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Clinical Utility of Biomarkers in Localized Prostate Cancer

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Abstract A new generation of prostate cancer (PCa) biomarkers has emerged, including diagnostic serum and urine markers aimed at refining the identification high-grade tumors and tissue-based gene expression assays offering prognostic and predictive clinical information. Such tests seek to improve treatment-related decisions at multiple decision points, including initial diagnosis and following initial primary therapy. In this review, we aim to contextualize the body of evidence surrounding these emerging tests, with attention on studies addressing clinical utility.

Keywords Clinical utility · Prostate cancer · Biomarkers · Gene expression tests

Introduction

Prostate cancer (PCa) is a commonly diagnosed malignancy characterized by non-uniformity in clinical outcomes [1]. Indeed, a significant proportion of men diagnosed each year with PCa will harbor low-risk grade, favorable-risk disease on the basis of conventional clinical risk assessment, while a minority will exhibit aggressive disease progression and eventually succumb to the disease. Despite relatively good accuracy of risk stratification based on standard clinical parameters, residual inadequacies in the stratification of disease outcomes have been identified as a major source of imprecision in management, culminating in both overtreatment of indolent disease and undertreatment of high-risk disease [2]. Well-recognized limitations of clinical models and conventional serum biomarkers—notably, prostate-specific antigen (PSA)—for risk prediction in the detection and prognosis of PCa have driven development and validation a new generation of biomarkers and tissue-based gene expression tests that are now available in the context of routine clinical practice [3–5].

These tools include biomarkers intended for implementation at numerous decision nodes within the disease course. Specifically, novel markers aim to refine selection for initial biopsy and improve clinical decisions in the setting on an elevated PSA or following an initially negative biopsy. In the initial post-diagnostic phase, tissue-based gene expression assays have received study for the ability to improve the certainty with which candidacy for active surveillance (AS) or early definitive intervention. Further along the disease spectrum, genomic signatures have also been validated to predict the risk of subsequent cancer-related events including recurrence, metastatic progression, and death.

A guiding principle that frames our following review is that the value of a novel tool is directly proportionate to its ability to effect real improvements in clinical care. It is clear that enthusiasm abounds for biomarkers offering improvements in the discrimination of various disease-related outcomes. And, while performance in clinical validation studies may reasonably imply a justification for widespread adoption, care must be taken when evaluating the magnitude and context of

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benefit and particularly prior to implementation on a broad scale. In this review, we aim to critically address the contemporary body of novel PCa biomarkers and provide special attention to the existence and quality of evidence addressing clinical utility.

Molecular Markers in PCa

The ever-expanding collection of molecular markers in PCa may be further classified by the clinical context for which they are intended. These include *diagnostic markers*, which principally serve to identify the presence of the disease, but may or may not offer additional information regarding the nature or characteristics of the disease. Contemporary examples include pre-diagnostic assays incorporating novel PSA isoforms (Prostate Health Index, phi, and the 4Kscore) which have been developed for the identification of any PCa and higher Gleason grade (3+4) disease. *Prognostic markers* offer a measure of a pre-specified clinical endpoint and may include tests that yield a prediction of adverse surgical pathology, clinical recurrence, metastasis, or death from PCa [6]. A *predictive* diagnostic marker refers to those that may offer a prediction of an outcome in the context of a treatment or management course. Examples include gene-expression-based assays that have received investigation for identifying patients most likely to benefit from adjuvant radiotherapy after radical prostatectomy. It is important to note that a biomarker may serve in multiple different categories; genomic assays, for example, have been studied in both prognostic and predictive scenarios, though the former are by far more common [7].

Evaluating Clinical Utility

The nomination and development of new cancer biomarkers are a complex, multi-step process drawing from expanding advances in the understanding of PCa molecular biology and complementary gains in cancer genomics and bio-informatics. Broadly speaking, such tests are measured on the ability to delineate a particular endpoint or outcome and are evaluated through statistical measures of association appropriate for these contexts. For example, the ability of a test to predict a clinical occurrence (e.g., the presence of PCa on biopsy) may be reported on the basis of various familiar statistical properties including the area under the receiver operator characteristic curve (AUC), sensitivity, specificity, and the corresponding properties including negative predictive value and positive predictive value. By extension, the performance of any test will exist along a range of values and will also likely vary when implemented in a patient care setting and in subjects bearing differences from discovery and validation cohorts.

