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Review – Prostate Cancer

Genomic Markers in Prostate Cancer Decision Making

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Abstract

Context: Although the widespread use of prostate-specific antigen (PSA) has led to an early detection of prostate cancer (PCa) and a reduction of metastatic disease at diagnosis, PSA remains one of the most controversial biomarkers due to its limited specificity. As part of emerging efforts to improve both detection and management decision making, a number of new genomic tools have recently been developed.
Objective: This review summarizes the ability of genomic biomarkers to recognize men at high risk of developing PCa, discriminate clinically insignificant and aggressive tumors, and facilitate the selection of therapies in patients with advanced disease.
Evidence acquisition: A PubMed-based literature search was conducted up to May 2017. We selected the most recent and relevant original articles and clinical trials that have provided indispensable information to guide treatment decisions.
Evidence synthesis: Genome-wide association studies have identified several genetic polymorphisms and inherited variants associated with PCa susceptibility. Moreover, the urine-based assays SelectMDx, Mi-Prostate Score, and ExoDx have provided new insights into the identification of patients who may benefit from prostate biopsy. In men with previous negative pathological findings, Prostate Cancer Antigen 3 and ConfirmMDx predicted the outcome of subsequent biopsy. Commercially available tools (Decipher, Oncotype DX, and Prolaris) improved PCa risk stratification, identifying men at the highest risk of adverse outcome. Furthermore, other biomarkers could assist in treatment selection in castration-resistant PCa. AR-V7 expression predicts resistance to abiraterone/enzalutamide, while poly(ADP-ribose) polymerase-1 inhibitor and platinum-based chemotherapy could be indicated in metastatic patients who are carriers of mutations in DNA mismatch repair genes.
Conclusions: Introduction of genomic biomarkers has dramatically improved the detection, prognosis, and risk evaluation of PCa. Despite the progress made in discovering suitable biomarker candidates, few have been used in a clinical setting. Large-scale and multi-institutional studies are required to validate the efficacy and cost utility of these new technologies.
Patient summary: Prostate cancer is a heterogeneous disease with a wide variability. Genomic biomarkers in combination with clinical and pathological variables are useful tools to reduce the number of unnecessary biopsies, stratify low-risk from high-risk tumors, and guide personalized treatment decisions.

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1. Introduction

Prostate cancer (PCa) is the most frequent urological malignancy and the fifth leading cause of cancer death in men worldwide [1].

Prostate-specific antigen (PSA) is the most extensive screening biomarker adopted for PCa diagnosis and tumor monitoring. However, use of PSA testing in PCa screening is still controversial due to the absence of definitive data from randomized trials, and the lack of specificity between benign and malignant disease. Risk stratification based on traditional clinical parameters can stratify patients' risk of progression with relatively good reliability, but substantial heterogeneity persists within standard risk groups [2].

PCa genomic biomarkers include tools and technologies able to predict the likelihood of an initial positive biopsy; reduce the number of unnecessary repeat biopsies; substratify low-, intermediate-, and high-risk tumors; classify the extent of the disease; and predict and monitor clinical response to an intervention.

The widespread adoption of new biomarkers offering improvements in the discrimination of various disease-related outcomes need to match with a rigorous evaluation of their real benefit. To be clinically helpful, putative pre- and postdiagnosis biomarkers need to provide additive and independent information to clinical parameters. The use of prediction models obtained by adding genomic scores may be justified if, for any given risk defined by one of a number of validated multivariable instruments, they are able to better stratify PCa patient risk and prognosis than clinical variables alone.

The aim of this review is to critically examine the clinical and cost-related utility of novel PCa genomic biomarkers.

2. Evidence acquisition

A PubMed-based literature search was conducted up to May 2017. We selected the most recent and relevant original articles and clinical trials that have provided the most relevant information to guide treatment decisions.

Keywords included "biomarker," "genomic," "susceptibility," "stratification," "predictors of response," "treatment response," and "cost effectiveness." References cited in selected articles and review articles acquired in our search were also used to identify other papers not included in the initial search. The articles that provided the highest level of evidence were then evaluated and selected as the result of an interactive peer-reviewing process by the panel of coauthors.

According to their potential contribution to PCa decision making, we divided our findings into four categories: susceptibility biomarkers, biomarkers of disease risk, risk stratification biomarkers, and biomarkers for prediction of treatment response (Fig. 1).

3. Evidence synthesis

3.1. Susceptibility biomarkers

Family history, age, and race, with the additive role of the environment and lifestyle, have been considered the most relevant risk factors for PCa [3]. Although extensive resources have been invested in identifying the basis of genetic predisposition to PCa, the development of clinically available genomic biomarkers for predicting the susceptibility to the disease has only recently begun to gain traction.

3.1.1. Rare germline mutations

Rare and highly penetrant genetic variants have been studied to identify specific loci that can confer high risk for developing the disease, but difficulty persists in attributing significant value on susceptibility to common diseases to rare variants. Ewing et al [4] reported the association of the "G84E" germline mutation in the homeobox gene HOXB13, a regulator of growth in healthy and cancerous prostate biology, with a higher risk of hereditary PCa. G84E was observed in 0.6% of the control population and in 3.1% of patients with familiar and early-onset PCa (odds ratio 5.1).

