Review

Can We Predict Prostate Cancer Metastasis Based on Biomarkers? Where Are We Now?

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Can We Predict Prostate Cancer Metastasis Based on Biomarkers? Where Are We Now?

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Abstract: The incidence of prostate cancer (PC) has been risen annually. PC mortality is explained by the metastatic disease (mPC). There is an intermediate scenario in which patients have non mPC but will have initiated a metastatic cascade through an epithelial-mesenchymal transition. There is indeed a need for more and better tools to predict what patients will progress in the future to non-localized clinical disease or already have micrometastatic disease, and therefore, will clinically progress after primary treatment. Biomarkers for predicting mPC are still under development; there are few studies and not much evidence of their usefulness. This review is focused on tissue-based genomic biomarkers (TBGB) for predicting metastatic disease. We developed four main research questions that will attempt to answer according to the current evidence. Why is important to predict metastatic disease? Which tests are available to predict metastatic disease? What impact should there be on clinical guidelines and clinical practice in predicting metastatic disease? What are current prostate cancer treatments? The importance of predicting metastasis is fundamental, given that once metastasis is diagnosed, the quality of life (QoL) and survival drop dramatically. There is still a need and space for more cost-effective TBGB tests that predict mPC disease.

Keywords: prostate cancer; metastasis; tissue-based genomic biomarkers

Introduction

Approximately 288,300 men will be diagnosed with prostate cancer (PC) in 2023 in the US with an expected death rate of 34,700 cases, which is the second cause of death by cancer in men. The incidence of prostate cancer has been risen 3% annually. This increment is driven by annual increases of regional-stage and distant-stage diagnoses that began as early as 2011. Localized-stage disease has also begun to increase, although the trend is not yet statistically significant [1]. Worldwide, in 2020 an estimated 1,414,259 men were diagnosed with prostate cancer and 375,304 died from the disease at a crude rate of 9.5%. Approximately 15% of the cases were metastatic at the diagnosis, with a 5-year survival rate of 31% [2]. Once the diagnosis is made with a non-metastatic, clinically significant PC according risk criteria, a local curative treatment should be offer in order to reduce the risk of metastatic disease and eventually risk of mortality [3-5]. On the other hand, if metastatic prostate cancer (mPC) is diagnosed, only palliative management can be used in order to improve survival and quality of life (QoL). Any curative intent is impossible at this stage, especially when patients are in the last stage of non-metastatic (nmCRPC) or metastatic castrate resistant prostate cancer (mCRPC) despite multiple new drugs and tools that have developed the last few years [6-13]. Without a doubt there is an intermediate scenario in which patients have no mPC but will have initiated a metastatic

cascade through an epithelial-mesenchymal transition [14]. Still, even if we invested many resources, we would not be able to identify those patients. Current tools that are utilized with several limitations, such as clinical, biochemical and histological parameters, clearly are not sufficient to identify patients that are going to progress to mPC and whose not [15, 16]. In general adjuvant treatments after local therapy using the above criteria have not shown better outcomes than observation or early salvage treatment [17, 18]. From the perspective of a clinical setting, there are still several questions with no clear answers. For example, are local treatments such as radical prostatectomy (RP) or radiotherapy (RT) with or without androgen deprivation therapy (ADT) capable of killing or eradicating prostate cancer cells from the body? Should adjuvant therapy be used more frequently as personalized therapy? Is PSMA PET/CT showing early metastatic disease clinically useful? Does it reduce mortality? Is there a better way to classify localized, high-risk patients? There is indeed a need for more and better tools to predict what patients will progress in the future to non-localized clinical disease or already have micrometastatic disease, and therefore, will clinically progress after primary treatment. Knowing this information could help determine which patients may need multimodal or adjuvant treatment even with a localized disease, and in consequence, what patients do not need more than a single modality of treatment. It is well known that patients with unfavorable intermediate- and high-risk features are at higher risk of recurrence and develop metastatic disease after primary treatment; therefore, probably theses group of patients are the best candidates for testing new potential biomarkers to predict mPC.

Biomarkers are molecules that can provide information about the diagnosis, progression, prognosis, and prediction of pharmacological response. These include the presence of specific cell types, proteins, metabolites, RNA, DNA mutation, polymorphism, or epigenetic modification [19]. Different types of biomarkers have been studied in PC as tools for analysis of risk of progression, with the potential of application to the accurate identification of candidates for active surveillance (AS), adjuvant therapy and/or new therapy modalities. We recently published a review of the role of biomarkers in AS [20]. This review included urine, blood and tissue biomarkers. In addition, several studies in the past few years have shown the role of imaging as a tool for the diagnosis, staging and therapy of mPC. In this vein, multiparametric magnetic resonance imaging (mpMRI) [21] and PET/CT [22-24] represent important tools in the diagnosis, staging, and monitoring of PC patients.

