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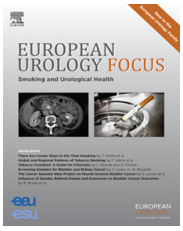

Review – Prostate Cancer

Prognostic Biomarkers Used for Localised Prostate Cancer Management: A Systematic Review

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Abstract

Context: Prostate cancer stratification is based on tumour size, pretreatment PSA level, and Gleason score, but it remains imperfect. Current research focuses on the discovery and validation of novel prognostic biomarkers to improve the identification of patients at risk of aggressive cancer or of tumour relapse.
Objective: This systematic review by the Intergroupe Coopérateur Francophone de Recherche en Onco-urologie (ICFuro) analysed new evidence on the analytical validity and clinical validity and utility of six prognostic biomarkers (PHI, 4Kscore, MiPS, GPS, Prolaris, Decipher).
Evidence acquisition: All available data for the six biomarkers published between January 2002 and April 2015 were systematically searched and reviewed. The main endpoints were aggressive prostate cancer prediction, additional value compared to classical prognostic parameters, and clinical benefit for patients with localised prostate cancer.
Evidence synthesis: The preanalytical and analytical validations were heterogeneous for all tests and often not adequate for the molecular signatures. Each biomarker was studied for specific indications (candidates for a first or second biopsy, and potential candidates for active surveillance, radical prostatectomy, or adjuvant treatment) for which the level of evidence (LOE) was variable. PHI and 4Kscore were the biomarkers with the highest LOE for discriminating aggressive and indolent tumours in different indications.
Conclusions: Blood biomarkers (PHI and 4Kscore) have the highest LOE for the prediction of more aggressive prostate cancer and could help clinicians to manage patients with localised prostate cancer. The other biomarkers show a potential prognostic value; however, they should be evaluated in additional studies to confirm their clinical validity.
Patient summary: We reviewed studies assessing the value of six prognostic biomarkers for prostate cancer. On the basis of the available evidence, some biomarkers could help in discriminating between aggressive and non-aggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians.

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1. Introduction

Prostate cancer is the most frequent tumour in Europe (400 364 new cases in 2012). Although its prognosis is often good, it was responsible for approximately 92 328 deaths in 2012 and is the third leading cause of death among men [1]. Currently, discussions focus on the possible limitations of early cancer detection by prostate-specific antigen (PSA) testing, on postponing or avoiding prostate biopsies (invasive diagnostic examination), and on substituting active treatment by active surveillance in patients with low PSA values. The broad use of PSA testing has led to the identification of very small-volume cancers with PSA values from 4 to 10 ng/ml. With these values, the risk of prostate cancer diagnosis by biopsy is 25%, and PSA testing does not allow differentiation between highly and less aggressive tumours, thus leading to the risk of unnecessary biopsies and overdiagnosis. Besides the Gleason score, the reproducibility of which is not optimal, and PSA testing, no prognostic biological marker has been validated yet for prostate cancer management. Many blood, urinary, and tissue biomarkers have been developed to meet the need to personalise patient management. Biomarkers might be useful particularly to limit the use of biopsy when the risk of finding a prostate cancer is low (for instance, in cases with a moderate PSA increase) and to differentiate between aggressive and nonaggressive tumours during the therapeutic decision-making process to optimise cancer treatment.

The objective of this systematic review was to evaluate the clinical validity, level of evidence (LOE) for, and potential clinical utility of six prognostic biomarkers: two blood tests (Prostate Health Index [PHI], Beckman Coulter, Brea, CA, USA; 4Kscore, OPKO, Miami, FL, USA), one urinary test (Mi Prostate Score Urine test [MiPS], MLabs, Ann Arbor, MI, USA), and three molecular signatures (Genomic Prostate Score [GPS], Genomic Health, Redwood City, CA, USA; Prolaris Cell Cycle Progression score [CCP], Myriad Genetics, Salt Lake City, UT, USA; and Decipher Genomic Score [GC], GenomeDx, San Diego, CA, USA). These tests are commercially available in the USA and/or in Europe and are described in Table 1. Selection criteria are reported in Supplementary Table 1 and the biomarker descriptions and clinical indications are reported in Supplementary Table 2.

2. Data acquisition

2.1. Literature search

The literature search was based on a systematic review of the available data for each selected biomarker. The search algorithms (Supplementary Table 3) included the population of interest (patients with confirmed prostate cancer or candidates for biopsy testing), the prognostic biomarker under study, and the search period (January 2002–April 2015). All publications (with the exception of general reviews, editorials, and conference abstracts) were searched. The literature data were completed by literature monitoring (up to 6 July 2015) and by suggestions from the working group members, particularly for studies that were

Table 1 – Selected biomarkers and studies included in the analysis.

Biomarker	Laboratory	Sample	Method of measurement	Regulatory data	Studies
PHI (Prostate Health Index) ([−2]proPSA/free PSA) × $\sqrt{}$PSA	Beckman Coulter (Brea, CA, USA)	Blood	Immunoassay (by chemiluminescence)	CE-IVD Approved by FDA (June 2012)	[3–6,13–20, 31–33, 37–42,44]
4Kscore test (4 kallikreins panel: free PSA, total PSA, intact PSA and hK2)	OPKO Diagnostics (Miami, FL, USA)	Blood	Immunoassay (by fluorescence or chemiluminescence) Combination in an algorithm of the four kallikreins levels and of clinical data	CAP accreditation	[7,20–28, 30,43]
MiPS (combines plasma PSA and urine TMPRSS2:ERG and PCA3)	MLabs (University of Michigan, Ann Arbor, MI, USA)	Urine	Transcription-mediated amplification + hybrid protection assay	PCA3: approved by FDA (February 2012) *TMPRRS2:ERG* or T2 score: CLIA accreditation	[9–11,34, 44,59]
GPS (Genomic Prostate Score) Signature of 17 genes (12 cancer-specific and 5 reference genes)	Genomic Health (Redwood City, CA, USA)	FFPE prostate tissue (from biopsy or prostatectomy)	Real-time RT-PCR (mRNA on FFPE tissues), centralised in the USA Quantitative method	CLIA and CAP accreditations and licenses in 6 states that require their own audit before validation of a test	[12,35,36]
Prolaris (Cell Cycle Progression, or CCP score) Signature of 46 genes (31 cancer-specific and 15 reference genes)	Myriad Genetics (Salt Lake City, UT, USA)	FFPE prostate tissue (from biopsy or prostatectomy)	RNA expression (selected on chips) centralised in the USA Semi-quantitative method	CLIA and CAP accreditations CE-IVD marking (March 2015)	[45–50,60]
Decipher (Genomic score, or GC score) Signature of 22 genes	GenomeDx (San Diego, CA, USA)	FFPE prostate tissue	RNA expression (selected on chips) centralised in the USA Semi-quantitative method	CLIA accreditation	[51–58]

PSA = prostate-specific antigen; CE-IVD = Conformité Européene In Vitro Diagnostic; FDA = US Food and Drug Administration; CA*p* = College of American Pathologists; CLIA = Clinical Laboratory Improvement Amendments; RT-PCR = reverse transcriptase polymerase chain reaction; FFPE = formalin-fixed, paraffin-embedded.