Rare germline aberrations in DNA damage repair genes have been associated with higher rates of PCa diagnoses. Although mutations in *BRCA1* and *BRCA2* genes confer a 3.8- and 8.6-fold increased risk of developing PCa, respectively, there is an open debate on how to manage these men and about the impact of DNA repair defects on PCa outcome [3]. Castro et al [5] in a cohort of 2019 PCa patients (18-BRCA1 carriers, 61-BRCA2 carriers, and 1940 noncarriers) confirmed that BRCA1/2 mutations are associated with more aggressive disease ($p = 0.00003$), higher probability of nodal involvement ($p = 0.00005$), distant metastasis at diagnosis ($p = 0.005$), and shorter life expectancy (12.9 vs 8.1 yr; $p = 1 \times 10^{-7}$).

Although the IMPACT study [6] showed higher accuracy of biopsy for detecting intermediate/high-grade PCa in BRCA2 relative to controls (2.38% vs 0.71%; $p = 0.04$), further strong data supporting a change in PSA screening and biopsy recommendations are needed [7].

3.1.2. Single nucleotide polymorphisms

Numerous large genome-wide association studies, using high-throughput technologies and involving thousands of patients, have been conducted to simultaneously scan single nucleotide polymorphisms (SNPs) of various genes or loci associated with PCa. Although these common variants (>5% population frequency) confer relatively small increments in risk for developing the disease (1.1–1.5-fold), their risk levels increase multiplicatively [8]. More than 100 statistically significant PCa-associated loci, which explain 33% of PCa susceptibility, have been identified, but unfortunately, the power of the associations is often too weak to be introduced in a clinical setting [9].

Zheng et al [10] evaluated 16 SNPs from five chromosomal regions in a Swedish population. In men who had five or more of the germline genetic markers correlated to PCa, the odds ratio was 9.46 in relation to men without any of the factors.

Genotyping 25 PCa susceptibility SNPs in more than 40 000 cases and controls, Al Olama et al [11] estimated that PCa risk for men in the first percentile of the polygenic risk score distribution increases 30.6-fold compared with men

