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CRITICAL REVIEW

Genomic Classifiers in Personalized Prostate Cancer Radiation Therapy Approaches: A Systematic Review and Future Perspectives Based on International Consensus



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employee of Veracyte, manufacturer of Decipher. A.R. is a consultant and/or speaker for Astellas, Bayer, Pfizer, Blue Earth, Lantheus, Janssen, Tempus, and Veracyte. X.G. is on the consulting/advisory board for Bayer, Myovant, and Guardant Health.

Data sharing statement: The results of the systematic review are included in the article. All data generated during the Delphi consensus are included in the article and supplementary material. The corresponding author is available for any further questions on the data.

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Abstract: Current risk-stratification systems for prostate cancer (PCa) do not sufficiently reflect the disease heterogeneity. Genomic classifiers (GC) enable improved risk stratification after surgery, but less data exist for patients treated with definitive radiation therapy (RT) or RT in oligo-/metastatic disease stages. To guide future perspectives of GCs for RT, we conducted (1) a systematic review on the evidence of GCs for patients treated with RT and (2) a survey of experts using the Delphi method, addressing the role of GCs in personalized treatments to identify relevant fields of future clinical and translational research. We performed a systematic review and screened ongoing clinical trials on ClinicalTrials.gov. Based on these results, a multidisciplinary international team of experts received an adapted Delphi method survey. Thirty-one and 30 experts answered round 1 and round 2, respectively. Questions with $\geq 75\%$ agreement were considered relevant and included in the qualitative synthesis. Evidence for GCs as predictive biomarkers is mainly available to the postoperative RT setting. Validation of GCs as prognostic markers in the definitive RT setting is emerging. Experts used GCs in patients with PCa with extensive metastases (30%), in postoperative settings (27%), and in newly diagnosed PCa (23%). Forty-seven percent of experts do not currently use GCs in clinical practice. Expert consensus demonstrates that GCs are promising tools to improve risk-stratification in primary and oligo-/metastatic patients in addition to existing classifications. Experts were convinced that GCs might guide treatment decisions in terms of RT-field definition and intensification/deintensification in various disease stages. This work confirms the value of GCs and the promising evidence of GC utility in the setting of RT. Additional studies of GCs as prognostic biomarkers are anticipated and form the basis for future studies addressing predictive capabilities of GCs to optimize RT and systemic therapy. The expert consensus points out future directions for GC research in the management of PCa. © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Prostate cancer (PCa) is the second most common malignancy in men worldwide.¹ Improvements in screening and diagnostics have led to an increased number of patients with all stages of PCa.^{2,3} Radiation therapy (RT) plays a central role in the management of patients with PCa and can be applied in a curative setting or as part of a palliative treatment concept. However, current risk stratification systems are imperfect—novel prognostic and predictive biomarkers are urgently needed to enable better patient selection for appropriate treatment in the future. Several biomarkers evaluating blood, urine, or tissue have been

developed to aid with risk stratification. Genomic classifiers (GC), or mRNA-based gene expression profiles from tissue, have shown promise to reliably enable identification of aggressive PCa and guide treatment decisions with different commercially available profiling panels, including Prolaris, Oncotype DX, and Decipher (for overview, see references^{4,5}). Additionally, the PAM50 classifier has been demonstrated to differentiate between luminal and basal PCa, with luminal B tumors being associated with favorable response to postoperative androgen deprivation therapy (ADT).⁶

Most evidence is available for the Decipher GC after radical prostatectomy (RP), improving risk stratification and

consequently guiding postoperative disease management.⁷ Less data exist for patients treated with definitive RT or RT in the (oligo)metastatic setting, but GC might facilitate personalized oncologic treatments in various perspectives in all disease stages. The aim of this work was to (1) summarize the role of GCs for patients with PCa in all disease stages treated with RT, because this is an aspect that has not previously been highlighted, and (2) point out relevant clinical and translational issues for future fields of research. We therefore conducted (1) a systematic review and (2) a survey of experts and key opinion leaders using the Delphi method. See Fig. 1 for a summarizing overview.