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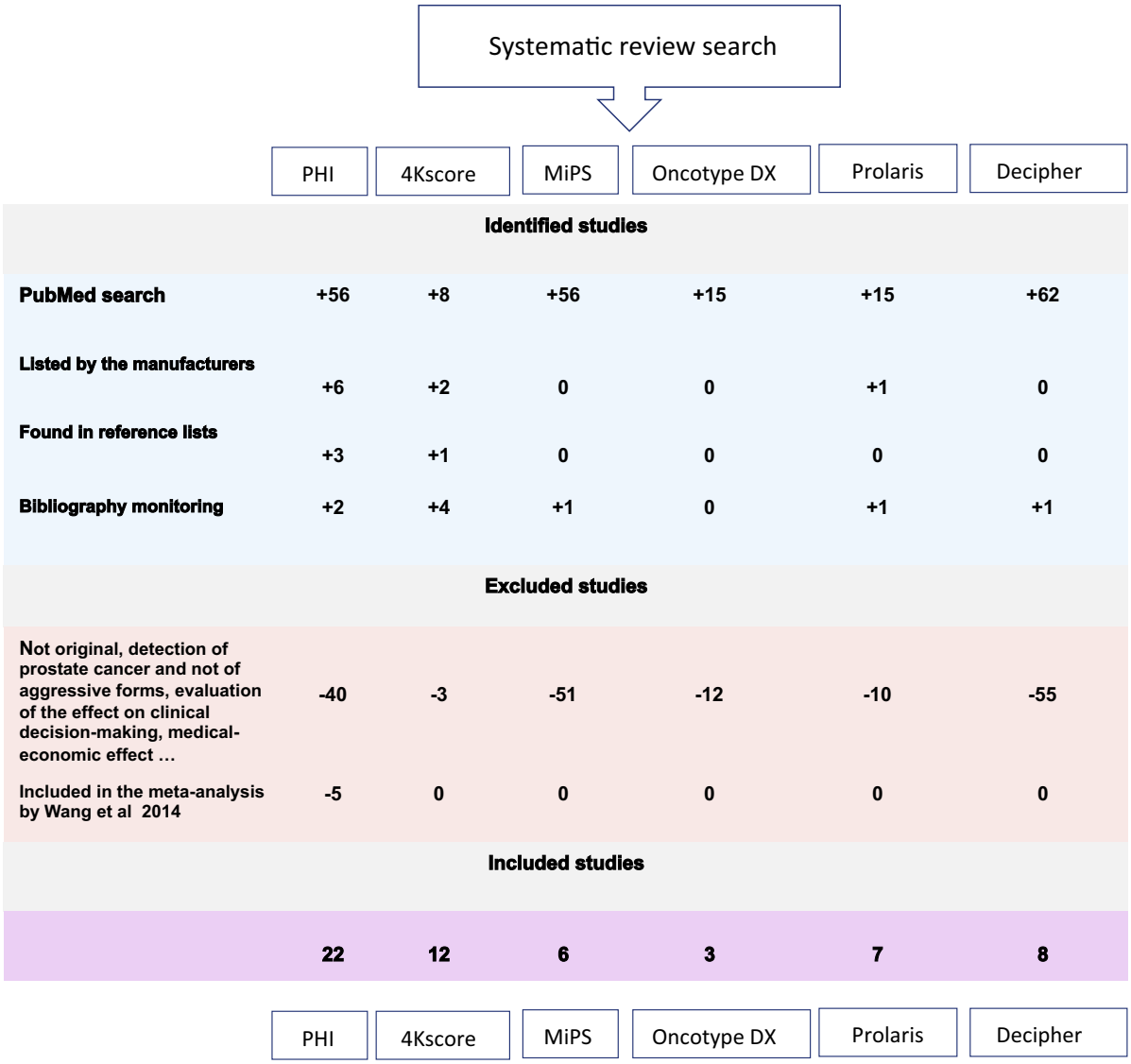

Fig. 1 – Study flow diagram describing the selection of eligible studies. A summary of the publications that were evaluated is provided in Supplementary Table 5.

not indexed in Medline at the time of the literature search (April 24, 2015). Fig. 1 shows the study flow chart.

2.2. *Study selection*

The inclusion and exclusion criteria were defined a priori. The main eligibility criterion was assessment of the test of interest for the identification of aggressive prostate cancer or for its prognostic value in patients with localised prostate cancer. Publications were deemed not eligible using a minimum set of exclusion criteria: (1) studies on the test cost-benefit, because such studies are largely dependent on the health care system of each country; (2) studies evaluating only early detection of prostate cancer or very low or very high PSA levels; and (3) studies that analysed the test influence on clinical decision-making (practice pattern surveys).

Studies were selected by the methodologist on the basis of these criteria after reading the abstract. The selection was validated by the working group.

2.3. *Project methodology*

This project was carried out by the Biologie du Cancer de la Prostate (Prostate Cancer Clinical Biology) working group of the Intergroupe Coopérateur Francophone de Recherche en Onco-urologie (ICFuro) that is composed of clinical biologists, oncologists, pathologists, radiologists, radiotherapists,

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urologists, and one methodologist with expertise in the field of prostate cancer and/or biomarker testing.

For each marker (or group of markers), the available data were used to evaluate: (1) its discriminative prognostic value and its independence from classical prognostic parameters according to multivariate analyses; (2) its additional value according to the statistical significance of the difference between area under the receiver operatic characteristic curve (AUC) values with classical prognostic parameters; and (3) the net clinical benefit according to decision curve analysis (DCA) and calculated in terms of biopsies avoided and "aggressive" cancers missed.