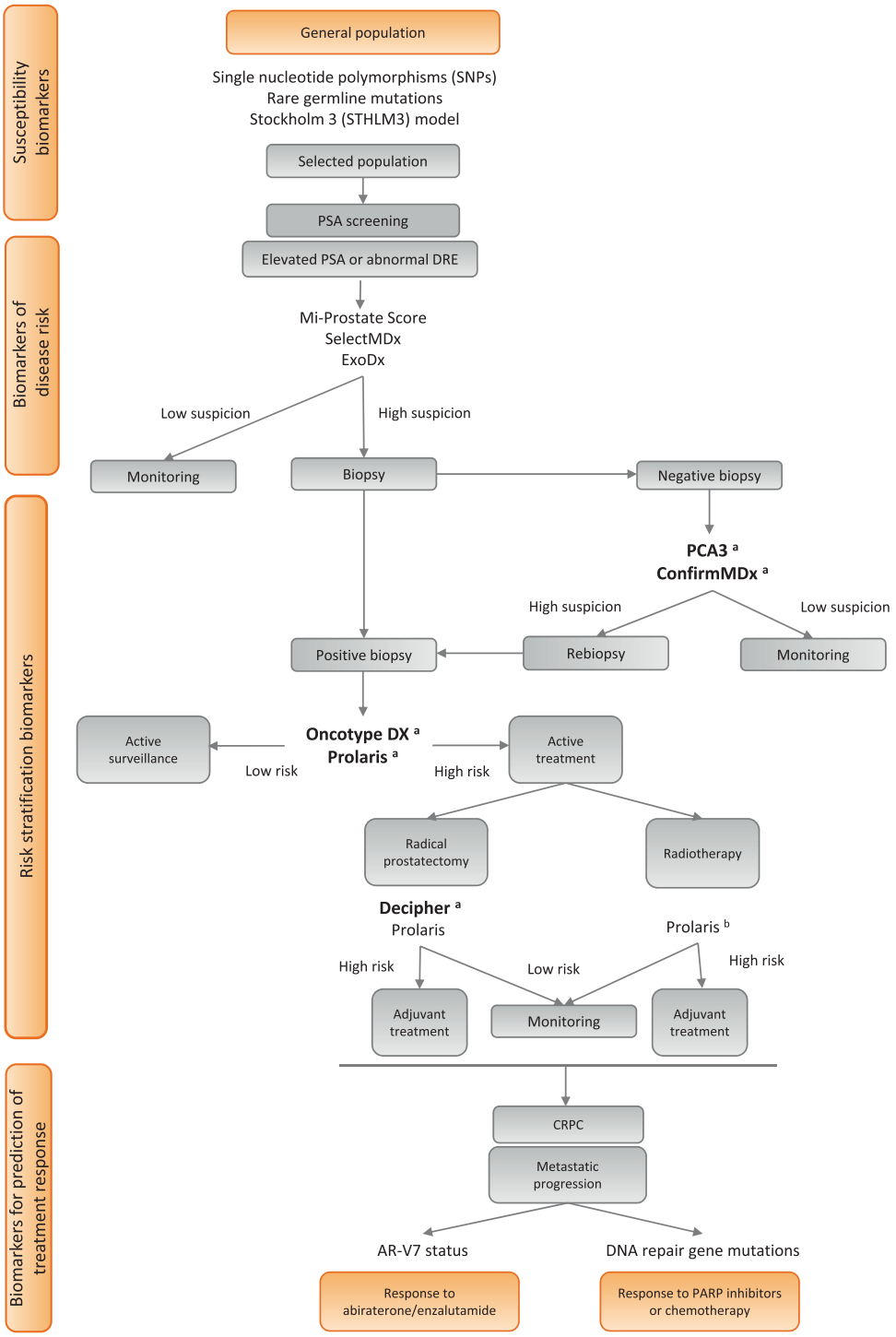

Fig. 1 – Flowchart of genomic prostate cancer biomarkers that have a diagnostic, prognostic, and predictive potential. Diagnostic biomarkers include those that help clinicians select the right person who can benefit from a PSA screening technique, or decide when to perform a biopsy or a rebiopsy. In addition, some genomic markers may have a prognostic/predictive potential to guide decision making on active surveillance/active treatment, immediate/referred adjuvant therapy after radiotherapy or radical prostatectomy, and finally, the response to therapy in a CRPC/metastatic setting. AR = androgen receptor; CRPC = castration-resistant prostate cancer; DRE = digital rectal examination; PARP = poly(ADP-ribose) polymerase; PCA3 = Prostate Cancer Antigen 3; PSA = prostate-specific antigen. [a] Genomic markers recommended by the National Comprehensive Cancer Network guidelines. [b] Not validated.

in the last percentile and 4.2-fold compared with the population average.

Despite these promising results, other studies offered opposite conclusions. Klein et al [12] highlighted that genetic markers alone (area under the curve [AUC] = 0.571) or in combination with PSA (AUC = 0.791) were less accurate than PSA (AUC = 0.792) to predict PCa in a population not routinely screened for the disease. A study

by Chatterjee et al [13] demonstrated that the predictive ability of polygenic models alone in PCa improves when the sample size increases, but they still remain modest with an AUC of <0.7. Again, because the risks associated with these variants are modest, large studies are required to predict their risks precisely.

The Stockholm 3 (STHLM3) model, a personalized risk-based diagnostic tool that combines plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic polymorphisms (232 SNPs), and clinical variables (age, family, history, previous prostate biopsy, and prostate examination), has been developed and validated in a Swedish population without PCa [14]. STHLM3 model showed a higher ability (AUC = 0.74) in the identification of high-risk disease (Gleason score ≥7) compared with PSA alone (AUC = 0.56), and it reduced the number of biopsies by 32% using a PSA cutoff of ≥3 ng/ml for recommending biopsy.

As a first screen suitable for use in the primary care setting, PSA remains the standard of care for the foreseeable future. To date, considering both accuracy and practicality, germline genetic testing can only optimally identify age for first screening or interpretation of PSA results once available.

3.2. Biomarkers of disease risk

3.2.1. Mi-Prostate Score

The noncoding RNA Prostate Cancer Antigen 3 (PCA3) is a PCa-specific early-detection biomarker quantifiable in tissues and in urine collected after digital rectal examination (DRE) that has been used in counseling and confirming initial and repeat biopsy [15]. The Progensa PCA3 test (Hologic, Marlborough, MA, USA) showed promising results as an indicator of repeat biopsy (AUC = 0.71–0.75, combined with PSA and clinical variables) but not in a prebiopsy setting [15]. Owing to the paucity of studies that have found a correlation with PCa aggressiveness, there is still a lack of consensus regarding the use of PCA3 on repeat biopsy setting compared with PSA alone or other clinical variables [16]. However, PCA3 has been recommended in the National Comprehensive Cancer Network (NCCN) guidelines for men at a higher risk of PCa with at least one prior negative biopsy [7].

Given the fact that TMPRSS2-ERG fusion-gene transcripts have an independent additional predictive value to PCA3, recent studies suggest that the combination of the two biomarkers could lead to a considerable reduction in the need for prostate biopsies [17]. Hessels et al [18] showed in 108 prebiopsy post-DRE urine samples (72% diagnosed with PCa) that PCA3 plus TMPRSS2:ERG increase the test sensitivity from 62% for PCA3 alone to 73% for both markers. Despite the small number of patients enrolled, Salami et al [19] suggested that combining serum PSA, PCA3 (sensitivity 93%), and TMPRSS2:ERG (specificity 87%) in a multivariable algorithm, optimized for clinical utility, improved PCa prediction with an AUC of 0.88, 90% of specificity, and 80% of sensitivity.

In a recent prospective multicenter study including 443 men at risk of PCa, Leyten et al [20] highlighted the independent additional predictive value of urinary TMPRSS2:ERG to PCA3 and the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculator parameters. The predictive power of the ERSPC risk calculator alone (AUC = 0.799) substantially increases in a comprehensive model including ERSPC risk calculator, PCA3, and TMPRSS2:ERG (AUC = 0.842). TMPRSS2:ERG has been proved to be the most specific biomarker for clinically significant PCa (specificity 93.2%, sensitivity 24.3%) and, when added to PCA3, was able to increase the sensitivity to 88.1% without compromising PCA3 specificity (49.6%).

The performance of PSA or the multivariate Prostate Cancer Prevention Trial (PCPT) risk calculator has recently been shown in a validation cohort of 1244 men to be significantly improved by TMPRSS2:ERG plus PCA3 in predicting PCa and high-risk disease (AUC = 0.762 and 0.779, respectively) [21].

Using as a positive test result TMPRSS2:ERG >8, PCA3 >20, or PSA >10 ng/ml, a recent prospective validation study showed a higher prediction of aggressive PCa (Gleason score ≥7) with specificity of 33.4% and sensitivity of 92.6% compared with PSA alone (specificity 16.7%, sensitivity 91.2%) in a cohort of 516 men presenting for first-time biopsy. The AUC of PCPT risk calculator alone or plus TMPRSS2:ERG and PCA3 was 0.74 or 0.81, respectively [22]. The logistic regression model Mi-Prostate score is a clinically available tool for individualized risk assessment provided by the University of Michigan (MLabs, Ann Arbor, MI, USA).