Methods and Materials

Systematic review

Studies eligible for inclusion were original articles on GC in PCa in the setting of RT, comprising primary definitive, postoperative, and metastasis-directed (MDT) RT. In general, 3 types of articles were included: (A) articles on oncologic outcomes after RT, (B) the role of GCs in the RT decision process, and (C) correlation studies between other biomarkers and GCs. Inclusion criteria comprised the following: (A1) patients treated with RT (definitive, postoperative, MDT); (A2) clinical results with the following

endpoints: clinical recurrence, biochemical recurrence (BR), distant metastases (DM), prostate cancer–specific mortality (PCSM), and overall survival; (A3) articles with retrospective and prospective data (n patients >50); (B1) translational work addressing correlation of GCs with imaging, biomarkers, or biological features (radioresistance, androgen signaling, etc); and (C1) effect of GCs in the RT treatment decision processes. Exclusion criteria were (1) articles not written in English and (2) nonoriginal articles. S.K.B.S. and C.Z. performed a PubMed/MEDLINE, Embase, and Cochrane Library database search for the following terms:

PubMed:

(prostatic neoplasms [MeSH Terms⁶] or (prostatic neoplas* [tiab OR prostate neoplas* [tiab] OR prostatic cancer* [tiab] OR prostate cancer* [tiab] OR prostatic carcinoma* [tiab] OR prostate carcinoma* [tiab] OR prostatic adenocarcinoma* [tiab] OR prostate adenocarcinoma* [tiab] OR prostatic tumor* [tiab] OR prostate tumor* [tiab] OR prostatic tumour* [tiab] OR prostate tumour* [tiab]) AND (Radiotherapy⁸) or (radiotherapy [Subheading]) or (radiotherap* [tiab] OR radiati* [tiab] OR irradiati* [tiab] OR “x ray therapy” [tiab] OR “x ray therapies” [tiab] OR radioimmunotherap* [tiab] OR immunoradiotherap* [tiab]) AND (genomic* classif* [tiab] OR decipher* [tiab])

Embase and Cochrane:

(‘prostate cancer’/exp OR ‘prostate cancer’) AND (‘radiotherapy’/exp OR ‘radiotherapy’) AND (‘genomic classifier’/exp OR ‘genomic classifier’)

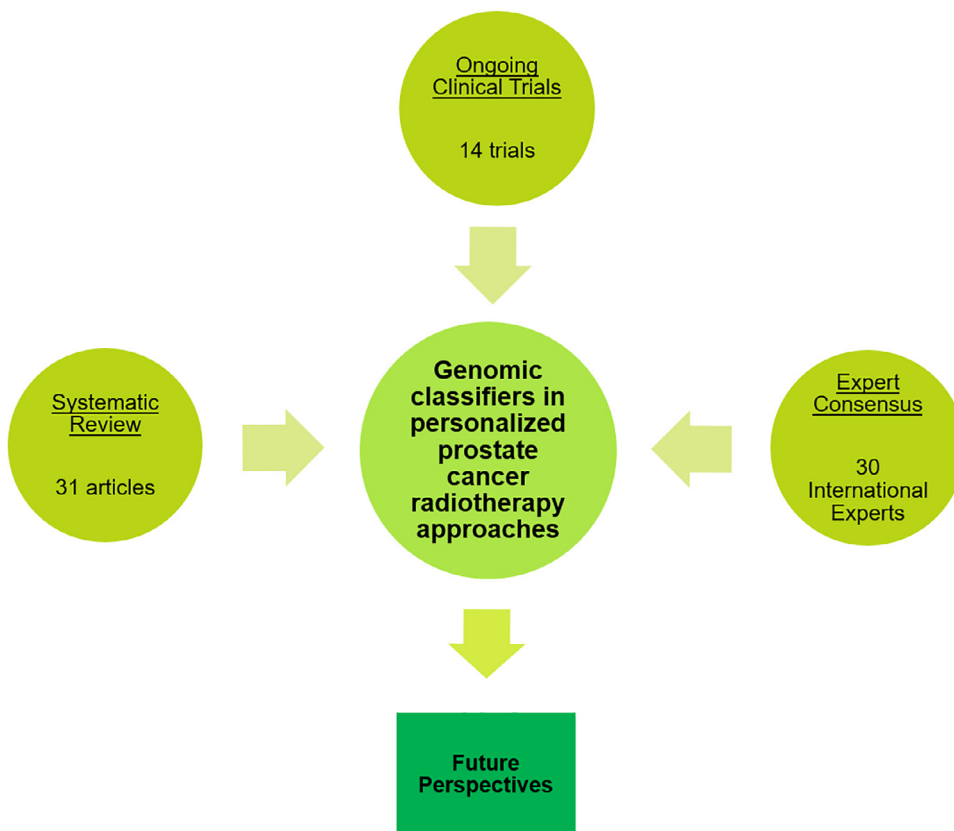


Fig. 1. Summarizing overview.