The best approach for monitoring remains challenging for clinicians; biomarkers are being developed and may play an important role. Biomarkers for predicting mPC are still under development; there are few studies and not much evidence of their usefulness. This paper seeks to address the limited literature in the field.

We know that biochemical failure or persistent elevated PSA after primary treatment and the appearance of clinical metastasis can take several years [25-27]. Currently, with the use of PSMA PET/CT, this time has been shortened [24]. However, PSMA PET/CT imaging is still under development, not universally available and the evidence of its clinical utility, especially in reducing mortality, is still under research. Developing and better understanding the role of biomarkers in predicting metastatic disease may be essential to improving PC management and eventually reducing PC mortality. We can obtain these biomarkers through needle biopsies or RP tissue specimens - years before the theorical appearance of metastasis - in order to cure patients before they have metastasis but with a high risk of developing it or even with circulating tumor cells (CTC) waiting to nest in the bones and/or lymph nodes. To date, most of the literature related to tissue-based genomic biomarkers (TBGB) is focused on Oncotype DX, Prolaris and Decipher. However, their role has been better demonstrated in AS rather than advanced disease [28-33]. This review is focused on TBGM for predicting metastatic disease. We developed 4 main research questions that will attempt to answer according to the current evidence.

i) Why is important to predict metastatic disease?

ii) Which tests are available to predict metastatic disease? What is the evidence and the efficacy of commercialized tissue prognostic tests Prolaris (Myriad Genetics), Oncotype DX Prostate (Exact Sciences), and Decipher (Genome DX Biosciences)?

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iii) What impact should there be on clinical guidelines and clinical practice in predicting metastatic disease?

iv) What are current prostate cancer treatments? and potential new therapeutic opportunities using TBGM for predicting metastasis.

i) Why is important to predict metastatic disease?

Metastatic hormone-sensitive PC (mHSPC) will inevitably lead to death in a 10-years period. Therefore, is crucial to treat patients during localized disease and eventually before detecting any signs of clinical metastasis. Currently, biomarkers for predicting metastatic disease are being studied. Current tools are biochemical and histological variables such as PSA, Gleason score, margin status and tumor volume [16]. In some cases, these variables are used to decide when to add adjuvant therapy as radiotherapy post RP based on the T stage and margin status [34-37]. However, as with any treatment, the risk of overtreatment and loss of QoL associated with the treatment are important elements to consider. Therefore, a biomarker needs to be accurate.

Much has been written about the mechanism of PC development into metastasis. Epithelial-mesenchymal transition [14] and circulating tumor cells are involved in this mechanism [38] . Bone metastasis is the most frequently seen in PC because, in part, of the action of cytokines/chemokines and growth factors [39, 40].There is a latent period of many years between the metastatic cells leaving the prostate and developing metastatic disease. It is not known exactly which is the moment of no return in terms of curation. Is a cell that exits the prostate always going to produce radiologic metastasis? What proportion of cases with CTC will develop metastasis? During what point of the disease will a biomarker have the best chance of being a good predictor and therefore allow the curing of a patient?

MPC is by far the main cause of PC mortality. In the last few years, the incidence of mPC has increased from 18% to 25%. The age at diagnosis has decreased from 71 to 68 years of age, and non-Hispanic Asian, low-income, and unmarried men are more likely to die of mPC, respectively [41, 42]. This is explained by less frequent PSA screening as a result of the recommendation from the US Preventive Service Task Force against routine PC screening for men of all ages in 2012 [43]. This point is relevant since the median survival of patients with a new diagnosis of mPC is 42 months with ADT alone. However, this population is heterogenous since the diagnosis can be provided as *de novo* oligometastases (defined as ≤ 3 to 5 metastases) or polimetastases, or metachronous metastatic disease after primary treatment for localized disease [10]. It has been found that men with prostate cancer metastases have a 29.8% five-year survival rate, as compared to a 100% survival rate in men with localized prostate cancer. The primary goal of any cancer treatment is to reduce the cancer-specific mortality. The way to measure this is through metastasis-free survival, which is a surrogate endpoint for the risk of disease death [44] and overall survival [45].

Having mPC is not only related to mortality but also QoL. There is a long list of potential complications from metastatic disease such as bone fractures, cord compressions, lymph edemas, renal failures secondary to urinary obstructions [46]. In addition the treatment of androgen blockage production or action and/or radiotherapy can result in side effects that include fatigue, anemia, breast enlargement and tenderness, hot flashes, loss of libido, erectile dysfunction, loss of muscle mass and strength, fatigue, anemia, depression, hair loss, osteoporosis, fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease [47]. Other side effects are more specific, depending on which treatment is used, for example, abiraterone (hyperkalemia, elevation of liver enzymes), apalutamide (rash), enzalutamide (falls), Docetaxel (febrile neutropenia), and PARP inhibitors (anemia and fatigue) [9, 12, 48-50]. Therefore, it is important to prevent and eventually detect and treat these adverse effects (AE), for example, by preventing bone fractures with vitamin D/calcium, Bisphosphonates or human monoclonal antibodies against RANKL. The effect on QoL has been well studied and demonstrate in this stage [51], and new therapies have demonstrated that they improve survival and also QoL [52]. Bone metastasis is by far the most frequent complication (80%) in PC [53], therefore bone health is a very important concept in men with metastasis. Skeletal-related events (SREs) include pathologic fracture, spinal cord compression, palliative radiation,