3.2.2. SelectMDx

SelectMDx (MDxHealth, Irvine, CA, USA) is a post-DRE urine methylation assay available in clinical practice to improve patient selection for initial biopsy. Leyten et al [23], after identifying 39 PCa biomarkers using gene expression profiling data, selected eight biomarkers according to a quantitative polymerase chain reaction (PCR) analysis of tissue specimens and urinary sediments. A validated urinary three-gene panel (*HOXC6*, *TDRD1*, and *DLX1*) showed higher accuracy (AUC = 0.77) for the detection of clinically significant PCa (Gleason score ≥7) compared with PSA and the Progensa PCA3 test (AUC = 0.72 and 0.68, respectively). Van Neste et al [24] validated these promising results in two independent prospective multicenter clinical trials. Not only the two-gene risk score that combines HOXC6 and DLX1 messenger RNA (mRNA) expression levels with traditional risk factors (ie, PSA density, DRE, PSA, age, history of prostate biopsy, and family history) is able to predict high-grade PCa on biopsy (AUC = 0.90), but its use could also reduce the number of unnecessary biopsies and potential overtreatment. A low-risk SelectMDx score correlates with 90% probability that a man does not have PCa and 98% likely that he does not have high-risk PCa.

3.2.3. ExoDx

ExoDx Prostate Intelliscore (Exosome Diagnostics, Cambridge, MA, USA) is a novel urinary exosome-gene expression assay able to estimate initial biopsy results. By detecting PCA3 and TMPRSS:ERG exosomal mRNAs in urine samples of PCa patients, Nilsson et al [25] elucidated the

potential contribution of these extracellular, double-lipid membrane, small vesicles as a source of noninvasive biomarkers.

EXO106, an algorithm that associates PCA3 and ERG exosomal mRNA levels normalized with SPDEF (SAM pointed domain-containing ETS transcription factor), demonstrated good clinical performance in predicting high-grade disease (Gleason score ≥7) with negative predictive value (NPV) and positive predictive value of 97.5% and 34.5%, respectively, in 195 urine samples of men undergoing a prostate biopsy [26].

The ExoDx Prostate (expressed as a risk score ranging from 0 to 100) was recently validated in 519 patients' non-DRE urine samples. The association of the exosome-gene expression with clinical parameters (PSA, age, race, and family history) resulted in better discriminative power between insignificant and aggressive disease (AUC = 0.73) compared with the standard of care alone (AUC = 0.63) [27].

3.2.4. ConfirmMDx

The methylation marker test, ConfirmMDx (MDxHealth), is a tissue-based assay that studies the epigenetic alteration surrounding the tumor lesions ("halo" effect) in order to reduce the number of unnecessary repeat biopsies [28]. This test identifies the hypermethylation pattern of CpG island promoter regions of three genes (*GSTP1*, *APC*, and *RASSF*) in men after a negative biopsy. After validation in a European and a US cohorts of which all patients had two consecutive biopsies within 24–30 mo, ConfirmMDx achieved an NPV of 88–90% compared with 70% for histopathology alone [29,30].

Recently, Van Neste et al [31] developed a novel algorithm named EpiScore to better stratify methylation-positive patients for the risk of harboring high-grade cancer. By weighing the DNA-methylation intensities of GSTP1, RASSF1, and APC, EpiScore improved the identification of those men at higher need of a repeat biopsy (Gleason score ≥7), resulting in an NPV of 96% for high-grade cancer. This test is an option in the NCCN guidelines for men with at least one prior negative biopsy [7], but long-term data are necessary to evaluate the real clinical benefit.

3.3. Risk stratification biomarkers

3.3.1. Decipher

The tissue-based genomic classifier (GC) Decipher was codeveloped and validated by GenomeDx Biosciences (Vancouver, BC, Canada) and Mayo Clinic (Rochester, MN, USA). Based on 22 RNA biomarkers (screened from over 1.4 million protein-coding genes and noncoding RNA markers) related to cell proliferation, differentiation, motility, immune modulation, and androgen receptor (AR) signaling, GenomeDx continuous risk score (0–1) is able to predict the risk of clinical metastasis development after surgery [32].

A recent meta-analysis of five different studies examined the performance of Decipher to prognosticate the risk of metastases in 855 men with adverse pathology at the time of radical prostatectomy (RP) [33]. Low-, intermediate-, and high-risk Decipher categories, using 0.45 and 0.60 as thresholds, showed 10-yr cumulative incidences of metastasis of 5.5%, 15.0%, and 26.7%, respectively. Decipher emerged as an independent predictor of metastasis (even after adjusting for adjuvant treatments) and improved the 10-yr distant metastasis predictive accuracy of clinical parameters from an AUC of 0.76 to 0.81. Moreover, Cooperberg et al [34] highlighted Decipher's increased discrimination ability (AUC = 0.78) to predict PCa-specific mortality compared with clinicopathological variables expressed as Cancer of the Prostate Risk Assessment (CAPRA) score (AUC = 0.75).

GenomeDx GC has also been shown to guide treatment decisions after RP [35]. Analyzing a cohort of 188 high-risk patients treated with RP and radiotherapy (RT), Den et al [36] revealed that models including GC (alone or plus CAPRA score) have a higher ability to predict the occurrence of metastases (AUC = 0.83–85) than clinicopathological parameters alone (AUC = 0.66). Patients with a GC of ≥0.4 undergoing adjuvant or salvage RT showed a cumulative incidence of metastasis at 5 yr of 6% or 23%, respectively ($p = 0.008$).

