced metastasis, the Decipher score showed a strong correlation with the cumulative incidence of biochemical recurrence, metastasis, and PCa-specific mortality ($P<0.01$) [65].

Several reports have shown that Decipher test results had an important impact on decision-making in contemporary clinical practice. Among subspecialized urologists and radiation oncologists, the Decipher results changed aRT decisions in 30%–45% of cases, and observation was offered to nearly 80% of patients with a low Decipher score [76-79].

Although showing early promise, the long-term effects of Decipher-based testing need to be validated with prospective studies to incorporate the Decipher score into PCa therapy decision making.

Prolaris

The Prolaris test can be performed in post-prostatectomy specimens as a prognostic genomic marker. However, long-term guidance for adjuvant treatment requires future clinical trials.

WHO IS A GOOD CANDIDATE FOR SECONDARY HORMONAL MANIPULATION IN CASTRATION-RESISTANT PCa?

Androgen deprivation therapy is the standard treatment for

Table 1. Summary of the contemporary molecular markers in prostate cancer management

	Marker	Description	Sampling specimen	Features
Who needs to be biopsied?	PSA	Protein biomarker used to screen prostate cancer	Serum	Lack of ideal sensitivity or specificity in prostate cancer early detection
	%fPSA	Unbound protein form of PSA	Serum	Limited improvement in prediction accuracy of PCa detection in men with PSA 2–10 ng/mL
	PHI	tPSA, fPSA, and [-2]proPSA incorporated into an equation	Serum	Increases the power to detect PCa, especially high risk (Gleason≥7) PCa
	4K score	4 Kallikrein markers: total PSA, free PSA, intact PSA, and human kallikrein 2, incorporated with patient's age, DRE prior biopsy results	Serum	Better accuracy in the detection of clinically significant cancer (Gleason score≥7) and potential to reduce the number of unnecessary biopsies
	PCA3	A noncoding, prostate specific RNA	Urine	It is not recommended for use in primary biopsy If the PCA3 score cutoff is set at 60, the positive predict value can be at 80%
	Prostarix	Measurement of metabolites in the urine: sarcosine, alanine, glycine and glutamate	Urine	Need future validation
	TMPRSS2-ERG	RT-PCR assay to detect TMPRSS2:ERG fusion transcripts Reported in 50% of PSA screened PCa	Urine	May represent a new method to increase accuracy to detect clinically significant PCa
Who should be rebiopsied?	PSA	As described prior	Serum	As described prior
	%fPSA		Serum	
	PHI		Serum	
	4K score		Serum	
	PCA3		Serum	
	Prostarix		Serum	
	TMPRSS2-ERG		Serum	
	Confirm MDx	A quantitative methylation specific polymerase chain reaction assay to analysis methylation of 3 genes from negative biopsy specimen	Tissue	High negative predictive values to reduce unnecessary repeat prostate biopsies
Who should be offered curative treatment or surveillance?	Oncotype DX	A genomic based tissue test that measures 12 cancer-related genes representing 4 different biological pathways	Tissue	Improves risk discrimination of PCa into very low, low and modified intermediate risk in order to help clinicians select appropriate candidates for active surveillance vs curative treatment
	Prolaris	Measures 31 cell cycle progression genes and 15 housekeeping genes selected by their correlation with PCa proliferation	Tissue	Reports as 10-year PCa mortality to predict grade of risk in pretreatment PCa patients to guide management plan
	Decipher prostate test (biopsy based test)	Uses the expression of 22 selected RNA markers to predict adverse pathology and metastasis after surgery	Tissue	A potential genomic tool to stratify biopsy positive PCa patients in treatment planning
	ProMark	8 Biomarkers representing PCa aggressiveness and lethality were selected from 160 candidate proteomic markers using a quantitative proteomic approach	Tissue	Aims to stratify aggressiveness of PCa in Gleason scores of 3+3 and 3+4 in biopsy specimen to guide treatment
Who needs adjuvant therapy after radical prostatectomy?	Decipher prostate test	As described prior	Tissue	Shows strong correlation with increased cumulative incidence of biochemical recurrence, metastasis, and PCa-specific mortality Application is limited by a lack of prospective studies
	Prolaris	As described prior	Tissue	Prolaris test can be performed in post-prostatectomy specimen as prognostic genomic markers Long term guidance of adjuvant treatment still need future clinical trials to elucidate
Who is a good candidate for secondary hormonal manipulation in castration resistant PCa?	AR-V7	Measurement of an AR-V7	Circulating cells	Avoid treatment with abiraterone and enzalutamide in AR-V7 positive CRPC patients. Earlier chemotherapy would be beneficial

PSA, prostate-specific antigen; fPSA, free PSA; PHI, prostate health index; tPSA, total PSA; PCa, prostate cancer; DRE, digital rectal examination; RT-PCR, reverse transcription-polymerase chain reaction; AR-V7, androgen-receptor splice variant 7; CRPC, castration resistant prostate cancer.

metastatic PCa. However, metastatic PCa eventually becomes castration-resistant [80]. Six new therapies have shown benefits affecting survival in men with metastatic castration-resistant prostate cancer (mCRPC). These therapies include secondary androgen receptor (AR)-inhibiting therapies (abiraterone acetate [81] and enzalutamide [82]), taxane chemotherapies (docetaxel [83] and cabazitaxel [84]), immunotherapies (sipuleucel-T [85]), and bone-targeting radiopharmaceuticals (radium-223) [86]. Of these, the most widely used are secondary AR manipulation with abiraterone/enzalutamide and the chemotherapies. Currently, no molecular biomarkers have been identified to help guide optimal treatment choices in these patients.

Of the patients who receive abiraterone or enzalutamide for the treatment of mCRPC, 20%–40% have primary resistance; that is, no PSA response. Furthermore, the development of secondary resistance is common. Interestingly, the presence of AR splice variants (AR-Vs) may be a cause of AR therapy failure, as the expression of AR-Vs has been observed in xenograft-based models of resistance to abiraterone, and high AR-V levels were found in PCa cell lines resistant to enzalutamide [87,88].

However, although the presence of splicing variant AR-V7 has been implicated in primary resistance to abiraterone and enzalutamide [89], a recent study found that AR-V7 status in 36 men with mCRPC was not related to primary resistance to taxane chemotherapy [90].

These seminal findings regarding AR-Vs may represent a field of research with the promise of furthering precision medicine in selecting treatments for PCa and other cancers.

CONCLUSION

With better interpretation and understanding of genomics, proteomics, transcriptomics and metabolomics, precision medicine will be incorporated into PCa management to an increasing extent.

The contemporary molecular markers in prostate cancer management are summarized in Table 1.

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