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or surgery to bone, and change in antineoplastic therapy secondary to bone pain. All of these complications can dramatically affect the QoL and survival. For example, pathological bone fracture in prostate cancer patients increases mortality by 20% [54], and having bone metastasis increases mortality by 6 times with no SRE and by 10 times with SRE [55]. Consequently algorithms have been created to better treat and follow patients with ADT and/or bone metastasis in order to maintain bone health [56].

Strategies to better and early detect metastatic disease to minimize AE of systemic treatment and perhaps improve survival have been developed. PSMA PET/CT and directed metastasis therapy are good examples of these strategies, respectively.

PSMA PET/CT versus conventional imaging. PSMA PET/CT has been implemented for the past few years and it has shown a better sensitivity, specificity and accuracy than conventional imaging (CT and bone scan) in the detection of metastatic disease [22, 57]. However, it is still unclear if the improved performance of PET/CT will result in a greater cancer rate survival and overall survival. ^{18}F-DCFPyL recently received FDA approval for the staging of biochemically recurrent prostate cancer. The main role of PSMA PET/CT has been shown in staging in high-risk patients [22] and also in detecting location and number of metastases in men with biochemical recurrence after primary treatment with radical prostatectomy [24].

Directed metastatic therapy (DMT). One of the major concerns about treating patients with metastatic disease is the adverse effects from ADT, as described above. This is the main reason why DMT has been used for oligometastatic disease [58, 59]. Series of patients have been published using PET and conventional imaging [23, 58-60]. The objective is to delay the use of ADT, which probably does not affect the oncologic outcome.

It is important to understand that predicting/preventing metastatic disease is crucial to survival because once a patient has metastatic disease, there is no curative window of time and treatment; there is only palliative treatment that can prolong life.

ii) Which tests are available to predict metastatic disease? What is the evidence and the efficacy of commercialized tissue prognostic tests?

There are 3 TBGBs available in the market that may play a role in predicting mPC and which will be discussed below.

Oncotype DX is a biopsy-based genomic test designed as a reverse transcription polymerase chain reaction assay that has been analytically validated to measure the expression of 17 genes in RNA extracted from fixed tumor tissue from prostate needle biopsies [33]. The test provides a Genomic Prostate Score (GPS) result, scale 0–100, with increasing scores indicating more biologically aggressive disease. It has been clinically validated as a strong, independent predictor of adverse pathology (AP) (defined as Gleason score [GS] ≥ 4 + 3 and/or non– organ-confined disease) [33, 61] and biochemical recurrence (BCR) after RP in men with clinically very low–, low-, and intermediate-risk PCC [61]. In addition, the use of GPS has been associated with the increased recommendation and utilization of AS in men with very low–, low-, and favorable intermediate–risk patients because it can differentiate clinically indolent from aggressive PC and is designed to address heterogenicity, multifocality and limited biopsy sampling [33]. The 17-gene GPS has been shown to be an independent predictor of AP in a prospectively designed validation study of a large, contemporary cohort of men with low- to low-intermediate risk PC who were candidates for AS. Several publications have shown the role of oncotype DX in predicting AP in male candidates for AS [61-63]. Cullen et al. [61] showed an association between GPS and the risk of recurrence in a racially diverse cohort who underwent RP. The analysis was done in biopsies of men with very low, low, and intermediate risk. GPS was a significant predictor of BCR in univariate analyses and after adjusting for clinical and pathology covariates. GPS was also a predictor of aggressive disease; however, the event number was too small and therefore inconclusive. In terms of metastatic disease, Van Den Eeden [64] showed the association of Oncotype DX and the risk of metastatic disease in a 10-year risk study. They used diagnostic biopsy specimens of patients with low-, intermediate-, and high-risk PC. The median follow-up was of 9.8 years. Of the 259 patients evaluated, 79 had metastatic disease and 180 had non-metastatic disease. GPS was a significant predictor of time to metastasis, and GPS was independently associated with