To identify men who could benefit from adjuvant RT versus initial observation, Dalela et al [37] developed a simple risk stratification tool (score 1–4) based on the cumulative number of risk factors (pT3b/T4 disease, pathological Gleason score 8–10, lymph node invasion, and GC >0.6). Specifically, adjuvant RT significantly reduced the 10-yr clinical recurrence rate only in patients with a risk score of ≥2 (10.1% in the adjuvant RT group and 42.1% in initial observation group; $p = 0.012$), suggesting that patients with unfavorable pathological characteristics and a higher GenomeDx score should be taken into consideration for adjuvant treatment.

Using an Affymetrix full exome expression array rather than reverse transcription PCR, Decipher permits further genetic investigations on previously run samples, facilitating both future research and additional prognostic scores. A different 24-gene signature based on these data (Post-Operative Radiation Therapy Outcomes Score) has been shown to be particularly useful in predicting response to adjuvant RT [38]. Although additional validation studies are needed, NCCN guidelines recommend its utilization in patients with positive surgical margins, any pT3 disease, or rising PSA after RP [39].

3.3.2. Oncotype Dx Genomic Prostate Score

Oncotype Dx Genomic Prostate Score (GPS; Genomic Health Inc., Redwood City, CA, USA) is a quantitative real-time PCR assay performed on small fixed paraffin-embedded tissue samples obtained by needle biopsy. This assay includes 12 cancer-related genes involved in four different biological pathways (androgen pathway, cellular organization, proliferation, and stromal response) and five reference housekeeping genes algorithmically combined to calculate the GPS [40].

The GPS, expressed on a scale of 0–100, has been investigated as a risk predictor of adverse pathology at RP in patients diagnosed with low or intermediate disease on biopsy. The GPS may guide clinicians in stratifying

patients for active surveillance versus therapeutic intervention [41,42].

An independent validation study was performed by Klein et al [43] in a cohort of 395 PCa patients with low and intermediate risk who underwent RP. The 17-gene assay combined with clinical parameters (age, PSA, clinical stage, and biopsy Gleason score) or the CAPRA score [2] was proved to be an independent and better predictor of high-grade (primary Gleason score of 4 or any pattern of 5) and/or high-stage disease (pT3 or higher) at the time of RP. A further retrospective validation of Oncotype Dx in 431 patients confirmed the ability of this genomic test in the pretherapy scenario to ameliorate the prediction of adverse pathological features at RP and time to biochemical recurrence (BCR) with a hazard ratio of 2.93 for every 20-unit increase in the GPS [44]. The lack of large and prospective evaluations of its correlation with oncological outcome may limit the real clinical benefit of this assay.

According to the NCCN guidelines, Oncotype DX may be used for postbiopsy NCCN very-low- and low-risk PCa patients with 10–20 yr of life expectancy [39].

3.3.3. Prolaris

The commercially available Prolaris test is a 46-gene panel (31 cell-cycle progression [CCP] genes and 15 housekeeping genes) developed by Myriad Genetics (Salt Lake City, UT, USA). The Prolaris assay, performed in prostate biopsy or RP specimens, could help in the decision making between active surveillance and active treatment in low-risk PCa, and it may also suggest the use of adjuvant therapy in high-risk patients with adverse pathological features after surgery [45].

Cuzick et al [46] investigated the impact of the CCP score based on the Prolaris assay in two different populations of PCa patients treated with RP ($n = 366$) or transurethral resection of the prostate ($n = 337$). The CCP score was able to predict the risk of BCR after RP and the 10-yr specific mortality in patients conservatively managed. Two further studies evaluating the performance of Prolaris test in 349 [47] and 582 [48] prostate biopsies showed the role of CCP score as an independent predictor of PCa death, BCR, and metastasis after RP.

Cooperberg et al [49] confirmed the ability of the CCP score to predict BCR after RP and found that a combined model incorporating the CCP with the CAPRA score has a better prognostic value for both the overall cohort and a low-risk subset.

Even among men undergoing RT as primary therapy, this assay has been significantly associated with BCR, denoting the role of CCP score in identifying high-risk men who may benefit from adjuvant therapy [50]. Even if other prospective clinical-utility and cost-effectiveness studies are required, NCCN guidelines include the use of the Prolaris test for NCCN very-low- and low-risk PCa patients after a positive biopsy with at least 10-yr life expectancy [39].

Table 1 summarizes the key features of the clinically available genomic assays that have shown excellent diagnostic and prognostic ability.

3.3.4. Clinical utility and cost effectiveness

Although we have seen significant progress in the technological discovery of biomarkers, their adoption into clinical practice has been more modest. In the absence of long-term and prospective investigations, the real net benefit and effect of genetic markers on patient oncological outcomes (eg, overall/cancer-specific survival or biochemical/clinical recurrence) are currently unknown [51].

Another contingent limitation for routine use of genomic biomarkers may be attributed to the absence of large-scale cost-effectiveness and cost-utility studies able to examine their economic benefits in addition to their clinical utility. Recent analyses revealed that overdiagnosis and overtreatment should be decreased by choosing an appropriate test with consequent reduction in medical costs and a gain in patients' quality of life (Table 2). Specifically, the use of SelectMDx [52], Oncotype DX [53], and ConfirmMDx [54] demonstrated a positive economic impact on the healthcare costs, whereas the incorporation of other markers may be uncertain (Decipher [55] and Mi-Prostate Score [22]) or negative (PCA3 [56] and Prolaris [57]). Unfortunately, these models are based only on assumptions and long-term projections. Their results may change in the future after a more accurate evaluation of health economic burden.