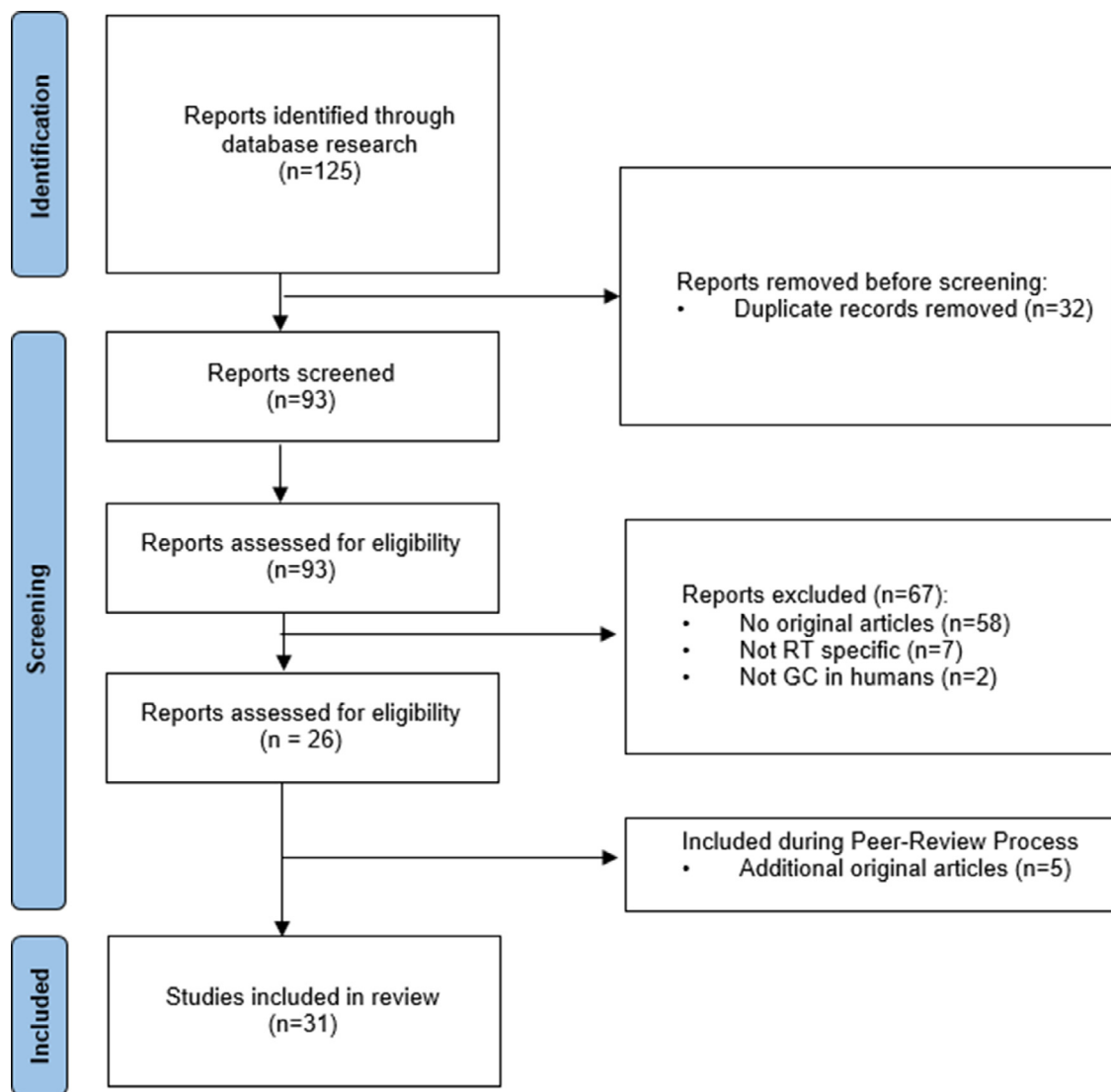


Fig. 2. PRISMA flow diagram of the systematic database search and excluded records. Abbreviations: GC = genomic classifier; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RT = radiation therapy.