For each study, the working group carried out a critical analysis of the analytical data, methodological quality, and clinical relevance. Data were collected in STARD-type files modified by the working group (Supplementary Table 4). The methodological limitations of the study were identified to attribute the LOE of the conclusions and to integrate these remarks in the design of future studies.

The LOE ranking was based on the system described by Simon and co-workers [2] (A = highest LOE; D = lowest LOE) and by inference on the basis of the concordance among studies (high level of evidence: LOE IA, LOE IB; intermediate level of evidence: LOE IIB, LOE IIC; weak level of evidence: LOE IIIC, LOE IV–VD; Supplementary Table 5).

3. Data synthesis

3.1. Preanalytical and analytical validity

Overall, only a few studies on the preanalytical or analytical validity of the biomarkers tested were identified. Samples originated mainly from retrospective studies with methodological limitations (eg, population size or development of the technique). Most studies did not report any information on the inter- and intralaboratory reproducibility or on blind testing (without knowledge of the clinical data). The working group reviewed the preanalytical or analytical validity of each biomarker when dedicated studies were identified.

3.1.1. PHI

Three studies assessed the required preanalytical conditions of the PHI. Reliable measurements of the [−2] precursor PSA isoform ([−2]proPSA) were obtained when blood samples were centrifuged within 1 h after sample collection if blood was stored at room temperature, and within 3 h if blood was kept at 4 °C [3]. In the case of delayed measurement, it was recommended to centrifuge blood samples as soon as possible (<3 h) and then store them at −20 °C [4]. When serum samples were kept at room temperature, the PHI values increased by up to 10% at 3 h after collection, but then did not change up to 24 h [5]. The analytical performance of [−2]proPSA measurement with a chemiluminescent test (Access Hybritech) was evaluated and validated by a study that involved five centres [6].

In the absence of dedicated studies, the preanalytical and analytical data for the other tests were identified from clinical studies.

3.1.2. 4Kscore

The 4Kscore showed good analytical validity. In initial studies using samples from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, total and free PSA were measured using the US Food and Drug Administration (FDA)-approved Prostatus PerkinElmer Auto DELFIA method. However, the 4Kscore test was then validated by OPKO Health [7] using the FDA-approved Elecsys assays for total and free PSA (Roche Cobas instrument). Data on the validation of this method change are not available. The concentrations of intact PSA and of human kallikrein-related peptidase 2 (hK2) were obtained using immunological sandwich tests that were developed and analytically validated by Vaisanen et al [8]. There are no data on the preanalytical stability of hK2 and intact PSA.

3.1.3. MiPS

The MiPS test showed good analytical validity. Threshold values were defined by specifying the sensitivity and specificity levels. Nevertheless, the LOE is limited by the fact that these threshold values were not validated in an independent study [9,10]. Sample analysis was based on the transcription-mediated amplification technique. The accuracy of this technique was compared with *TMPRRS2:ERG* gene rearrangement rates obtained by fluorescence in situ hybridisation. The concordance between techniques was 92% [11].

3.1.4. GPS

Among the three molecular signatures, only the GPS analytical validity was evaluated in a dedicated study [12]. The authors found good analytical validity. However, this analysis should be completed by data on the influence of the tissue fixation method and tissue block age. Among prostate biopsies of variable volumes, the smallest recorded volume was 0.0225 mm^3 and the smallest quantity of total RNA extracted was 19 ng. The GPS score could be measured because it requires a minimum RNA quantity of 5 ng, but a cDNA preamplification step was added. Polymerase chain reaction (PCR) efficacy evaluated for each gene ranged from 88% to 100%, which implies a non-negligible difference in the quantification of gene expression. Moreover, quantification of some genes was performed at the limit of quantification for quantitative PCR (crossing point [Cp] between 33 and 35). GPS precision and reproducibility were evaluated using different machines and/or reagent lots by different operators and using RNA from different samples. The analytical variability was lower than 9.7%. The standard deviations were acceptable (1.86–2.11 GPS units on a scale from 0 to 100).

3.1.5. Prolaris

The Prolaris test is a multigene test in which the number of genes analysed can vary (from 21 to 31) as a function of the sample quality (exclusion of genes that cannot be amplified). Consequently, its analytical validity needs to be completed by demonstration of a lack of influence of taking into account a variable number of genes chosen on the basis of their amplification quality. The limits of gene quantification,

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particularly Cp, and the test reproducibility were not reported. The procedure for tissue block selection was described. The analysis was carried out using at least 25 μm of tumour tissue sections with macrodissection of the tumour area. Prolaris could be evaluated in 85–90% of the available tumour samples. The RNA quantity was sufficient to perform the test if a cDNA preamplification step was carried out. The RNA quality of each sample was assessed by amplifying 15 reference genes with precise guidelines for quality assessment. The authors reported that the proportion of valid tests was lower for old samples and higher for freshly fixed ones.

3.1.6. Decipher

Few data are available on analytical validity for the Decipher test. The retrospective analyses used different threshold values. This led to between-study heterogeneity that is an issue for the test interpretation and validation. Approximately 10% of samples were eliminated because of analytical problems. Affymetrix chips were used, but very few details were found on the implementation and quality control. The inter- and intra-assay reproducibility were not reported, or the quality control procedure for RNA samples and the inter-lot normalisation.

For all molecular signatures, the preanalytical validity (sample collection and storage and RNA extraction) was not reported.

3.2. Clinical validity and clinical utility

The clinical validity for a given endpoint (eg, tumour aggressiveness or clinical recurrence) corresponds to the biomarker discriminatory power and to its ability to divide, independently of other classical markers, a group of patients into subgroups. The clinical utility corresponds to the additional value relative to the usual markers and to the benefit/risk ratio linked to the use of that biomarker (eg, number of unnecessary biopsies avoided/number of aggressive cancers missed). This utility needs to be significant enough to lead to a change in patient management.

All studies compared the biomarker under study with classical clinicopathological criteria or with already validated clinical nomograms (Cancer of the Prostate Risk Assessment [CAPRA], Steyerberg and Eggener); however, none of them included magnetic resonance imaging (MRI) data as a reference for assessing the discriminatory power or additional value. Moreover, none used MRI/ultrasound fusion–guided prostate biopsies for prostate cancer detection. All the patient characteristics are reported in Supplementary Table 6.