3.4. Biomarkers for prediction of treatment response

Since the discovery that PCa is dependent on androgens, androgen deprivation therapy has been the gold standard treatment for patients with advanced disease. However, after an initial period of therapeutic response, PCa becomes insensitive and progresses to castration-resistant PCa (CRPC). Despite the recent introduction of the next-generation hormonal therapies, resistance to these agents limits therapeutic efficacy for many patients. Predicting and monitoring response to treatment and disease progression is one of the most studied areas in urological research.

3.4.1. AR-V7 in circulating tumor cells or cell-free DNA

Constitutively active AR variants, resulting from alternative splicing of the human AR gene, represent an emerging key mechanism responsible for tumor progression.

AR-V7 is the most clinically meaningful AR splice variant. The AR-V7 mRNA expression, detected in circulating tumor cells (CTCs) from CRPC patients receiving enzalutamide or abiraterone, has been associated with drug resistance. Antonarakis et al [58] suggested that positive detection of AR-V7 in CTCs was sufficient to predict poor prognosis compared with their AR-V7–negative counterparts. The CTC +/AR-V7+ patients not only failed to respond to the anti-AR agents (abiraterone/enzalutamide) [58], but also showed lower PSA response rates, and shorter radiographic progression-free and overall survival than CTC+/AR-V7– and CTC– patients [59]. Interestingly, AR-V7+ CRPC patients appear to benefit more from taxanes than from AR-targeted therapies, while in AR-V7– patients, the efficacy is not related to the treatment type [60]. Scher et al [61] confirmed these previous findings and demonstrated in 161 metastatic CRPC (mCRPC) men that the CTC expression of nuclear

Table 1 – Clinically available genomic markers proposed to guide prostate cancer clinical decision making

Test	Company	Tissue type	No. of genes or proteins	Main results	Utility assessment	Reference
Biomarkers of disease risk						
Mi-Prostate Score	University of Michigan, MLabs	Post-DRE urine	2	TMPRSS2:ERG plus PCA3 in combination with PCPT risk calculator improve the prediction of aggressive PCa (AUC = 0.81).	Initial biopsy	[22]
SelectMDx	MDxHealth	Post-DRE urine	2	Risk calculator including urinary HOXC6 and DLX1 mRNA levels is a good predictor (AUC = 0.90) for the detection of clinically significant PCa (GS $\geq$ 7).	Initial biopsy	[24]
ExoDx	Exosome Diagnostics	Urine	3	Association of the exosome-gene expression with clinical parameters (PSA, age, race, or family history) can discriminate between insignificant and aggressive disease (AUC = 0.73).	Initial biopsy	[27]
PCA3	Hologic	Post-DRE urine	1	PCA3 score predicts biopsy outcome in combination with PSA, DRE, and other clinical parameters (AUC = 0.71–0.75).	Rebiopsy	[15]
ConfirmMDx	MDxHealth	Prostate biopsy	3	Methylation status of three genes (*GSTP1*, *APC*, and *RASSF*) is able to identify men at higher need of a repeat biopsy (NPV of 88–90%).	Rebiopsy	[29,30]
Risk stratification biomarkers						
Decipher	GenomeDX Biosciences	Radical prostatectomy	22	Decipher scores, in addition to clinical variables, predict 10-yr distant metastasis after surgery (AUC = 0.81). GC (alone or plus CAPRA score) has a higher ability to predict the occurrence of metastases (AUC = 0.83–85).	Adjuvant treatment after radical prostatectomy	[33,36]
Oncotype DX	Genomic Health Inc.	Prostate biopsy	17	GPS combined with clinical parameters (age, PSA, clinical stage, and biopsy GS) or with the CAPRA score is a predictor of high-grade (primary GS of 4 or any pattern of 5) or high-stage disease (pT3 or higher), and BCR.	Active surveillance or active treatment	[43,44]
Prolaris	Myriad Genetics	Prostate biopsy	31	CCP score is an independent predictor of PCa death, BCR, and metastasis after radical prostatectomy and radiation therapy.	Active surveillance or active treatment	[47–50]
		Radical prostatectomy		The combination of CCP and the CAPRA score achieves a higher prognostic power.	Adjuvant therapy in high-risk patients	

AUC = area under the curve; BCR = biochemical recurrence; CAPRA = Cancer of the Prostate Risk Assessment; CCP = cell cycle progression; DRE = digital rectal examination; GC = genomic classifier; GS = Gleason score; GPS = Genomic Prostate Score; NPV = negative predictive value; PCa = prostate cancer; PCA3 = Prostate Cancer Antigen 3; PCPT = Prostate Cancer Prevention Trial; PSA = prostate-specific antigen.

AR-V7 protein is statistically associated with superior survival on taxane over AR-directed therapy.

Although the role of CTCs as a biomarker has widely been explored in recent years, the clinical utility of current CTC tests is limited mainly due to their scarcity and methodological constraints. Under the assumption that tumor-specific transcripts in blood are most likely derived from CTCs, and to bypass the isolation of CTCs, Qu et al [62] analyzed the expression of both AR-V7 and PSA transcripts in the peripheral blood mononuclear cell fraction in CRPC patients treated with abiraterone acetate or enzalutamide. PSA and AR-V7 transcript levels were associated with shorter survival, highlighting the potential role of this new technique as a useful biomarker for predicting response to therapy.

A clinical-grade assay to detect AR-V7 mRNA status in circulating CTCs is available through Johns Hopkins' Molecular Diagnostics Lab.