Accuracy of PCa risk stratification based on standard clinical variables alone, using validated multi-variable instruments such as the Cancer of the Prostate Risk Assessment (CAPRA) score or a variety of nomograms, is as high as 80 %, so the bar for a putative marker to prove improved accuracy is relatively high [8, 9]. This point bears additional emphasis: demonstration only that a marker can sub-stratify Gleason score or the AUA/NCCN risk group is insufficient; this can be done instantly and with no cost using the tools noted above.

An assumption that often drives great enthusiasm for many emerging markers is that favorable performance characteristics in clinical validation will translate into improved clinical outcomes when implemented in real-world clinical scenarios. While evidence in the validation phase is a necessary prerequisite for clinical relevance, improved accuracy alone is not sufficient, rather the ability of a new test or marker to meaningfully alter clinical decision-making or patient outcomes (clinical utility) influenced by many other factors. These include the ability to improve outcomes across a broad range of probabilities, the magnitude of difference observed in comparison to available markers, the existence of effective interventions that may be undertaken, and economic considerations that may restrict access. For example, if a new diagnostic marker can improve the detection of PCa largely by identifying more tumors with limited biological significance, and in whom treatment will not improve cancer-related morbidity or mortality, such a test may demonstrate good performance yet may have limited clinical value (or in fact would yield net harm for many men). Another consideration that may drive discordance between performance in validation studies and real-world use is that the indications and constraints of an even ideal biomarker may be misinterpreted or inadequately utilized. Longitudinal studies are therefore required to truly assess the utility of a particular test when implemented on a broad level.

The concept of clinical utility is essential to the endeavor of development and practical utilization of new markers. Due to the numerous factors that affect outcomes, such studies, when performed prior to empirical use, are complex and often utilize modeling estimates to estimate the magnitude of clinical impact. The decision curve analysis (DCA) method offers a visual depiction of the net benefit of a test (y-axis) in influencing clinical decisions across a range of theoretical threshold probabilities for intervention (x-axis) [10, 11]. Such approaches offer insights into the proposed advantages of a particular tool in various clinical situations. At the extremes of these probabilities—situations in which decisions (e.g., to proceed with biopsy, definitive treatment, or adjuvant therapy) will likely be made regardless of a novel decision aid—clinical benefit may be limited; however, in intermediate ranges, DCA may illustrate impact across a dynamic scale.

Payers—particularly CMS—are increasingly demanding evidence of clinical utility as well as analytic validity in making coverage decisions on PCa biomarkers. A growing number of such studies are therefore appearing in the literature.

These studies employ a variety of designs, but the most common framework is to record a clinical decision at the point of care in a "real-world" setting before the biomarker is available, then to provide the patient and clinician with the marker result, and to determine frequency of decision change. This design is prone to significant potential bias since participating clinicians are aware of the study design and goals and are generally remunerated for participation. They might, therefore, record a pre-marker treatment recommendation, which may differ from the recommendation that would actually be made outside the study context.

Emerging Serum Biomarkers

Several *diagnostic* biomarkers offering improved detection of PCa and, in particular, *clinically significant* PCa are beginning to see clinical implementation. The Prostate Health Index (phi) is a biomarker panel that includes free PSA, total PSA, and [−2]proPSA. The phi score is subsequently derived as follows: ([−2]proPSA / free PSA) ∗ (√total PSA). To date, the commercially available assay (Beckman Coulter Incorporated, Carlsbad, CA) has been evaluated in several large international studies within the USA, Europe, and Asia [12–15]. Catalona et al. evaluated the performance of the phi score to discriminate Gleason ≥3+4 disease in a prospective cohort of 892 men without PCa and total PSA 2–10 ng/mL undergoing prostate biopsy. The AUC for the detection of high-grade disease for the phi score was 0.703, which was significantly higher than the each individual analyte [16]. Similarly, Loeb recently reported on a prospective multicentered study including 685 men, aged 50 and older with PSA in the range of 4–10 ng/mL in which the AUC for detection of any PCa was 0.708 and 0.707 for Gleason 3+4 or higher disease on biopsy. Moreover, in a meta-analysis incorporating 16 studies and 5856 patients, the pooled sensitivity and specificity were 0.85 (95 % CI, 0.83–0.86) and 0.45 (95 % CI, 0.44–0.47) for phi for overall PCa detection, respectively, and 0.90 (95 % CI 0.87–0.92) and 0.17 (95 % CI 0.14–0.19) for Gleason ≥3+4 disease [17].