3.2.1. Patients eligible for a first or second biopsy and identification of patients at risk of aggressive cancer

3.2.1.1. PHI. For prediction of tumour aggressiveness according to the Gleason score or the Epstein or Prostate Cancer Research International Active Surveillance (PRIAS) criteria assessed on biopsy, PHI showed discriminatory power [13–19] (LOE IA) and additional value compared to total and/or free PSA [16,15,20] (LOE IA). In terms of clinical utility, the best discriminatory power was found in the study by Loeb and al [15]. These results are in agreement with those of the meta-analysis by Wang et al [14]. The additional value was confirmed by the increase in AUC value (between 2% and 11%; Table 2).

3.2.1.2. 4Kscore. The 4Kscore might allow prediction of tumour aggressiveness estimated according the Gleason score or the Epstein criteria on biopsy [7] (LOE IA) or total prostatectomy samples [21] (LOE IIB), respectively. No multivariate analysis is available to determine the 4Kscore independence relative to the classical clinicopathological variables. Compared to total PSA ("biological model"), the 4Kscore has additional value in patients enrolled in the first [22,23] and successive rounds [24,25] (LOE IB) of the ERSPC trial. Similar results were obtained when the four kallikreins were measured in plasma [26,27] (LOE IIB). In all patients, a 4Kscore benefit relative to the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) nomogram has been demonstrated [7] (LOE IA). With the exception of the study by Parekh et al [7], all studies were performed by the same group on retrospectively analysed samples from the ERSPC trial [29], which was not dedicated to 4Kscore evaluation. These studies included more than two-thirds of patients from the original population (Dutch, Swedish, and French) of the ERSPC trial. Therefore, they can aim at LOE I. These studies had the same methodological limitations as the original trial. Specifically, six biopsies were performed and biopsy was indicated only in patients with high PSA level, without taking into account the physical examination and the patient's personal or family history. This is not representative of routine practice, with the exception of the study by Benchikh et al [30]. The DCA results showed that the 4Kscore has a net clinical benefit compared to the biological or clinical model for prediction of aggressive tumours, according to the Gleason score on biopsy, in patients included in the first round of a screening programme [22,24] and in those included in the second or following rounds [24,25], or in the case of a previous negative biopsy [28].

As reported in many noncomparative studies, the discriminatory power of the 4Kscore seems to be higher than that of the PHI. Only one comparative study reported that these two biomarkers have similar discriminatory power that is higher than that of total PSA (AUC increase 12.2%; $p < 0.0001$) [20].

3.2.1.3. MiPS. MiPS could improve the selection of patient candidates for biopsy. It showed high discriminatory ability for prediction of cancers with a Gleason score $\geq$7 or according to the Epstein clinical criteria [11] (LOE IIIC). It also had a superior AUC compared to the ERSPC risk calculator, which includes PSA, digital rectal examination, transrectal ultrasound, and prostate volume (+4.3%; p value not indicated) [9] (LOE IIIC), and compared to total PSA (+12.1%; $p < 0.001$) and the Prostate Cancer Prevention Trial High Grade (PCPThg) multivariate risk calculator (+7.2%; $p < 0.001$) [10] (LOE IIIC). For clinical benefit for the endpoint prediction of Gleason score $\geq$7 prostate cancer, DCA results show

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Table 2 – Identification of aggressive cancers in patients eligible for a first or second biopsy: summary of the results and level of evidence.

Test (LOE for conclusion for each biomarker and each indication)	Material	Reference (LOE)	Endpoint	Main results
PHI Clinical validity, LOE IA AV/total PSA and/or % [−2] proPSA, LOE IA	Biopsies	[13] (B)	Gleason ≥7	Discriminant; PHI score (Gleason <7 vs ≥7): 34.20 vs 43.03; $p < 0.0001$
	RP specimen		Gleason ≥7	Discriminant; PHI score (Gleason <7 vs ≥7): 36.32 vs 42.38; $p = 0.02$
	Biopsies	[14] [a]	Gleason ≥7	Sensitivity: 0.90, 95% CI 0.87–0.92; specificity: 0.17, 95% CI 0.14–0.19 OR 3.06, 95% CI 1.61–5.84; AUC 0.67, 95% CI 0.57–0.77
	Biopsies	[17] (C)	Gleason ≥7	AV for PSA >20 ng/ml with AUC (PHI vs total PSA): 0.76, 95% CI 0.62–0.89 vs 0.71, 95% CI 0.57–0.86; $p = 0.0502$ Net clinical benefit/% free PSA and % [−2]proPSA
	Biopsies	[15] (A)	Gleason ≥7	Discriminant, independent; OR 5.36, 95% CI 3.00–9.56; $p < 0.001$ AV, but no p value: PHI vs % free PSA vs [−2]proPSA vs total PSA 0.707 vs 0.661 vs 0.558 vs 0.551 Net clinical benefit relative to % free PSA
			ESC	Discriminant, independent; OR 4.83, 95% CI 2.85–8.20; $p < 0.001$ AV, but no p value: PHI vs % free PSA vs [−2]proPSA vs total PSA 0.698 vs 0.654 vs 0.550 vs 0.549
	Biopsies	[19] (A)	PRIAS	Discriminant, AUC 0.72, 95% CI 0.68–0.76; $p < 0.0001$ AV/age, prostate volume, DRE, total PSA and % free PSA; AUC gain 0.01–0.02; $p < 0.05$
	Biopsies	[18] (C)	Gleason ≥7	Discriminant, AUC 0.78–0.81 PHI threshold 34.3: sensitivity 80%, specificity 64.8% PHI threshold 27.5: sensitivity 90%, specificity 45.2% PHI threshold 24.4: sensitivity 95%, specificity 36.0%
	Biopsies	[16] (C)	Gleason ≥7	Discriminant, AUC 0.72–0.79 AV/total PSA 7.7%; $p = 0.03$ Net clinical benefit of PHI + CM relative to PCPT or CM + PSA
	Biopsies	[20] (C)	Gleason ≥7	AV/PSA 11.5%; $p < 0.0001$ PHI equivalent to the 4Kscore, no net clinical benefit
4K score test Measured in serum samples Clinical validity, LOE IA AV/BM or CM, LOE IB AV/PCPTRC nomogram, LOE IA AV/CM or Steyerberg nomogram, LOE IIB	Biopsies First round of screening	[22] (B) [23](B)	Gleason ≥7	AV/BM; AUC gain 6.6%, $p = 0.04$; OR 4.9%, $p = 0.008$ No AV/CM:;AUC gain 3.5%, $p = 0.16$; OR 3.1%, $p = 0.08$ Net clinical benefit/BM or CM
	Biopsies First screening round + physical examination + personal/family history	[30] (B)	Gleason ≥7	AV/CM; AUC gain 10.3%; no p value provided Net clinical benefit/BM or CM
	Biopsies Second and additional screening rounds	[24] (B) [25] (B)	Gleason ≥7	AV/BM; AUC gain 16.1%, $p < 0.001$; OR 9.4%, $p = 0.003$ AV/CM; AUC gain 11.1%, $p = 0.009$; OR 8.9%, $p = 0.001$ Net clinical benefit/BM or CM
		[28] (B)	Gleason ≥7	AV/CM; AUC gain 10.9%; $p = 0.003$ No AV when prostate volume added to the model; $p = 0.2$ Net clinical benefit/CM
	Biopsies First or additional screening rounds	[7] (A)	Gleason ≥7	Discriminant, AUC 0.821 AV/PCPTRC; AUC gain 8.1%; $p < 0.0001$ Net clinical benefit not demonstrated
	Biopsies Candidates for first biopsy	[20] (B)	Gleason ≥7	No AV/PHI; AUC gain 0.7%; $p < 0.77$ AV/PSA; AUC gain 12.2%; $p < 0.0001$ No net clinical benefit
	Biopsies	[26] (B)	Gleason ≥7	AV/BM; AUC gain 7.5%; $p < 0.001$ Net clinical benefit/BM
	RP First and second screening round	[21] (B)	ECE, TV >0.5 ml, or GG >3 component	AV/CM; AUC gain 3%; $p < 0.0005$ Low clinical risk: AUC gain 6%; $p < 0.0005$ Net clinical benefit/CM
4Kscore test in plasma samples AV/BM, LOE IIB AV/CM, LOE IIIC	Biopsies First screening round	[26] (B)	Gleason ≥7	AV/BM; AUC gain 8.2%; $p < 0.001$
		[27] (C)	Gleason ≥7	AV/BM; AUC gain 5.7%; $p = 0.002$ AV/BM + DRE; AUC gain 4.8%; $p = 0.001$ Net clinical benefit/BM