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NCCN risk groups, AUA risk groups and CAPRA score groups in multivariate analyses. In other analyses, GPS was also associated with BCR and prostate cancer-specific death. In addition, Brooks and colleagues [65] studied the association of oncotype DX and long-term outcomes [distant metastasis and prostate cancer-specific mortality (PCSM) after RP] using tissue from the index lesion of an RP specimen. GPS was independently associated with a 20-year risk of distant metastasis and PCSM. In multivariate analyses with RM correction, a 20-unit increase in GPS resulted in estimated hazard ratios of 2.24 (95% CI, 1.49 to 3.53) and 2.30 (95% CI, 1.45 to 4.36) for distant metastasis and PCSM, respectively. Both studies from Van der Eeden and Brooks had similar results, even with independent cohorts. Van der Eeden found that the HR/20 GPS units for distant metastasis was 2.34 (95% CI, 1.42 to 3.86) and the HR/20 GPS units for PCSM was 2.69 (95% CI, 1.50 to 4.82), and Brooks had equivalent results (HR, 2.24; 95% CI, 1.49 to 3.53 and HR, 2.30; 95% CI, 1.45 to 4.36, respectively). Interestingly, higher GPS scores were associated with a cribriform pattern and a stromagenic pattern as well as higher levels of progression in men in AS. The limitations of these studies, as the authors mention, are that they are exploratory, because the test was developed in the same samples. External validation is necessary. To our knowledge there are no more studies that associate oncotype DX with the risk of metastatic disease at the time of diagnosis or after primary treatment.

Prolaris. This commercial test is a gene-expression classifier test that combines the Cancer of the Prostate Risk Assessment (CAPRA) score with a cell cycle progression (CCP) score derived from a tumor RNA expression profile to produce a personalized metastasis risk score after the definitive treatment for localized prostate cancer. CCP molecular score was defined originally in 2011 in a retrospective cohort [66] and then was combined with CAPRA to create a CCR score first described in 2015 by Cusick et al. [29] using samples from needle biopsies in a cohort of patients on AS. The CCR score is a good predictor of outcomes in men who underwent primary treatment for localized PC in AS, surgery or radiotherapy [67, 68]. Cusick et al. [29] published a validation study in a cohort of patients managed conservatively using CCP as a predictor of death. They used needle biopsies, and in multivariate analyses the CCP score's overall hazard ratio was 1.76 (95% CI (1.44, 2.14) and the CCR's score was highly predictive, with a hazard ratio of 2.17 (95% CI (1.83, 2.57). Swanson et al. published [69] a study of 360 men in 2021 using sample tissue form radical prostatectomy specimen in which CCR was demonstrated to be an independent predictor of metastatic disease and disease-specific mortality after RP, (HR = 3.03 [95% confidence interval (CI): 1.49, 6.20]; p = .003] and disease-specific mortality (HR = 3.40 [95% CI: 1.52, 7.59]; p = .004), respectively. One of the major potential benefits of using biomarkers is to determine the need for adjutant therapy. Tward et al. addressed this question in a study published in 2021 [70]. They used the CCR score and defined a multimodality therapy threshold for patients who had radiotherapy or surgery to assess the need of ADT or radiation, respectively. They studied patients with NCCN unfavorable intermediate- and high-risk. They estimated the risk of progression in men who underwent surgery or RT using the prognostic value of CCR scores below and above the threshold, stratified by single- or multimodality therapy for metastasis. In all cases, men with CCR scores above the threshold who received single-modality therapy had the worst outcomes. The clinical utility of this study is that it can provide guidance as to when to use adjuvant treatment in patients who underwent surgery or radiotherapy. For example, the authors found that the reduction in the Kaplan-Meier estimated risk for metastasis based on adding ADT to RT for the population of men below the threshold was 2.2%, whereas for those above the threshold, it was 20.3%. In 2022, Tward published an article [71] in which they addressed the utility of CCR scores in predicting the development of metastasis after primary radiation therapy. They also sought to validate the CCR score multimodality threshold described in their previous study in NCCN unfavorable intermediate-, high- and very high-risk patients who might consider RT alone rather than the current recommendation of RT plus ADT in these groups of patients. This was a multi-institutional study cohort of men with prostate cancer treated with dose-escalated external beam RT (EBRT) with or without ADT. The CCR score was highly prognostic for metastasis in the full cohort (HR, 2.22; 95% CI, 1.71-2.89; P < .001); however, the CAPRA score by itself was not a predictor of metastatic disease. In terms of the need for ADT associated with RT, the threshold was dichotomized in below or above a CCR score of 2.112. The risk of metastasis below the threshold was low, regardless

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of NCCN category. Furthermore, for men below the threshold, ADT of any duration did not significantly reduce the risk of 10-year metastasis as compared to patients treated only with RT (3,7% for each group). On the other hand, men in the above-threshold group who were treated with single-modality therapy had a more than 6-fold predicted risk of developing metastasis compared to those below the threshold.