Evidence addressing the clinical utility of the phi as a diagnostic test derives largely from numerous validation studies examining the performance of the marker panel. For example, data from Loeb et al. indicate that at a 90 % sensitivity cut point, corresponding to scores less than 28.6 for the phi test, suggests that 30.1 % of patients may be spared a biopsy, a proportion that compares favorably to the % free PSA (21.7 %). The phi test was also recently evaluated as a predictor of pathological outcomes among men undergoing treatment with radical prostatectomy in a prospective multicentered European study of 489 men. The addition of the phi to a multi-variable clinical risk prediction model resulted in a statistically significant improvement in discriminatory accuracy (AUC) for ≥pT3a and/or Gleason ≥3+4 findings from 0.78 (95 % CI 0.74–0.82) to 0.80 (95 % CI 0.76–0.84). However, in a DCA model, models including phi did not result in a greater net benefit at any threshold probability [18]. Taken together, these findings suggest that phi may offer diagnostic benefit in selecting men for biopsy, yet will not meaningfully assist in the discrimination of adverse pathologic findings at surgery. A summary of validation studies addressing the phi assay is presented in Table 1.

A panel of four serum kallikreins (total PSA, free PSA, intact PSA, and human kallikrein protein 2 (hK2) has received extensive evaluation in the pre-biopsy setting and is commercially marketed as the 4Kscore Test (4K, OPKO Lab, Nashville, TN) [19–23, 24•]. The algorithm representing these components was initially derived from data based on participants within the European Randomized Study of Prostate Cancer Screening (ERSPC) and Prostate Testing for Cancer and Treatment (ProtecT) studies. To date, the 4K test has been examined in over 15,000 patients within Europe and the USA. In one study, among 730 previously unscreened men within the Göteborg arm of the ERSPC, addition of the 4K to a base model improved the AUC for the prediction of PCa on biopsy from 0.87 to 0.90 [19]. Recently, Parekh et al. reported on a prospective multi-centered US study of the 4K test in men scheduled to undergo prostate biopsy for clinical suspicion of PCa due to abnormal DRE or elevated PSA. Among 1012 men, the predictive accuracy for biopsy Gleason ≥3+4 was significantly higher with the inclusion of the entire 4K panel: AUC 0.821 (95 % CI 0.790–0.852) versus 0.751 (95 % CI 0.714–0.789). In DCA comparing the 4K test to modified Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) strategies for selecting prostate biopsy, the 4K demonstrated higher net benefit across all threshold probabilities [24•]. A summary of studies addressing the performance characteristics of the 4K markers is outlined in Table 1.

Given the abundance of favorable evidence supporting *both* the 4K and PHI assays for the improved discrimination of high-grade PCa, clinicians may be faced with uncertainty when selecting among these tests in practice. Therefore, comparative study of biomarkers is highly valuable, as such investigation may allow direct evaluation of emerging tests within an identical population. Nordström et al. compared the 4K and PHI tests in a population of 531 biopsy-naive Swedish men with PSA levels between 3 and 15 ng/mL receiving first biopsy between 2010 and 2012. For the prediction of high-grade (Gleason ≥3+4) PCa, the 4K and PHI tests performed very similarly: both provided significantly higher predictive accuracy than a basic clinical model: 71.8 (95 % CI 66.8–76.7) and 71.1 (95 % CI 66.0–76.2), respectively, compared to the base model of 59.6 (95 % CI 54.1–65.8 %). DCA indicated that the 4K panel demonstrated net benefit at thresholds greater than 18 % for any PCa and 8 % for high-grade PCa, while PHI showed clinical utility at higher cutoff values. From this analysis, strategies incorporating 4K and PHI would result in

Table 1 Summary of clinical validation studies examining the Prostate Health Index (phi) and 4-kallikrein panel (4K test)