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Table 2 (*Continued*)

Test (LOE for conclusion for each biomarker and each indication)	Material	Reference (LOE)	Endpoint	Main results
MiPS Clinical validity, LOE IIIC AV/ERSPC score or total PSA or PCPThg score, LOE IIIC	Biopsies	[11] (C)	Gleason ≥7	Discriminant, independent; RR 5.9, 95% CI 3.9–8.8; $p < 0.001$ AV/PCPThg but no AUC gain
			ESC	Discriminant, no multivariate analysis
	Biopsies	[9] (C)	ESC	Increased sensitivity/individual scores: 88.1% vs 82.5% for PCA3 and 24.3% for TMPRSS2:ERG Unchanged specificity/PCA3: ~50% AV/ERSPC; AUC gain 4.3%; no p value provided
			Gleason ≥7	Net clinical benefit/PSA Calculated sensitivity: 91% Calculated specificity: 65%
	Biopsies	[10] (B)	Gleason ≥7	AV/PSA; AUC gain 12.1%; $p < 0.001$ AV/PCPThg; AUC gain 7.2%; $p < 0.001$ Net clinical benefit/PCPThg Calculated sensitivity: 97% Calculated specificity: 31%

LOE = level of evidence; ESC = Epstein significance criteria; AUC = area under the curve for the receiver operating characteristic; AV = additional value; BM = biological model; CM = clinical model; PSA = prostate-specific antigen; RP = radical prostatectomy; PRIAS = Prostate Cancer Research International Active Surveillance; PCPTRC = Prostate Cancer Prevention Trial risk calculator; PCPThg = Prostate Cancer Prevention Trial high-grade cancer risk calculator; ERSPC = European Randomized Study of Screening for Prostate Cancer; OR = odds ratio; RR = relative risk; CI = confidence interval; DRE = digital rectal examination; ECE = extracapsular extension; TV = tumour volume; GG = Gleason score grade.

[a] Meta-analysis, LOE not applicable.

that few unnecessary biopsies are avoided while aggressive cancers are missed when compared to total PSA or the PCPThg score [9,10].

3.2.2. *Patients eligible for active surveillance*

3.2.2.1. PHI. For the endpoint unfavourable histopathological reclassification according to the Epstein criteria, PHI (measured at diagnosis or during surveillance) has discriminatory power [31–33] (LOE IIB; Table 3). Data are missing on its additional value compared to classical parameters. In terms of clinical utility, the discriminatory power is similar among studies. It should be noted that the PCA3 and *TMPRRS2:ERG* scores, evaluated individually, do not show any added or discriminatory and independent value compared to PSA for prediction of Gleason score ≥7 tumours [34] (LOE IIB).

3.2.2.2. GPS. Two studies assessed the clinical validity of the GPS test for prediction of aggressive tumours at surgery (Gleason score ≥ 4 + 3 and/or pT3 stage). These studies focused on a selected population of patients at low or intermediate clinical risk according to the CAPRA score or National Comprehensive Cancer Network (NCCN) classification (www.nccn.org/professionals/physician_gls/f_guidelines.asp#prostate). The GPS test shows discriminatory power, independently of classical clinical variables (age, PSA, clinical stage, Gleason score on biopsy), CAPRA score, or NCCN staging [35,36] (LOE IIC). It could offer additional, albeit limited, value relative to these variables (4–9%, p value not specified) [36] (LOE IIIC).

3.2.3. *Patients eligible for radical prostatectomy*

3.2.3.1. PHI. For the endpoint prediction of tumour aggressiveness according to Gleason score or stage assessed on prostatectomy specimens, PHI has very weak discriminative ability (hazard ratio very close to 1) [37,38] (LOE IA, Table 4). Results from the other studies are not concordant or were obtained using questionable methodologies (eg, subjective measurement of tumour volume, non-independent value of the marker, and very low number of events) [39–41]. The PHI test has additional value compared to classical parameters (age, digital rectal examination, total PSA, free PSA, % free PSA, % positive cores, clinical stage [cT1c vs cT2], prostate volume, body mass index, and Gleason score on biopsy) [37,38,41,42] (LOE IA). Conversely, its influence on decision-making is limited (weak AUC improvement, between 2% and 8%).