Decipher. Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed in 2013 [72] to predict systemic progression after definitive treatment. Originally it was based on the expression of 22 RNA biomarkers related to androgen receptor signaling, cell proliferation, differentiation, motility, and immune modulation using radical prostatectomy specimen tissue samples; however, currently, there is also a Decipher® created from needle biopsy tissue samples. This resulted in a final set of 22 markers corresponding to RNAs from coding and non-protein coding regions of the genome and based on a majority rule criterion: the patients with GC, CC and GCC scores greater than 0.5 were classified as high risk whereas those with a score lower than or equal to 0.5 were classified as low risk. In multivariable analyses, after adjusting for post-RP treatment, GC remained the only significant prognostic variable (p,0.001), with an OR of 1.36 for every 10% increase in GC scores. The independent significance of GC suggests that a more direct measure of tumor biology (i.e., a 22-marker expression signature) adds significant prognostic information for the prediction of early metastasis after a rising PSA, which is not captured by the clinical variables available from pathological analyses. Cases with high GC Scores die earlier from prostate cancer. A randomized clinical trial [73] using radical prostatectomy tissue specimens validated Decipher as an independent predictor of distant metastasis and, with the secondary end points of prostate cancer-specific mortality and overall survival. Patients received salvage radiotherapy with or without 2 years of bicalutamide. In multivariable analysis, the GC (continuous variable, per 0.1 unit) was independently associated with DM (hazard ratio [HR], 1.17; 95% CI, 1.05-1.32; P = .006), PCSM (HR, 1.39; 95% CI, 1.20-1.63; P < .001), and OS (HR, 1.17; 95% CI, 1.06-1.29; P = .002) after adjusting for age, race/ethnicity, Gleason score, T stage, margin status, entry prostate-specific antigen, and treatment arm. Interestingly, the estimated absolute effect of bicalutamide on 12-year OS was less when comparing patients with lower vs higher GC scores (2.4% vs 8.9%). Patients received salvage radiotherapy with or without 2 years of bicalutamide. Spratt et al. [74] in a meta-analysis of five studies including 855 high risk patients with 8 years of follow-up analyzed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP as a predictor of metastasis development. The 10-year cumulative incidence metastases rates were 5.5%, 15.0%, and 26.7% ($p < 0.001$) for patients classified by Decipher as low, intermediate, and high-risk, respectively. The authors showed in multivariable analysis that Decipher was a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, $p < 0.001$). In a systematic review published by Jairath [75] which included 44 studies that address the role of Decipher in different settings such as localized, postprostatectomy, nonmetastatic castration-resistant, and metastatic hormone-sensitive PC, the GC was independently prognostic for all study endpoints (adverse pathology, biochemical failure, metastasis, cancer-specific and overall survival) in multivariable analyses. They concluded that the GC is most accurate for intermediate-risk PC and postprostatectomy decision-making. Further studies are needed to establish how to best incorporate Decipher in clinical decision-making, for example, using needle biopsy tissue specimens in predicting the recurrence of metastatic development.

Currently, there are ongoing clinical trials utilizing the Decipher genomic classifier for PC. These trials are assessing the potential utility of Decipher in different stages, including its use in predicting the usefulness of different new antiandrogen therapies as primary and adjutant treatments. Table 1 shows a summary of the three TBGB described above.

iii) Impact on clinical guidelines and clinical practice.

We performed a review of the present and current recommendations from different panels regarding the utility of different TBGB (Table 2). In this review we discuss AUA/ASTRO, NCCN, European and ASCO guidelines. Importantly, we summarize the recommendation written at the moment this review was written and, therefore, there could be some differences with future versions of the guidelines because they are dynamic and can be modified every few months or years.

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American Urological Association/American Society for Radiation Oncology (AUA/ASTRO) Guidelines 2022 [76-78]:

1) Clinically localized prostate cancer guidelines. Guideline statement/Risk assessment (part 1):

2. "Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision-making. (Expert Opinion)."
3. "Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B)". In terms of prediction of metastatic disease, the guidelines state clearly: "two studies using biopsy data have shown that a cell cycle progression panel (Prolaris) score was associated with the risks of biochemical recurrence, metastatic disease, and prostate cancer death; however, only one of those studies met inclusion criteria for the systematic review. The Oncotype Dx assay has been validated on needle biopsy tissue and found to be associated with adverse pathology, biochemical recurrence, metastasis, and prostate cancer death; again, however, the studies did not meet inclusion criteria for the systematic review. Meanwhile, a multi-institutional evaluation of Decipher Biopsy testing found that a high-risk Decipher score was associated with conversion from active surveillance to definitive treatment. Thus, based on the level of existing data, the Panel concluded that clinicians should not routinely use tissue based genomic biomarkers for risk stratification or clinical decision-making [76]. In part 3, Future directions/Genomic classifiers (GCs) the panel concludes, "The ability for commercially available GCs to improve the outcomes of patients with clinically localized prostate cancer has not been validated in prospective clinical trials to date. Prospective validation of the predictive capacity of GCs in localized disease will be important to support widespread use for treatment selection. Several ongoing clinical trials are indeed evaluating treatment intensification and de-intensification based on GC results in both intermediate- and high-risk patient populations."