Biomarker	Author	Study design	*N*	AUC (any grade)	AUC (Gleason ≥3+4)
Prostate Health Index (phi):	Le [46]	Patients undergoing prospective screening in Chicago, IL. Recommendations for biopsy included serum PSA >2.5 ng/mL or abnormal DRE.	2034	0.77	–
	Jansen [47]	Participants from the Rotterdam arm of the ERSPC trial (site 1) and the Innsbruck Medical University (site 2) referred for Bx	756	0.750 (1) 0.709 (2)	–
	Catalona [16]	Prospective multi-institutional trial of individuals with normal DRE, PSA 2–10 ng/mL, and six-core ore greater Bx	892	0.703	0.724 (GS 4+3)
	Loeb [48]	Prospective multi-institutional trial of individuals undergoing biopsy with re-calculation of WHO PSA values	892	0.704	–
	Guazzoni [49]	Observational prospective study in the clinical setting of men with total PSA 2–10 ng/mL and normal DRE scheduled for Bx at a tertiary academic center	268	0.83	0.81
	Lazzeri [50]	Observational prospective evaluation of men with 1 or 2 prior negative biopsies with persistent clinical suspicion of PCa	222	0.78	–
	Lazzeri [51]	Nested case-control study of the multi-centered European PROMEtheuS project including patient with first-degree relative with PCa undergoing Bx	1026	0.760	–
	Lazzeri [14]	Observational prospective cohort study of patients from five European centers with serum PSA 2–10 ng/mL undergoing initial Bx	646	0.712	0.672
	Stephan [52]	Multi-centered non-randomized case-control trial of men undergoing Bx with total PSA between 1.6 and 8 ng/mL	1362	0.75	–
	Ng [12]	Retrospective study of men >50 years with PSA 4–10 ng/mL and negative DRE undergoing first prostate Bx	231	0.792	–
	Loeb [53]	Prospective multi-center US evaluation of the phi assay including age ≥50, serum PSA 4–10 ng/mL and normal DRE undergoing Bx	658	0.708	0.707
	Nordstrom [25••]	Comparative study phi and 4Kscore in 531 men with PSA between 3 and 15 undergoing first time Bx	531	0.704	0.711
	Fossati [54]	Nested case-control study of participants in the PROMEtheuS project aged <60 years referred for Bx		0.770	–
4-Kallikrein panel (4K test)	Braun [55]	Patients referred for Bx due to elevated PSA ≥3 ng/mL, low % fPSA (<20 %), or abnormal DRE	749	0.690	0.784
	Nordstrom [25••]	Comparative study of phi and the 4K test in 531 men with PSA between 3 and 15 ng/mL undergoing first time Bx	531	0.69	0.718
	Vickers [19]	Previously unscreened men undergoing biopsy within the Goteborg arm of the ERSPC trial	740	0.836	0.903
	Benchikh [20]	Men undergoing Bx for elevated PSA ≥3 ng/mL within the ERSPC-Tarn, France	262	0.782	0.870
	Vickers [23]	Previously unscreened men undergoing biopsy for elevated PSA (≥3 ng/mL) in the Rotterdam section of the ERSPC	2914	0.778	0.837
	Vickers [21]	Previously screened men with elevated PSA (≥3 ng/mL)	1501	0.711	0.798
	Vickers [22]	Participants undergoing biopsy for elevated PSA during second or later visit within ERSPC trial (Gothenburg, Sweden)	1241	0.697	0.828
	Gupta [56]	Patients with previous negative biopsy and elevated PSA (≥3 ng/mL)	925	0.681	0.873
	Carlsson [57]	Participants diagnosed with PCa within the Rotterdam arm of the ERSPC trial with elevated PSA ≥3 ng/mL and subsequently treated with RP between 1994 and 2004. Prediction of grade ≥3+4, non-organ confined or tumor volume >0.5 cm^3	392	–	0.84
	Vickers [58]	Prediction of PCa among Malmo Diet and Cancer participants with PSA ≥3 ng/mL undergoing Bx	792	0.751	–
	Bryant [59]	Individuals participating in the ProtecT study undergoing ten-core Bx for elevated PSA (≥3 ng/mL)	4765	0.719	0.820
	Parekh [24•]	Prospective multi-institutional validation within US population of men undergoing biopsy without restrict for PSA or clinical findings	1012	–	0.821

AUC area under the curve, *Bx* biopsy, *PSA* prostate-specific antigen, *DRE* digital rectal examination, *PCa* prostate cancer, *WHO* World Health Organization, *ERSPC* European Randomized Study for Screening Prostate Cancer, *ProtecT* Prostate Testing for Cancer and Treatment trial, *PROMEtheuS* PRO-PSA Multicentric European Study

reductions of biopsies of nearly 30 % at the expense of missed diagnosis in 10 % of men with higher-grade tumors [25••].