3.2.3.2. 4Kscore. For the endpoint prediction of late metastases, the 4Kscore should have additional value (LOE IIIC) and a net clinical benefit compared to total PSA [43].

3.2.3.3. MiPS. The MiPS test is associated with prediction of aggressive cancer according to the Epstein clinical criteria [11] (LOE IIIC); however, the independent nature of this predictive value was not demonstrated. For prediction of a Gleason score ≥7 tumour, the PCA3, TMPRSS2:ERG, and PHI combination shows additional value compared to classical clinical parameters (AUC improvement of 13.8%; $p = 0.011$) [44] (LOE IIIC).

3.2.4. *Patients eligible for adjuvant treatment*

Some biomarkers could contribute to clinical decision-making after locoregional treatment (prostatectomy or radiotherapy) thanks to their prognostic value (Table 5).

3.2.4.1. GPS. For the endpoint time before biochemical recurrence after radical prostatectomy, the GPS test shows an

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Table 3 – Patients eligible for active monitoring: summary of the results and level of evidence.

Test (LOE of conclusion for each biomarker and each indication)	Material	Reference (LOE)	Endpoints	Main results
PHI Clinical validity, LOE IIB Additional value, NA	Biopsies	[31] (C)	Reclassification: favourable vs unfavourable biopsy	Discriminant, independent; HR 2.00, 95% CI 1.008–3.97; $p = 0.047$ AUC 0.69
	Biopsies	[32] (D)		Discriminant, independent; HR 1.04, 95% CI 1.02–1.06; $p < 0.008$
	Biopsies	[33] (B)		Discriminant, independent; OR 3.650, 95% CI 1.408–9.461; $p = 0.008$
GPS Clinical validity, prediction of aggressive tumour at surgery, LOE IIC AV/clinical, biological, histological, and imaging criteria, LOE IIIC	RP then biopsies	[35] (C)	Gleason ≥4 + 3	Discriminant, independent Adjustment for biopsy GS: OR 2.3, 95% CI 1.5-3.7; $p < 0.001$
			High clinical stage, pT3	Discriminant, independent Adjustment for biopsy GS: OR 1.9, 95% CI 1.2–2.8; $p = 0.003$
			Gleason ≥4 + 3 and/or high clinical stage	Discriminant, independent Adjustment for biopsy GS + age + PSA + clinical stage: OR 1.9, 95% CI 1.3–3.0; $p = 0.003$ Adjustment for CAPRA: OR 2.1; $p < 0.001$ Adjustment for NCCN classification: OR 1.9; $p = 0.001$
	RP		Clinical relapse	Discriminant, independent, adjustment for AUA score HR 2.32, 95% CI 1.81–3.00; $p < 0.001$
	Biopsies	[36] (C)	pT3 or GS ≥ 4 + 3 or clinical stage	Discriminant, independent, adjustment for NCCN classification OR 3.23, 95% CI 2.14–4.97; $p < 0.001$ AV/CAPRA; AUC gain 4%; no p value provided AV/NCCN classification; AUC gain 9%; no p value provided
PROLARIS Clinical validity, LOE IIC AV, NA	TURP	[46] (C)	Disease-specific mortality at 10 yr	Discriminant, independent (GS, PSA and Ki67) HR = 2.56; 95% CI [1.85-3.53]; $p = 1.3 \times 10^{-8}$
	Biopsies	[48] (C)		Less discriminant than GS, independent (GS, PSA, age at diagnosis, clinical stage, hormone therapy, extracapsular extension, Ki67) HR 1.65, 95% CI 1.31–2.09; $p = 2.6 \times 10^{-5}$
	Biopsies	[49] (C)		Discriminant, independent CAPRA: HR 1.76, 95% CI 1.44–2.14; $p = 4.1 \times 10^{-7}$ Clinical parameters: HR 1.76, 95% CI 1.47–2.14; $p = 1.14 \times 10^{-6}$ AV/CAPRA

LOE = level of evidence; OR = odds ratio; CI = confidence interval; RP = radical prostatectomy; TURP = transurethal resection of the prostate; HR = hazard ratio; AUC = area under the curve for the receiver operating characteristic; AV = additional value; CAPRA = Cancer of the Prostate Risk Assessment; NCCN = National Comprehensive Cancer Network; AUA = American Urological Association; GS = Gleason score; PSA = prostate-specific antigen.

independent prognostic value, even after adjustment for NCCN risk level [36] (LOE IIIC).

3.2.4.2. Prolaris. The Prolaris test performed on biopsies or total prostatectomy specimens allows prediction of biochemical recurrence at 10 yr after prostatectomy in patients with low clinical risk of relapse (LOE VD [45] and LOE IIC [46,47], respectively). This discriminatory power is independent of clinical variables (PSA, Gleason score on biopsy, clinical stage, percentage of positive cores, adjuvant treatment, age at diagnosis, lymph node involvement, Gleason score on surgical specimen, extracapsular extension, seminal vesicle invasion, and surgical margins) and brings additional value, mainly for patients classified as low risk according to the postsurgical CAPRA score (CAPRA-S) [47] (LOE IIIC). It should be noted that among the biopsies considered, some were simulated, which represents a real bias for data interpretation. For prediction of disease-specific mortality at 10 yr after conservative treatment, the CCP score on biopsy shows discriminatory power that is independent of classical clinical variables (Gleason score, PSA, Ki67, and CAPRA score) [48,49] (LOE IIC). Thus, within a group of patients classified as intermediate risk according to clinical criteria, it should allow identification of a subgroup of low-risk patients for whom the indication for radiotherapy with or without hormonal therapy can be discussed. Nevertheless, these studies have several methodological limits: short median follow-up for patients who did not progress after radiotherapy and a low number of events after 5 yr [50], and conservative treatment modalities were not documented or included in the multivariate analysis [48,49].

3.2.4.3. Decipher. In patients with high clinicopathological risk who did or did not receive adjuvant treatment, the Decipher test has prognostic value for metastasis prediction

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Table 4 – Patients eligible for radical prostatectomy: summary of results and level of evidence.