2) The advanced prostate cancer AUA/ASTRO/SUO guidelines published in 2021 [79, 80] and amended in 2023 [81] make no mention of genomic tissue biomarkers in the presence of biochemical recurrence without metastasis, MHSPC, nmCRPC or mCRPC in the statements of what clinicians should or may do for prognosis and treatment. In the 2021 guidelines part 2, in Future Directions the organization states, "As we move forward as a field, we need to focus on the biologic make-up of tumors and how these can be better leveraged to identify treatment options for patients." In the update published in 2023, in Future directions/Biomarkers and Other Systemic Therapies, there is no mention of genomic tissue biomarkers, but rather of germline and somatic tumor alterations such as DNA damage response genes and DNA mismatch repair genes.

NCCN guidelines. Version 1.2023 [82]. In *principles risk stratification,* the guidelines mention, "Patients with NCCN low, favorable intermediate, unfavorable intermediate, or high-risk disease and life expectancy ≥10 years may consider the use of the following tumor-based molecular assays: Decipher, Oncotype DX Prostate, and Prolaris" (PROS-D 2 of 4). Then, in a table (PROS-D 3 of 4), these three biomarkers are shown as prognostic but not predictive tools and only Decipher has an "endpoint trained for" or was designed to predict and optimize distant metastasis. In the same table the level of evidence for the validation of Decipher is described as level 1, indicating "validation in the context of multiple clinical trials with consistent results. Randomized trials are necessary for predictive biomarkers for validation." Prolaris is described as follows: "Like other biomarkers it has been validated for multiple endpoints, but the test was not specifically trained for an endpoint a priori". Oncotype DX prostate is described as having a role in showing adverse pathology. Following the principles risk stratification table, Prolaris and oncotype DX are indicated to have a level 3 of validation, which means "Validation in multiple independent retrospective studies with consistent results," None of these 3 biomarkers are part of *the initial risk stratification and staging workup for clinically localized disease* (PROS-2). However, in a section titled PROS-2A underneath the table, there is an explanation: "Tumor-based molecular assays and germline genetic testing are other tools that can assist

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with risk stratification." Decipher is not mentioned as one of the tools in a PSA persistence/recurrence patient (PROS-10). However, in the guideline's development, the section *Tumor multigene molecular testing* (MS-9), the panel recommends that the Decipher molecular assay should be used to inform adjuvant treatment if adverse features are found post-radical prostatectomy, The panel indicates that "patients with low or favorable intermediate disease and life expectancy greater than or equal to 10 years may consider the use of Decipher, Oncotype DX Prostate, or Prolaris during initial risk stratification. Patients with unfavorable intermediate- and high-risk disease and life expectancy greater than or equal to 10 years may consider the use of Decipher or Prolaris. In addition, Decipher may be considered to inform adjuvant treatment if adverse features are found after radical prostatectomy and during workup for radical prostatectomy PSA persistence or recurrence (category 2B for the latter setting). Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of patients with prostate cancer" (MS-10).

European Guidelines (EAU-EANM-ESTRO-ESUR-SIOG): 2023. [83, 84] Chapter 6. 6.2.1.1.2. *Tissue-based prognostic biomarkers testing*. Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark® are promising. However, further data will be needed before such markers can be used in standard clinical practice. 6.2.5.2.1. *Biomarker-based risk stratification after radical prostatectomy*. The guidelines only mention Decipher. There is no mention of Prolaris or Oncotype. Decipher was described as follows: "The Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analyzed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher® GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, $p < 0.001$) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic, and treatment subgroups. A systematic review of the evidence for the Decipher® GC has confirmed the clinical utility of this test in post-RP decision-making. Further studies are needed to establish how to best incorporate Decipher® GC in clinical decision-making." However, there is no mention of recommendations for using Decipher or any other biomarker for the decision-making process in patients who had a primary local treatment and then relapse. Furthermore, in chapter 6.3. *Management of PSA-only recurrence after treatment with curative intent*, there is no mention of a potential role of any biomarker.