ConfirmMDx

A considerable proportion of men with an initial negative biopsy in the setting of an elevated PSA will undergo additional biopsies. Based on the finding that there are genomic "halo" effects in histologically normal PCa adjacent to cancerous foci, the ConfirmMDx assay (MDx Health, Irvine, CA) measures methylation levels of GSTP1, APC, and RASSF1 in pathologically benign biopsy specimens to determine the risk of subsequent PCa detection [26, 27]. Clinical validation studies of the methylation assay have included a multi-institutional European study of 498 men undergoing initial negative biopsy followed by repeat biopsy within 30 months. The sensitivity and specificity of the assay for the detection of subsequent PCa were 68 and 64 % with negative predictive value (NPV) of 90 % (95 % CI 87–93 %) [28]. Similarly, in a multi-center US study consisting of 350 men receiving repeat biopsy following initial negative biopsy, the methylation assay was associated with a sensitivity of 62 and 64 % and NPV of 88 % (95 % CI 85–91) [29].

A clinical utility field study consisting of patients from five US sites in whom the epigenetic assay had been ordered in the setting of an initial negative prostate biopsy examined the rates of subsequent biopsy. Among 138 men with median PSA 4.7 ng/mL, only six patients (4.3 %) of men with a negative assay result underwent subsequent prostate biopsy, none of which demonstrated PCa [30]. While such studies imply a potential benefit associated with the practical implementation of the methylation assay, the retrospective and uncontrolled nature of the study design appears to warrant further investigation prior to confirming an independent value.

Prolaris

The Prolaris assay (Myriad Genetics, Salt Lake City, UT) includes a set of 31 genes relating to cell cycle progression (CCP) associated with PCa outcome. This gene signature was initially derived from a set of 126 candidate genes associated with CCP pathways and narrowed down based on analyses of correlation among the candidate genes. The CCP signature has been evaluated in formalin-fixed paraffin-embedded (FFPE) PCa specimens derived from both radical prostatectomy and prostate biopsy specimens [31]. In clinical validation studies, the CCP signature has demonstrated favorable performance for the prediction of downstream oncologic endpoints. Among men treated with external beam radiation therapy, the CCP was independently associated with biochemical recurrence (BCR) and PCa-specific mortality (PCSM) when adjusted for clinical- and treatment-related variables [32]. The association between CCP score derived from biopsy specimens and adverse outcomes after treatment was also seen in a radical prostatectomy cohort [33]. In the pre-treatment setting, the test provides a prediction of PCSM in untreated patients, a probability derived from an observational cohort of men undergoing conservative management [34].

The CCP assay has also been evaluated following radical prostatectomy. In a study of 413 men in whom the CCP assay was retrospectively calculated on FFPE archival tissue, the score was independently associated with risk of BCR and metastatic progression in models adjusted for clinical and pathological characteristics. When directly compared, the CCP assay alone did not outperform the CAPRA-S post-treatment clinical model; however, the addition of the CCP score to the CAPRA-S yielded improved accuracy in predicting disease recurrence compared to either assay alone (Table 2) [35••].

The clinical utility of the CCP assay to impact clinical management in men with PCa has been evaluated at several junctures within the disease process. Crawford et al. examined the impact of the CCP report on treatment recommendations in 305 cases in which physicians completed surveys indicating the effect of the assay result. CCP testing resulted in a 37.2 % reduction in interventional treatment among men initially recommended for treatment; among men initially recommended for non-interventional treatment, the CCP assay resulted in a shift toward intervention in 23.4 %. On third-party audit, high concordance existed between the post-CCP testing treatment recommendation and actual treatment [36]. Similarly, Shore et al. retrospectively surveyed 15 US community group practices regarding treatment recommendations for 294 patients with localized disease. In practical application, providers suggested that in 55 % of cases, the assay resulted in a mortality risk that was higher or lower than expected, and in 32 %, this resulted in a definite or possible change in treatment [37]. In both studies, it is important to note that patients were identified retrospectively and that factors driving treatment decisions were not explicitly identified in the analysis. These studies do indicate a potential role in modifying clinical decision-making but are also subject to possible bias as discussed above.