Test (LOE of conclusion for each biomarker and indication)	Material	Reference (LOE)	Endpoint	Main results
PHI Clinical validity, LOE IA AV/classical parameters, LOE IA	RP	[37] (A)	GS ≥7	Discriminant but weakly, independent; OR 1.02, 95% CI 1.009–1.034; $p = 0.0001$ AV; AUC gain 5%; $p = 0.004$
			Reclassification (favourable vs unfavourable)	Discriminant but weakly, independent; OR 1.045, 95% CI 1.019–1.071; $p < 0.001$ AV; AUC gain 5.6%; $p < 0.05$
			TV <0.5 ml	Not discriminant; OR 0.937, 95% CI 0.901–0.975; $p = 0.001$ AV; AUC gain 2.2%; NS
	RP	[38] (A)	GS ≥7 or pT3	Discriminant, AUC 0.80; AV 2.3%, $p = 0.003$ No net clinical benefit/total PSA, DRE, biopsy GS, % positive cores, even after adding [−2]proPSA or % [−2] proPSA to the model
			GS ≥7 and pT3	Discriminant, AUC 0.82; AV 2.4%, $p = 0.01$
	RP	[39] (A)	GS ≥7 or pT3/T4	Not discriminant, OR 1.003, 95% CI 0.990–1.017; $p = 0.619$ No AV; AUC gain 0
	RP	[44] (C)	TV ≥0.5 ml or GS ≥7 or pT3 or multifocality	Not independent
			TV ≥0.5 ml or GS ≥7	No AV
	RP	[41] (B)	pT3	Weakly discriminant; OR 1.079, 95% CI 1.001–1.163; $p = 0.048$ AV; AUC gain 6.3%; $p < 0.05$
			pT3 and/or GS ≥8 and/or lymph node invasion	Weakly discriminant; OR 1.083, 95% CI 1.003–1.170; $p = 0.042$ AV; AUC gain 4.2%; $p < 0.05$
			Surgical margins status	Weakly discriminant; OR 1.151, 95% CI 1.013–1.308; $p = 0.031$ No AV
			GS ≥8 or lymph node invasion or unfavourable reclassification	Not discriminant No AV value
	RP	[40] (C)	pT3	AUC 0.85; p value not provided
			GS ≥7	AUC 0.83; p value not provided
			TV ≥0.5 ml	AUC 0.94; p value not provided
	RP	[42] (C)	TV ≥0.5 ml	Discriminant, independent; OR 1.36, 95% CI 1.11–1.67; $p < 0.01$ AV; AUC gain 7.9%; $p < 0.05$
			Epstein significance criteria	Discriminant, independent; OR 1.22, 95% CI 1.09–1.37; $p < 0.01$ AV; AUC gain 7.6%; $p < 0.05$
			GS ≥7	Not discriminant; OR 1.02, 95% CI 0.990–1.02; $p < 0.01$ AV; AUC gain: 5.9%; $p < 0.05$
			Extracapsular extension	Very weakly discriminant; OR 1.01, 95% CI 1.00–1.02; $p = 0.02$ AV; AUC gain 8.0%; $p < 0.05$
			Seminal vesicle invasion	Very weakly discriminant; OR 1.01, 95% CI 1.00–1.02: $p < 0.01$ AV; AUC gain 3.6%; $p < 0.05$
MiPS Clinical validity, LOE IIIC AV/classical clinical parameters, LOE IIIC	Biopsies	[11] (C)	Epstein significance criteria	Discriminant
MiPS Clinical validity, LOE IIIC AV/classical clinical parameters, LOE IIIC	Biopsies	[34] (B)	GS ≥7	No significant AV/PSA
	Biopsies	[59] (C)	Gleason grade 4 component	Not discriminant, not independent
	Biopsies	[44] (C)	TV ≥0.5 ml	AV/clinical model (age, DRE, total PSA, biopsy GS); AUC gain 6.3%; $p = 0.052$

LOE = level of evidence; AV = additional value; RP = radical prostatectomy; TV = tumor volume; GS = Gleason score; OR = odds ratio; CI = confidence interval; AUC = area under the curve for the receiver operating characteristic; NS = not significant; PSA = prostate-specific antigen; DRE = digital rectal examination.

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Table 5 – Patients with locoregional treatment: summary of results and level of evidence.

Test (LOE for conclusion by biomarker and indication)	Material	Reference (LOE)	Endpoint	Main results
After RP				
4Kscore AV/total PSA, LOE IIIC	NA	[43] (C)	Mets at 15–20 yr	AV when PSA >2 ng/ml, age 50–60 yr; AUC gain 7.0–11.2% (no p value given) Net clinical benefit/PSA
GPS Clinical validity, prediction of BCR after RP, LOE IIIC	RP	[36] (C)	BCR	Discriminant, independent, adjustment for NCCN classification: HR 2.73, 95% CI 1.84–3.96; $p < 0.001$
Prolaris Clinical validity on RP specimens, LOE IIC AV/patients at low risk according to post-RP CAPRA, LOE IIIC Clinical validity on biopsy, prediction of BCR, LOE VD	RP	[46] (C)	BCR at 10 yr	Discriminant, independent (PSA, GS, LNI, pT stage): HR 1.77, 95% CI 1.40–2.22; $p = 4.3 \times 10^{-6}$ Not independent in intermediate or high clinical risk (GS $\geq$7 and PSA >10 ng/ml)
	RP	[47] (C)	BCR at 10 yr	Discriminant, independent (age at diagnosis, year of surgery, PSA, RP GS, ECE, seminal vesicle invasion, LNI, surgical margins): HR 2.0, 95% CI 1.4–2.8; $p < 0.001$ Discriminant, independent (CAPRA, especially for low risk): HR 2.3, 95% CI 1.4–3.7; $p = 0.003$
	Biopsies	[45] (D)	BCR	Discriminant, independent (PSA, GS, cT stage, % positive cores, adjuvant treatment, age at diagnosis): HR 1.47, 95% CI 1.23–1.76; $p = 4.7 \times 10^{-5}$
			Mets	Discriminant, independent (PSA, GS, cT stage, % positive cores, adjuvant treatment, age at diagnosis): HR 4.19, 95% CI 2.08–8.45; $p = 8.2 \times 10^{-6}$
Decipher *Mets prediction after RP* Clinical validity, discriminant especially for patients at high clinical risk, LOE IIIC AV/patients at intermediate or high risk according to GS, CAPRA-S, Stephenson or Eggener nomograms, LOE IIIC *Mets prediction after BCR* Clinical validity, discriminant especially in patients at high clinical risk, LOE IIC AV, NA *CSM prediction after RP* Clinical validity, discriminant especially in patients at high clinical risk, LOE IIIC AV/CAPRA-S, LOE IIIC *Prediction of BCR after RP* Clinical validity, discriminant especially in patients at high clinical risk, LOE VD AV/CAPRA-S or Stephenson, LOE VD	RP	[51] (C)	Mets	AUC gain 0.79, 95% CI 0.68–0.87 but no statistical comparison with other parameters Discriminant, independent (classical parameters): HR 1.51, 95% CI 1.29–1.76; $p < 0.001$ Same for the other parameters AV/GS, but no AUC data
	RP	[52] (D)	Mets	Discriminant + independent in the absence of adjuvant treatment (classical parameters): OR 1.48; 95% CI 1.07–2.05; $p = 0.018$ AV/Stephenson nomogram but no statistical comparison
	RP	[53] (D)	Mets	Discriminant + independent in the absence of adjuvant treatment: Classical parameters: HR 1.26; $p < 0.01$ CAPRA-S: HR 1.32, 95% CI 1.17–1.51; $p < 0.01$ Eggener nomogram: HR 1.39, 95% CI 1.20–1.62; $p < 0.01$ AV/CAPRA-S and Eggener nomogram especially if high clinical risk, but no statistical comparison
	RP	[54] (C)	Mets after BCR	Discriminant, independent (classical parameters): HR 1.36, 95% CI 1.16–1.60; $p < 0.001$ AV/GS or classical parameters, but no AUC data
	RP	[55] (C)	Mets after BCR	Discriminant, independent (classical parameters): HR 1.40, 95% CI 1.12–1.74; $p < 0.003$
	RP	[58] (C)	CSM	Discriminant, independent = CAPRA if low clinical risk: HR 1.81, 95% CI 1.48–2.25; $p < 0.001$ > CAPRA if high clinical risk: HR 11.26, 95% CI 4.69–30.37; $p < 0.001$ AV/CAPRA-S, especially if high clinical risk, but no statistical comparison