Mapped terms “genomic classifier” mapped to ‘genomic classifier.’

In case of discrepant findings ($n = 3$), a third reviewer (C.e. D.r.) provided a final decision. The period considered in this review was from June 6, 2013, to December 1, 2021. One hundred twenty-six articles were identified and 32 duplicates were removed. After applying inclusion and exclusion criteria, 26 studies were included for qualitative review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Fig. 2).⁹ This version was sent to the experts for the first round of the survey. Between round 1 and 2 of the survey, a second round of literature research was performed considering articles until December 31, 2021. No additional studies matching inclusion and exclusion criteria were found. During the peer-review process an update of the literature search was performed, and 5 more studies and 1 more clinical trial were included by considering the period from June 6, 2013, to December 1, 2022.

Ongoing clinical trials

To provide an overview of clinical trials implementing GCs in treatment decisions, which serves to classify results of the expert survey, ongoing clinical trials were screened on ClinicalTrials.gov. Studies needed to be ongoing trials on GCs in PCa in the setting of RT. S.K.B.S. performed the search for the terms (“Condition or disease: prostate cancer” AND “genomic classifier” OR “radiotherapy”). Five clinical trials on GCs in RT were located.

Expert opinion

The multidisciplinary team of expert professionals included radiation oncologists, urologic oncologists, and pathologists. Experts were characterized by long-time experience in care and/or clinical trials of patients with PCa, scientific research,

and their role as key opinion leaders. An adapted Delphi method was used to identify the most relevant questions for future perspectives of GC. Because predictive biomarkers are ultimately warranted to guide personalized treatments, we focused on the putative capability of GCs to identify patients who might benefit from a certain treatment. In round 1 (R1), preliminary results of literature search and key questions were prepared by S.K.B.S. and C.Z. and e-mailed to 46 PCa experts, receiving 27 replies. The survey was designed using the online tool SurveyMonkey. Based on the recommendations of the participants, we sent an additional 9 invitations, with 4 replies. In total, 31 experts answered R1 (response rate: 56%). After completion of R1, S.K.B.S. and C.Z. consolidated questionnaires and prepared round 2 (R2), in which participant feedback and questions that did not reach consensus (defined as 50%-75% of votes) were included. These results were prepared by S.K.B.S. and C.Z. and distributed to all participants (n = 31). Thirty experts provided answers in R2 (response rate: 97%). Finally, only questions with $\geq 75\%$ agreement were considered as relevant and included into the qualitative synthesis. The detailed results of the adapted Delphi rounds can be found in the Supplementary Materials Appendix E1.

Results

GC in the literature: Methodological aspects

The literature search revealed 31 original papers addressing GCs in the setting of RT (see Table 1 for details). Most of the studies (n = 26) included retrospectively collected patient collectives, while 5 studies analyzed GC in prospectively collected patient cohorts. Only 2 studies performed an external validation.^{10,11} With 20 (65%) studies, the Decipher test was used in the vast majority.^{10,12–30}

In 24 (77%) studies, RP specimens were used to obtain tissue for genomic analyses.^{10–25,27,29,34–37,39,40} In 1 study (3%), the Decipher test was applied to both RP and biopsy specimens,²⁷ while 6 studies (19%) solely used biopsy specimens for further analyses.^{28–33} Most studies (n = 18, 58%) investigated the associations between GCs and oncological outcomes such as DM (n = 12, 39%),^{13–15,27–30,32–36} PCSM (n = 3, 10%),^{15,29,32} overall survival (n = 1, 3%),¹⁵ clinical recurrence (n = 3, 10%),^{10,12,16} and BR (n = 6, 19%).^{14,16,28,31,32,37} The other studies reported on the role of GCs on treatment decision making (n = 9, 29%)^{17–25} or correlated GCs with other biomarkers (n = 4, 13%).^{11,26,39,40}