American Society of Clinical Oncology (ASCO) guidelines. For localized prostate cancer, published in 2018 [85], there is only a mention in point 32 of Table 1 regarding AS. "Tissue based genomic biomarkers have not shown a clear role in active surveillance for localized prostate cancer and are not necessary for follow up. (Expert Opinion)." There is no mention of tissue biomarkers in high-risk patients or post prostatectomy or radiotherapy follow-up for predicting metastasis or their role in the decision making for subsequent therapy. Then, in the section on molecular biomarkers in localized prostate cancer published in 2020 [86] the guidelines delineate 4 questions (Table 1 of the guidelines). The first one is related to the role of biomarkers in the selection patients for AS, the second one is about the usefulness of biomarkers for the diagnosis of clinically significant prostate cancer, the third is related to the role of biomarkers in the decision-making of adjuvant o salvage therapy after radical prostatectomy, and the fourth is about the comparison of genomics vs MRI in identifying clinically significant prostate cancer. In response to questions 1 and 2 the panel's recommendation is that a "routine ordering of molecular biomarkers is not recommended" based on insufficient evidence with a moderate grade of recommendation. In their answer to question 3, they mention Decipher Genomic Classifier as the only option; however, "in the absence of prospective clinical trial data, routine use of genomic biomarkers in the post prostatectomy setting to determine adjuvant versus salvage radiation or to initiate systemic therapies should not be offered," based on insufficient evidence. And finally, for the fourth question, the panel recommends using them only when the results are likely to affect clinical management. These tests may provide information independent of the clinical parameters and independent of one another, indicating a weak grade of recommendation.

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Finally, in a section on non-castrated advanced, recurrent and mPC, updated in 2023 [87], there is no mention of biomarkers in predicting metastasis or their usefulness in the management of these patients.

In conclusion, the panels of the four associations that we analyzed are very consistent in that TBGB may be utilized in some cases; however, there is not enough evidence to support a recommendation that tissue biomarkers should be used. Still, biochemical, histological, and clinical parameters have stronger evidence and therefore, guidelines put them over tissue-biomarker as a tool for biochemical recurrence and metastatic development. Our belief is that positive or negative biomarkers are a very important need to improve the risk probability of recurrence and eventually of adjuvant treatment or closing follow-up.

iv) Current prostate cancer treatments and potential new therapeutic opportunities using tissue-based biomarkers for predicting metastasis.

There is a real need for biomarkers to determine which patients will have metastasis in the future to better determine the primary treatment. We describe current treatment according to the evidence for different stages where a TBGB tissue-based biomarker could play an important role in modifying and improving treatment.

Localized prostate cancer. For localized low- and favorable intermediate-risk PC, currently, the best treatment options are radical prostatectomy, radiation therapy, or AS. Biomarkers to define the best candidates for these treatments in AS are not addressed in this current review because they were reviewed in previous work [20]. For unfavorable intermediate- and high-risk PC current treatments, including RP plus extended lymphadenectomy, radiotherapy plus ADT, and possibly abiraterone for high-risk patients [77, 83, 85]. PSMA PET/CT has a relatively new role in staging high-risk prostate cancer patients. According to a proPSMA multicenter randomized phase 3 study published by Hofman et al. in 2020 [22] PSA had 27% greater accuracy than conventional imaging in detecting metastasis as a first-line imaging and also showed a higher rate of management changes than conventional imaging (28% vs 15%). For TBGB currently, there is no clear space in staging or defining the presence of micrometastasis or predicting clinical metastasis as was explained above. The evidence is still limited and based on non-randomized clinical trials. There is a need to have TBGB to better define, for example, what patients will need an adjuvant treatment after local primary treatment. These biomarkers should not compete with imaging, but they should complement each other.

Biochemical recurrence: Defined as two consecutive PSA values of ≥ 0.2 ng/ml post-RP or 2 points above nadir post Radiation therapy, biochemical recurrence is an attractive subject, and the discussion is still open and very dynamic on how to manage these patients. Histology variables such as Gleason grade, tumor volume/extension, and margin status are predictors of relapse after primary treatment. In the worst-case scenario, patients with ISUP grade > 2 in combination with EPE (pT3a) and particularly those with SV invasion (pT3b) and/or positive surgical margins are at a high risk of progression, which can be as high as 50% after 5 years [88]. LN involvement, capsular penetration of LN, LN density, and the number of LN involved are also good predictors of recurrence [25, 89, 90]. PET CT has been demonstrated to detect recurrence post-primary treatment at a rate of 59%-66%, localization at a rate of 84%-87%, and a change in management in 64% of patients at this stage [24]. Currently, treatment for biochemical recurrence is mostly based on radiotherapy and sometimes ADT. There is a major potential role of a TBGM in this setting in terms of predicting biochemical recurrence and defining what patients with BCR are better candidates for starting a new type of treatment. For example, if a patient is ISUP group 2 or 3, with a negative margin but the biomarker is highly predictive of developing metastasis, that patient may be a good candidate for early radiotherapy or systemic treatment.

Adjuvant (ART) vs. Salvage Radiotherapy (SRT). ART vs.3 early SRT and the efficacy of adjuvant ADT have been compared in three prospective randomized clinical trials (RCTs: the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [34], the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [35], and the Groupe d´Etude des Tumeurs UroGenitales (GETUG-AFU 17) [36]. A meta-analysis including the 3 of them has been published [37]. The three RCTs have

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shown no differences between the two treatments in terms of biochemical progression free survival. The studies showed that SRT had lower levels of ≥ 2 grade complications. Additionally, in recent years ultrasensitive PSA has been introduced. Taking into account both of these factors in favor of SRT, the use of ART has shifted to early SRT.