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Table 5 (*Continued*)

Test (LOE for conclusion by biomarker and indication)	Material	Reference (LOE)	Endpoint	Main results
	RP	[56] (D)	BCR after RP	Discriminant, independent (= PSA) High GC (vs low GC): HR 8.13; 95% CI 3.40–19.46; $p < 0.0001$ (S) AV/CAPRA-S or Stephenson nomogram especially if high clinical risk, but no statistical comparison
After external-beam RT				
Prolaris Clinical validity, LOE VD	Biopsies	[50] (D)	BCR at 10 yr after RT	Independence not demonstrated; 10-yr prediction not linear: first 5 yr >> last 5 yr
Decipher Clinical validity, discriminant especially, in patients at high clinical risk, LOE IIIC AV NA	RP	[56] (D)	Mets after adjuvant RT	Discriminant, independent (=PSA) High GC (vs low GC): HR 14.28, 95% CI 2.13–210.38; $p < 0.005$ (S)
		[57] (C)	Mets after adjuvant or salvage RT	Intermediate or high GC (≥0.4), cumulative incidence of mets at 5 yr higher after salvage than adjuvant RT (23% vs 6%; $p = 0.008$) AUC: weak difference if low GC (<0.4; $p = 0.79$) AV/Stephenson nomogram and CAPRA-S, but no statistical comparison

LOE = level of evidence; RP = radical prostatectomy; AUC = area under the curve for the receiver operating characteristic; NCCN = National Comprehensive Cancer Network; HR = hazard ratio; CI = confidence interval; CAPRA = Cancer of the Prostate Risk Assessment; CAPRA-S: CAPRA post-surgical; AV = additional value; mets = metastases; BCR = biochemical recurrence; PSA = prostate-specific antigen; GS = Gleason score; ECE = extracapsular extension; LNI = lymph node invasion; RT = radiation therapy; NA = not applicable; CSM = cancer-specific mortality GC = genomic classifier score; NA = not applicable.

after radical prostatectomy (LOE IIIC [51] and LOE IVD [52]). The clinical influence is moderate. Decipher could offer additional value relative to the Gleason score [51] (LOE IIIC) or the CAPRA-S, Stephenson, or Eggener nomograms [52,53] (LOE IVD) when their scores are intermediate or elevated, independently of receipt or not of adjuvant treatment. The test also has clinical validity for the endpoints metastasis prediction after biochemical recurrence [54,55] (LOE IIC) and metastasis prediction after adjuvant radiotherapy [56,57] (LOE IIIC). Thus, patients with a high GC score would benefit more from adjuvant radiotherapy than from salvage radiotherapy [57] (LOE IIIC). Similar results were also obtained for prediction of biochemical recurrence after radical prostatectomy [56] (LOE VD) with additional value relative to the CAPRA-S and Stephenson nomograms [56] (LOE VD) and for the endpoint disease-specific mortality after prostatectomy [58] (LOE IIIC) with additional value relative to CAPRA-S alone when the two scores are high [56] (LOE IIIC). Nevertheless, the results of several studies should be considered with caution because the AUC differences between the Decipher test and the other markers were not statistically analysed [51–53,56]. Sometimes, the study design did not allow assessment of "real" metastasis-free survival because the multivariate analysis was not adjusted for adjuvant treatment or salvage treatment. Most studies used patient cohorts that were overlapping [51,56–58]. Multiple analyses using the same patient cohort for different clinical questions bring methodological limitations to the data interpretation.

4. Conclusions

The preanalytical and analytical validations of the tests evaluated were heterogeneous. We stress the importance of quality control considerations for molecular tests. Only the PHI and the 4Kscore present LOE = 1 for discriminating between aggressive and indolent prostate tumours with an additional value compared to the classical parameters. The other biomarkers did not reach the LOE required for routine clinical use and should be evaluated in additional studies. In addition, the place of these biomarkers in association with MRI was not analysed and their cost effectiveness should be assessed before recommending their use in clinical practice.

Author contributions: Pierre-Jean Lamy 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: Lamy, Allory, Gauchez, Kassab-Chahmi, Descotes, Rébillard.
Acquisition of data: Lamy, Kassab-Chahmi, de Cremoux, Lehmann-Che, Schlageter, Gauchez, Allory, Rébillard.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Lamy, Allory, Gauchez, Kassab-Chahmi, Descotes, Rébillard.
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Appendix A. Supplementary data

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