All studies included in this review reported on the role of GC as prognostic biomarkers for patients with PCa. To correctly assess the predictive value of a biomarker in a study, at least 2 comparison groups must be available (in the best case, 2 treatment arms in a randomized controlled trial [RCT]).⁴¹ This prerequisite was not fulfilled by any study in this review. However, 5 studies suggested a predictive role for GC in the setting of adjuvant RT after surgery,

and 1 study supposed a predictive role of GC in the response to ADT in the definitive RT setting.^{10,13,14,33–35}

GC in the literature: GCs for outcome prediction in RT for primary localized PCa

In total, 7 studies included 1551 patients treated with definitive RT.^{27–33}

Tosoian et al²⁷ performed a retrospective analysis of 405 men with high-risk PCa, of which 80 were treated with definitive RT \pm ADT. A subset analysis showed that GC was an independent prognosticator for patients treated with RT (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.08–2.40). Berlin et al²⁸ analyzed 121 patients with National Comprehensive Cancer Network (NCCN) intermediate-risk PCa treated with definitive RT without ADT. The GC outperformed all other indices in prediction of DM (HR, 2.05; 95% CI, 1.24–4.24). Nguyen et al²⁹ investigated retrospectively the Decipher biopsy test as a prognosticator for DM and PCSM in intermediate- and high-risk patients treated with RP or RT \pm ADT, respectively. In the mixed cohort, the GC test was a significant predictor for DM (HR, 1.37 per 0.1 score increase; 95% CI, 1.06–1.78) and PCSM (HR, 1.57 per 0.1 score increase; 95% CI, 1.03–2.48). Another study by Nguyen et al³⁰ included patients with intermediate- and high-risk PCa. Each GC score increase was a significant predictor for DM in multivariate analysis (HR, 1.36; 95% CI, 1.04–1.83). Furthermore, patients with a GC > 0.6 (high-risk) had a 20% cumulative incidence of metastasis at 5 years after RT, whereas patients with a low-risk GC score of ≤ 0.2 had 0% cumulative incidence. Tward et al³³ showed that a clinical cell-cycle risk score (Cancer of the Prostate Risk Assessment [CAPRA] score + Prolaris GC) prognosticated DM with an HR per unit score of 2.22 (95% CI, 1.71–2.89) after dose-escalated RT \pm ADT in intermediate- and high-risk patients. Additionally, the authors suggested a multimodality threshold defining men in which adding ADT may not significantly reduce their risk of DM. Freedland et al³¹ included patients with low-, intermediate-, and high-risk PCa and evaluated the prognostic utility of the Polaris score for BR after primary RT \pm ADT. In the multivariate analysis, the GC was a significant predictor for BR (HR, 2.11; 95% CI, 1.05–4.25). Comparable results in a similar collective were observed by the study from Janes et al³² by also considering the endpoints DM (HR, 4.28; 95% CI, 2.43–7.75) and PCSM (HR, 6.11; 95% CI, 2.93–14.33).

GC in the literature: GCs for outcome prediction in RT for postoperative PCa

In total 10 studies (adjuvant RT or salvage RT [SRT]: n = 7, SRT: n = 3) with 9792 patients evaluated the role of GC in the postoperative RT setting.^{10,12–16,34–37} Dalela et al¹⁰ proposed a nomogram for the prediction of clinical progression in the postoperative RT setting. By including the Decipher score in the model, a C-index of 0.85 was obtained.

Table 1 List of included articles on GC in PCa in the setting of RT structured after prognostic and predictive oncological endpoints, decision making, and other biomarker studies