OncotypeDX GPS

The OncotypeDX Genomic Prostate Score (GPS) (Genomic Health, Redwood City, CA) assay is a signature based on 12 genes associated with PCa aggressiveness, benchmarked to five housekeeper reference genes. These genes were narrowed down from a pool of 732 candidate genes based on their association with clinical recurrence from radical prostatectomy (RP) and biopsy cohorts [38]. In a clinical validation study including 395 men with low-

Table 2 Summary of external validation studies for commercially available prostate cancer tissue-based gene expression tests

Assay	Author	Cohort	Endpoint	Main findings
Prolaris	Cooperberg et al. [35••]	413 patients receiving treatment with RP followed for a median of 85 months.	BCR	CCP-independent predictor of BCR; combination of CCP with clinical information (CAPRA) yielded improved performance over individual clinical or genomic information.
	Bishoff et al. [33]	Aggregate 582 specimens from diagnostic or simulated biopsy among patients treated with RP	BCR, MFS	CCP score derived from biopsy was independently associated with BCR and MFS when adjusting for clinical variables
	Cuzick et al. [60]	349 conservatively managed patients diagnosed between 1990 and 1996 and followed for a median of 11.8 years.	PCSM	CCP score outperformed clinical variables in the prediction of PCa-specific survival.
	Freedland et al. [32]	141 men treated with definitive EBRT; CCP scores retrospectively derived from needle biopsies	BCR PCSM	CCP score outperformed clinical parameters in the prediction of BCR following EBRT; with 10-year censoring assay associated with PCSM ($p = 0.013$).
OncotypeDX GPS	Klein et al. [39]	Primary validation cohort of 395 retrospectively collected needle biopsies of low- and intermediate-clinical-risk patients treated with RP	Adverse pathology (≥pT3a; GS ≥4+3; N1)	17-gene signature independent predictor of high-grade and high-stage disease at RP, adjusted for clinical risk factors. DCA indicated improved net benefit of GPS clinical model.
	Cullen J. et al. [40]	Racially diverse (20.4 % AA) cohort of needle biopsy specimens ($N = 431$), median follow-up 5.2 years.	Adverse pathology; BCR	Adjusting for clinical factors, GPS independently associated with BCR and adverse pathology. Median GPS values identical among AA and Caucasian individuals, distributions similar.
Decipher	Ross et al. [61]	Case-control study of patients experiencing BCR after RP	MFS	Genomic classifier outperformed clinical parameters in the prediction of metastatic progression; greater net benefit in DCA
	Karnes [42]	Case-cohort study of 219 patients with high-risk pathological features at RP followed for a median of 6.7 years.	MFS	Decipher assay independent predictor of 5-year metastatic progression (AUC 0.79), out-performed clinical characteristics
	Den [44]	139 patients identified who received post-RP radiation therapy for pT3 disease or PSM.	BCR MFS	Decipher classifier independent predictor of BCR and MFS. Addition of genomic profile to Stephenson model improved AUC for prediction from 0.70 and 0.70 to 0.78 and 0.80 for BCR and MFS, respectively.
	Cooperberg et al. [43],	Case-cohort study of 185 men at high risk for recurrence following RP followed for a median of 6.4 years	PCSM	Decipher classifier and CAPRA-S clinical model independent predictors of PCSM. Combined Decipher-CAPRA-S did not improve AUC; those with both high genomic and adverse clinical profiles 45 % 10-year CSM risk.
	Klein et al. [62]	169 patients treated with RP with high-risk features (lymph node negative) with undetectable post-RP PSA who did not receive adjuvant therapy	MFS	Decipher signature independently associated with metastatic progression and had highest c-index (0.77) compared with Stephenson and CAPRA-S models. Combination of Decipher with Stephenson increased c-index from 0.75 to 0.79.

FFPE formalin-fixed paraffin-embedded, *RP* radical prostatectomy, *BCR* biochemical recurrence, *MFS* metastasis free survival, *CCP* cell cycle progression, *CAPRA* Cancer of the Prostate Risk Assessment, *Bx* biopsy, *CSS* cancer-specific survival, *EBRT* external beam radiation therapy, *GS* Gleason score

and intermediate-clinical-risk disease—ostensibly candidates for AS—the GPS assay was examined for the prediction of adverse surgical pathology, defined as primary Gleason pattern 4 or higher, and/or non-organ confined disease (≥pT3a or lymph node positive) [39]. In a second recent study examining a cohort of 402 men, the GPS assay was independently associated with risk of BCR and metastatic progression (Table 2) [40].