3.4.2. *DNA repair gene mutations*

Recent advances in high-throughput genotyping and next-generation sequencing technologies contribute to better understand the potential application of genomic aberrations in the DNA damage repair pathways for PCa risk prediction and response to therapy.

The Cancer Genome Atlas Research Networking and the Stand Up To Cancer Prostate Cancer Foundation International Dream Team (SU2C-PCF2) recently analyzed the genomic landscape of 333 patients with localized PCa and 150 biopsies from mCRPC, respectively. Despite the fact that 19% of localized PCa patients carried germline or somatic aberrations in genes involved in the DNA damage repair pathway (BRCA2, BRCA1, CDK12, ATM, FANCD2, and RAD51C), men with mCRPC were found to have a higher prevalence of aberrations in key DNA repair genes (23%) compared with those with localized disease [63].

Poly(ADP-ribose) polymerase (PARP) inhibitors have been considered an effective therapeutic option for tumors with impaired homologous recombination DNA repair, based on the biological theory of the synthetic lethal effect. The recent phase-2 TOPARP trial [64] investigated the antitumoral activity of olaparib, a PARP inhibitor family member, in mCRPC patients progressing on standard

Table 2 – Summary of clinical utility and cost-effectiveness studies for "disease risk" and "risk stratification" genomic biomarkers

Biomarker	Clinical utility		Cost effectiveness	
	Study	Main findings	Study	Main findings
Biomarkers of disease risk				
Mi-Prostate Score	Tomlins et al (2016) [21]	*Cohort:* MiPS models were applied to a cohort of 1244 men presenting for prostate biopsy. *Results:* Using MiPS, compared with the PCPT risk calculator, led to a significant reduction of the number of biopsies by 17.6% (20% risk threshold) and 19% (30% risk threshold) and delayed only 0.5% and 1% of high-grade cancers, respectively.	Sanda et al (2017) [22]	A decision analytic model analyzed the cost of using a multiplex decision algorithm (TMPRSS2: ERG, PCA3, and PSA) versus PSA screening alone in patients at risk of PCa. The multiplex algorithm generated cost savings of $1200–2100 per patient, but the authors did not include the cost of PCA3 and T2:ERG testing.
SelectMDx	Van Neste et al (2016) [24]	*Cohort:* Independent validation cohort of 386 men with a suspected PCa (PSA ≥3 ng/ml, abnormal DRE, or a family history of PCa). *Results:* A decision curve analysis, using a cutoff with an NPV of 98% for GS ≥ 7, demonstrated that SelectMDx is able to reduce the unnecessary biopsies by 53% and decrease the number of biopsies by 42% compared with the PCPT risk calculator and the PCA3 assay. Moreover, the test provided the best performance in detecting high-grade disease.	Dijkstra et al (2017) [52]	A decision tree and Markov model evaluated, over a 18 yr time horizon, the cost effectiveness of SelectMDx test, relative to PSA-alone, in men with a PSA level of >3 ng/ml. SelectMDx strategy (cutoff sensitivity of 95.7%) led to 36% probability of undergoing an unnecessary biopsy compared with 77% of the PSA-alone group. SelectMDx assay contained the costs by €128 per patient compared with the PSA-alone strategy.
ExoDx	McKiernan et al (2016) [27]	*Cohort:* ExoDx was validated in 519 patients (age ≥50 yr, suspicious DRE, and/or PSA 2–20 ng/ml) scheduled for an initial or repeated prostate biopsy. *Results:* An ExoDx cutoff of >15.6 avoids 27% of biopsies (NPV = 91% and sensitivity = 92%) and misses 8% GS ≥ 7 diseases, when compared with PSA. A cutoff of 20 increases the rate of avoided biopsies (37% vs 27% using the original cut point) maintaining an NPV of 90% and sensitivity of 87%, but missing 12% of patients with ≥GS7.		Not reported
PCA3	Wei et al (2014) [16]	*Cohort:* A total of 297 men scheduled for repeat prostate biopsies (elevated PSA, high-grade prostate intraepithelial neoplasia, or abnormal DRE) received PCA3 test measurement. *Results:* A PCA3 score of ≤20, regardless of the PSA value, prevented 46% of prostate biopsies, missing 12% and 3% of PCa and high-risk disease, respectively.	Nicholson et al (2015) [56]	The PROSPERO study evaluated the clinical benefit of using the PCA3 assay alone or in combination with the existing tests in a rebiopsy setting. The results from the cost-effectiveness analyses revealed that PCA3 test is not cost effective.
ConfirmMDx	Wojno et al (2014) [28]	*Cohort:* A clinical utility field observation study enrolled 138 men (age: 63 yr; PSA: 4.7 ng/ml) with an initial negative prostate biopsy. *Results:* Only six patients (4.3%) with a negative epigenetic assay result underwent a subsequent prostate biopsy with no evidence of cancer on histopathology. Owing to the small number of patients who received a repeat biopsy and the retrospective nature of the study, it remains unclear if this assay may help reduce unnecessary rebiopsies.	Aubry et al (2013) [54]	A budget impact model, calculated over a 1-yr time horizon, revealed that the use of ConfirmMDx, in patients with elevated PSA levels and histopathologically negative biopsies, could reduce the overall healthcare costs. The epigenetic assay, in a commercial health plan with 1 million members, produced savings of $588 per patient management by truly distinguishing the true-negative prostate biopsy results.
Risk stratification biomarkers				
Decipher	Gore et al (2017) [35]	*Cohort:* The multicenter prospective PRO-IMPACT study enrolled a total of 265 patients (150 considering for ART and 115 considering for SRT). *Results:* Decipher test results influenced 18% of management recommendations in the ART arm (including 31% among high-risk patients) and 32% in the salvage arm (including 56% among high-risk patients). Moreover, the GC significantly reduced the fear of PCa disease recurrence in the ART arm and PCa-specific anxiety in the SRT arm among low-risk patients. Despite the interesting results, it is not known whether the recommendation changed the final treatment received. Second, no unexposed Decipher testing control group was used to demonstrate that the test can improve PCa-related outcomes.	Lobo et al (2017) [55]	A Markov model evaluated, during a 10-yr time horizon, the costs and QALYs associated with the incorporation of Decipher in postoperative setting. GC-based decision making results were more effective, but more expensive, than the usual care rates for adjuvant therapy after surgery. Furthermore, the data revealed the gain in terms of QALYs and a 16% reduction in the percentage of patients with distant metastasis at 5 yr (relative to the standard of care).