Studies analyzing oncological endpoints: Primary localized PCa					
First author	GC/function	Endpoint(s)	Treatment	Cohort details: Patients (n)/ study design/validation	C-index/HR with 95% CI/ P _{interaction} (if analyzed)
Tosoian et al. ²⁷	Decipher/prognostic	DM	Definitive RP or definitive RT ± ADT	n = 405 Multicentric Retrospective No dedicated external validation	HR for DM = 1.33 (1.19-1.48)
Berlin et al. ²⁸	Decipher/prognostic	BR, DM	Definitive RT	n = 121 Prospective registry Monocentric No dedicated external validation	HR for BR = 1.36 (1.09-1.71) HR for DM = 2.05 (1.24-4.24)
Nguyen et al. ²⁹	Decipher/prognostic	DM, PCSM	Definitive RP or definitive RT ± ADT	n = 235 Multicentric Retrospective No dedicated external validation	HR for DM = 1.37 (1.06-1.78) HR for PCSM = 1.57 (1.03-2.48)
Nguyen et al. ³⁰	Decipher/prognostic	DM	Definitive RT + ADT	n = 100 Retrospective Monocentric No dedicated external validation	HR for DM = 1.36 (1.04-1.83)
Freedland et al. ³¹	Prolaris/prognostic	BR	Definitive RT ± ADT	n = 141 Retrospective Monocentric No dedicated external validation	HR for BR: per 1-unit change in score = 2.11 (1.05-4.25)
Janes et al. ³²	Oncotype DX/prognostic	BR, DM, PCSM	Definitive RT ± ADT	n = 238 Retrospective Multicentric No dedicated external validation	HR for BR: per 20-unit increase = 3.62 (2.59-5.02) HR for DM: per 20-unit increase = 4.48 (2.75-7.38) HR for PCSM: per 20-unit increase = 5.36 (3.06-9.76)
Tward et al. ³³	Clinical cell-cycle risk score (CAPRA score + Prolaris)/ prognostic and predictive	DM	Definitive dose-escalated RT	n = 741 Retrospective Multicentric No dedicated external validation	HR for DM = 2.22 (1.71-2.89)

(Continued)

Table 1 (Continued)					
Studies analyzing oncological endpoints: Primary localized PCa					
First author	GC/function	Endpoint(s)	Treatment	Cohort details: Patients (n)/ study design/validation	C-index/HR with 95% CI/ P_{interaction} (if analyzed)
Studies analyzing oncological endpoints: Adjuvant RT or SRT after primary RP					
Lee et al. ¹²	Decipher/prognostic	CR, external validation of a GC based risk-stratification nomogram	ART or SRT after RP	n = 350 Monocentric Retrospective External validation of the Dalela et al ¹⁰ nomogram	C-index = 0.84
Mahal et al. ³⁴	Genomic expression of stromal infiltration markers/prognostic and predictive	DM	ART or SRT after RP	Three cohorts: prospective registry cohort (n = 5239), retrospective multicenter cohort (n = 1135), TCGA cohort (n = 498) No dedicated external validation	HR for DM = 2.15 (1.25-3.7) 10-y MPS for patient with high stromal scores 24% (no ART) vs 68%, P = .0015 (ART) P _{interaction} = 0.02
Dalela et al. ¹⁰	Decipher/prognostic and predictive	CR	ART or SRT after RP	n = 512 Multicentric Retrospective No dedicated external validation	C-index: Decipher = 0.71, Decipher + clinical model = 0.85 HR for CR (GC high vs low) = 2.93 (1.58-5.55)
Den et al. ¹³	Decipher/prognostic and predictive	DM	ART or SRT after RP	n = 188 Bicentric Retrospective No dedicated external validation	HR for clinical metastasis = 1.61 (1.2-2.15) Patients with high-risk GC: ART vs SRT HR = 0.2 (0.04-0.90)
Den et al. ¹⁴	Decipher/prognostic and predictive	BR, DM	ART or SRT after RP	n = 143 Monocentric Retrospective No dedicated external validation	HR for BR = 0.75 (0.67-0.94) HR for DM = 0.78 (0.64-0.91)
Zhao et al. ³⁵	PORTOS/prognostic and predictive	DM	ART or SRT after RP	n = 196 Matched training cohort n = 330 Pooled matched validation cohort Multicentric Retrospective	HR for DM after RT in the high PORTOS group: 0.15 (0.04-0.6) P _{interaction} = 0.016
Ross et al. ³⁶	Clinical-genomic risk (CAPRA score + Decipher)/prognostic	DM	ART or SRT after RP	n = 422 Multicentric Retrospective No dedicated external validation	HR for DM = 1.28 (1.08-1.52)

(Continued)