Clinically positive lymph nodes (N1). Patients with clinical N+ disease definitely need a multimodal therapy based mainly on radiotherapy plus ADT ± abiraterone or radical prostatectomy plus extended lymphadenectomy in selected cases [77, 83]. There is no literature on using tissue-based biomarkers in patients with clinical N+. Biomarkers may be useful in this scenario in which multimodal therapy is used in practically all patients.

Today, for patients with HSPC and mCRPC that are already advanced, tissue-based biomarkers for predicting metastasis are not necessary because they already have metastasis; however, in the group of nmCRPC patients that is reducing substantially due to the use of PET PSMA and because fewer patients are being treated with antiandrogen therapy in the status of biochemical recurrence. This group of patients never had metastasis. There are well-known randomized trials that showed apalutamide, enzalutamide or darolutamide improve metastatic, disease-free survival by 2 years in men who had a PSADT < 10 months. For men with PSADT > 10 months, observation is the best management option [48, 91, 92].

Conclusions and future directions.

This review arises from the need for better-known tools that currently exist for predicting PC metastasis. We performed a review of the literature in regard to the importance of diagnosing mPC, the TBGB that currently exist that can play a role in this prediction, the recommendation of different urological and oncologic guidelines, and finally recommendations for current treatment and the potential space for new therapies based on mPC prediction through TBGB. The importance of predicting metastasis is fundamental, given that once metastasis is diagnosed, the QoL and the survival drop dramatically. Oncotype DX, Prolaris and Decipher are currently TBGB that are in the market. Prolaris and Oncotype DX were designed primarily to predict local aggressiveness rather than distant metastasis. Decipher Genomic was designed as a predictor of metastasis using radical prostatectomy tissue specimens, and more recently using needle biopsy specimens. Today it is the only TBGB tool that can predict metastatic disease and has been used mainly with unfavorable intermediate and high risk to define better which patients will receive ADT complementing RT, and in biochemical relapse scenarios to define the best timing to initiate RT. However, there is still no strong evidence of its role in the management of unfavorable intermediate and high-risk non-mPC. We understand that currently there are two active phase III trials where intensification or de-intensification of hormonal treatment according to risk-based genomic tissue biomarkers. In these trials the main outcome is metastasis-free survival The first one, The PREDICT-RT Trial (ClinicalTrials.gov ID NCT04513717), uses Decipher as a tissue biomarker and compares less intense hormone therapy and radiation therapy with traditional hormone therapy and radiation therapy in treating patients with high-risk (NCCN) prostate cancer and low gene risk score. This trial also compares more intense hormone therapy (Apalutamide) and radiation therapy to traditional hormone therapy and radiation therapy in patients with high-risk prostate cancer and high gene risk score. In the second one, The Guidance Trial (ClinicalTrials.gov ID NCT05050084), patients with unfavorable intermediate prostate cancer (NCCN) and higher Decipher risk score are assigned either to the use of 6 months of the usual treatment (hormone therapy and radiation treatment) or to the use of darolutamide plus the usual treatment (intensification). On the other hand, patients with low Decipher risk scores are assigned to the part of the study that compares the use of radiation treatment alone (de-intensification) to the usual approach (6 months of hormone therapy plus radiation). The final results of these trials will be important to better define whether patients with non-metastatic unfavorable intermediate and high risk using the only predictor of metastatic disease available in the market (Decipher) will benefit from intensification or de-intensification of systemic treatments and address its definitive role and usefulness in prostate cancer management. However, even more, clinical trials will be necessary to answer this question. Guidelines such as AUA/ASTRO, NCCN, European, and ASCO do not give a special role to tissue-

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based biomarkers, especially in predicting metastatic disease due to a lack of strong evidence and consequently their underutilization. Current treatments for non-mPC, including localized, patients with BCR and clinical N+ are based on strong evidence for localized and weaker for BCR and clinical N+. With a high rate of biochemical relapse in unfavorable intermediate and high-risk PC, the best predictors are clinical, biochemical, and histological. Treatment and adjuvant therapies have not shown better outcomes over observation, probably because the tools used for defining candidates for adjutancy are low quality.

The use of TBGB for metastasis in PC aids the clinician's therapeutic decision-making, focalizing the treatment according to the cancer's aggressiveness. Although it is fundamental that a biomarker be of use for clinical practice, these biomarkers must be accessible to patients, which are currently $3,000-5,000. They also must be easy to implement from the point of view of the patient and the physician, with an aim to scaling quickly, becoming universal, and benefiting all patients with newly diagnosed prostate cancer. Therefore, we believe there is still a need and space for more cost-effective TBGB tests that predict mPC disease.

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