The clinical utility of the GPS assay to impact clinical decisions, particularly in early-stage disease, has been approached within the context of clinical validation data. DCA was performed to compare the net benefit of various decision schema to identify high-grade and/or high-stage disease composed of treatment of all patients, no patients, clinical risk alone (CAPRA score), or the combination of clinical risk and GPS derived from the clinical validation cohort of 395 patients [39]. In each scenario, combined clinical-GPS models generated higher net benefit across all threshold probabilities. Though promising, improvements in clinical decision-making and patient outcomes, as driven by the GPS assay, await empiric demonstration.

Decipher (GenomeDX, Vancouver, BC)

The Decipher genomic classifier is a 22-marker signature derived from transcriptosome-wide sequencing of a PCa cohort enriched for recurrence following treatment with RP [41]. Refinement of the high-density micro-arrays from roughly 1.4 million features was performed using machine learning algorithms to select a panel of markers highly associated with clinical outcomes. The Decipher score (reported on a 0–1 scale) predicting early metastatic progression following RP was examined in a cohort of men with adverse pathological features, where increases in the GC score were significantly associated with metastatic progression and PCSM, even after adjustment for the CAPRA-S score or other models incorporating post-prostatectomy data [42, 43]

The Decipher genomic classifier was evaluated for the ability to selectively identify men who may benefit from adjuvant radiation therapy following RP [44]. Den et al. reported on 188 men with pathological T3 or margin-positive PCa at surgery who were treated with adjuvant radiation therapy at two institutions between 1990 and 2009. The unadjusted incidence of metastatic progression at 5 years was 0, 9, and 29 % for low, average, and high GC scores, respectively ($p = 0.002$). The concordance index (c-index) for metastasis-free survival at 5 years was 0.66 (95 % CI 0.56–0.78) for a clinical model composed of post-surgical CAPRA-S alone, 0.83 (95 % CI 0.27–0.89) for GC alone, and 0.85 (95 % CI 0.79–0.93) for a model composed of CAPRA-S and GC [45••]. Interestingly, the GC resulted in risk reclassification in over 40 % of CAPRA-S intermediate- and high-risk patients, of whom 96 % remained disease free at follow-up. These findings are distinguished from other publications in support of *prediction* rather than *prognostication:* men with favorable Decipher scores can potentially be able to wait for radiation therapy, whereas those with high scores may benefit from earlier (adjuvant) therapy. It should be emphasized, however, that the use of the Decipher classifier to guide management decision has not been studied in a prospective fashion.

The performance of the Decipher GC to discriminate metastatic progression following post-prostatectomy RT compared with clinical models (CAPRA-S), combined GC-CAPRA-S, and strategies of uniform or no treatment were further examined with DCA. Models incorporating the GC demonstrated greater net benefit across all probability thresholds up to 25 %, suggesting that clinical management strategies incorporating the Decipher assay may improve the selection of post-prostatectomy radiotherapy. Caveats apply in the use of retrospective, validation datasets to establish clinical utility: patients were identified over a long interval (1990–2009) including some in the pre-PSA era, and it remains to be seen whether clinicians will practically alter treatment recommendations in light of this tool. Nevertheless, this evidence appears to imply a promising potential role for novel tools in the selection of post-prostatectomy radiotherapy.

Conclusion

A growing armamentarium of novel PCa biomarkers has emerged in recent years aimed at refining risk prediction at multiple PCa decision points. Evidence addressing clinical utility of a new generation of refined serum diagnostic assays has been derived from an array of trials evaluating men prior to biopsy indicating a potential benefit in reducing the number of unnecessary biopsies. Tissue-based gene expression tests in the post-biopsy phase aim to improve clinical decision-making by offering refined predictions of aggressive disease invoking multiple clinical endpoints. In the post-prostatectomy setting, genomic signatures have been validated to predict the subsequent risk of adverse oncologic outcome and may selectively identify individuals with adverse pathology who may benefit from early aggressive therapy. Due to their novelty, longitudinal studies addressing the clinical benefit of these tools when implemented outside of tightly controlled studies are warranted.

Ideally, a trial would randomize men to have a given marker run or not; then, the men would make their best decision and be followed for quality of life and cancer control outcomes. Unfortunately, given the prolonged natural history of most PCas, this is not a practical design in the foreseeable future. Large-scale registries such as MUSIC and AQUA

may provide future opportunities to track real-world uptake and use of emerging markers and to assess their impact on care decisions in analyses which will be retrospective but less prone to bias.

Compliance with Ethical Guidelines

Conflict of Interest Michael S. Leapman declares that he has no conflict of interest.

Hao G. Nguyen declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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