Table 2 (*Continued*)

Biomarker	Clinical utility		Cost effectiveness	
	Study	Main findings	Study	Main findings
Oncotype DX	Eure et al (2017) [42]	*Cohort:* A total of 505 patients (GPS group: 258; baseline group: 247) with clinically low-risk PCa, were enrolled in a prospective, multi-institutional, observational study. *Results:* Adoption of GPS test showed a 22% increase of recommendations for AS than the untested cohort, with a 21% higher rate of persistence in AS protocol after 1 yr.	Albala et al (2016) [53]	A prospective, noninterventional, decision impact and cost study evaluated, in a real-world setting, the clinical utility and economic impact of Oncotype DX assay for 100 men diagnosed with clinically low-risk PCa. The incorporation of GPS led to a 21% increase in the indication of AS between NCCN very-low- and low-risk men with average savings of $2286 per patient in the 180 d following the diagnosis.
Prolaris	Shore et al (2016) [45]	*Cohort:* The PROCEDE-1000 prospective registry analyzed how CCP score test can affect the medical decision making for 1206 newly diagnosed PCa patients. *Results:* The authors reported changes of the intended treatment in 47.8% of cases with an overall reduction in the number of therapies assigned but, interestingly, an increase in the number of high-risk patients receiving primary ADT. The concordance of 82% between treatment decisions, based on clinical factors alone or after the incorporation of the CCP assay, calls into question the real clinical benefit of the introduction of this genomic test in a clinical setting.	Health Quality Ontario (2017) [57]	A budget impact analysis (from the perspective of the Ontario Ministry of Health and Long-term Care) hypothesized the expenses of using the Prolaris CCP test for men with newly diagnosed, low- or intermediate-risk PCa over the next 5 yr. The CCP test resulted in a large increase in cost with very small cost savings by improving AS regimens.

ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; AS = active surveillance; CCP = cell cycle progression; DRE = digital rectal examination; GC = genomic classifier; GPS = Genomic Prostate Score; GS = Gleason score; MiPS = Mi-Prostate Score; NCCN = National Comprehensive Cancer Network; NPV = negative predictive value; PCa = prostate cancer; PCA3 = Prostate Cancer Antigen 3; PCPT = Prostate Cancer Prevention Trial; PSA = prostate-specific antigen; QALY = quality-adjusted life year; SRT = salvage radiotherapy.

treatments. Of the 49 men enrolled, 33% responded to the therapy with an increased patient response (88%) in the subset that was identified to carry defects in DNA repair pathways.

Moreover, a retrospective sequencing analysis of mCRPC patients who benefited from platinum chemotherapy in the absence of neuroendocrine differentiation suggested the potential role of BRCA2 biallelic germline/somatic inactivation as a prognostic biomarker for platinum-based chemotherapy sensitivity [65].

4. Conclusions

Current risk stratification systems for the management of men both before and after diagnosis of PCa are accurate when used correctly, but still suffer from important limitations.

Patients with the same histological and clinical PCa parameters can have strikingly varied presentations, molecular profiles, and clinical outcomes. It appears evident that reliable and more specific biomarkers are needed to identify the patient subsets that may benefit from alternate approaches. Newly available PCa biomarkers should be used to select patients for PCa screening, reduce unnecessary biopsies, discriminate a clinically insignificant disease from an aggressive one, and choose the best therapy in metastatic patients. The development of panels combining many different markers seems to ameliorate PCa diagnosis and management, especially those that can outperform/complement the currently used clinical and pathological prognostic factors.

The results provided by these biomarkers, mostly expressed as a percentage of risk, can lead to misinterpretations. These genetic scores should be considered as continuous variables and not categorized as negative or positive. These biological markers should ideally be evaluated together with other tumor-related features (eg, PSA, grade, Gleason score, percentage of biopsy involvement, and extension of the disease) and patient characteristics (age, comorbidities, and life expectancy).

Larger-scale, multi-institutional, and multinational studies will still be required to prospectively validate the utility of these markers, their cost effectiveness, and how they should truly be used in clinical practice. Nonetheless, we anticipate that the integration of genome information with transcriptomic, proteomic, and metabolomic data will help clinicians move the field toward personalized medicine, benefiting both patient quality of life and healthcare costs.

Author contributions: Christopher P. Evans had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Evans, Cucchiara.
Acquisition of data: Cucchiara, Cooperberg, Dall'Era, Lin, Montorsi, Schalken, Evans.
Analysis and interpretation of data: Cucchiara, Cooperberg, Dall'Era, Lin, Montorsi, Schalken, Evans.
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