Table 1 (Continued)					
Studies analyzing oncological endpoints: Primary localized PCa					
First author	GC/function	Endpoint(s)	Treatment	Cohort details: Patients (n)/ study design/validation	C-index/HR with 95% CI/ P_{interaction} (if analyzed)
Studies analyzing oncological endpoints: Salvage RT after primary RP					
Feng et al. ¹⁵	Decipher/ prognostic	DM, PCSM, OS	SRT ± ADT after RP	n = 486 Multicentric Prospective No dedicated external validation	HR for DM = 1.17 (1.05-1.32) HR for PCSM = 1.39 (1.20-1.63) HR for OS = 1.17 (1.06-1.29)
Koch et al. ³⁷	Prolaris/prognostic	BR	SRT after RP	n = 47 Retrospective Monocentric No dedicated external validation	Odds ratio for DM or nonresponse to SRT: per 1-unit change in score = 10.4 (2.05-90.1)
Dal Pra et al. ¹⁶	Decipher/prognostic	BR, CR	SRT after RP	n = 226 Cohort from RCT No dedicated external validation	HR for BR: GC continuous = 1.14 (1.04-1.25); GC categorical high vs low-intermediate = 2.21 (1.41-3.47). HR for CR: GC categorical (high vs low-intermediate) = 2.29 (1.32-3.98)
Studies analyzing oncological endpoints: Metastasis-directed therapy in oligometastatic PCa					
Deek et al. ³⁸	High-risk mutational signature (ATM, BRCA1/2, Rb1, or TP53)/prognostic	PFS	MDT (RT or surgery) in oligometastatic castration sensitive PCa	n = 70 Cohort from 2 prospective trials No dedicated external validation	HR for PFS: low vs high mutational burden = 0.57 (0.32-1.03); MDT vs observation in patients with high mutational burden = 0.05 (0.01-0.28); MDT vs observation in patients without high mutational burden = 0.42 (0.23-0.77)
Studies analyzing treatment decision making					
First author	GC classifier	Endpoint		Primary treatment	
Gore et al. ¹⁷	Decipher	Postoperative treatment decision		RP	
Marascio et al. ¹⁸	Decipher	Postoperative treatment decision		RP	
Gore et al. ¹⁹	Decipher	Postoperative treatment decision (ART or SRT)		RP	
	Decipher	Postoperative treatment decision in high-risk patients		RP	

(Continued)

Table 1 (Continued)					
Studies analyzing oncological endpoints: Primary localized PCa					
First author	GC/function	Endpoint(s)	Treatment	Cohort details: Patients (n)/ study design/validation	C-index/HR with 95% CI/ P_{interaction} (if analyzed)
Michalopoulos et al. ²⁰					
Badani et al. ²¹	Decipher	Postoperative treatment decision in high-risk patients			RP
Badani et al. ²²	Decipher	Postoperative treatment decision			RP
Nguyen et al. ²³	Decipher	Postoperative treatment recommendations from 20 US board certificated urologists and 26 radiation oncologists			RP
Lobo et al. ²⁴	Decipher	Markov model for decision of ART vs SRT after RP			RP
Lobo et al. ²⁵	Decipher	Markov model for cost effectiveness			RP
Biomarker studies					
First author	GC	Endpoint(s)			
Ben-Salem et al. ³⁹	Androgen receptor gene signatures	Androgen receptor activity in localized treatment-naive PCa and association with clinical risk factors, molecular markers, and PCa subtypes			
Yamoah et al. ²⁶	Decipher	Transcriptomic interactions between ICS and Decipher GC			
Awasthi et al. ⁴⁰	Whole transcriptome data from the Decipher GRID registry	Differences of immune-specific genes between AAM and EAM PCa tumor environment			
Mahal et al. ¹¹	Decipher genomic resource information database	PCSM, all-cause mortality, and genomic characterization of patients with PCa with low PSA and high-grade PCa			
<p>The third column includes endpoints and the fourth column identifies whether patients were primarily treated with RP or RT.</p> <p><i>Abbreviations:</i> AAM = African American men; ADT = androgen deprivation therapy; ART = adjuvant radiation therapy; BR = biochemical recurrence; CAPRA = Cancer of the Prostate Risk Assessment; CI = confidence interval; C-index = concordance index; CR = clinical recurrence; DM = distant metastases; EAM = European American men; GC = genomic classifier; GRID = Genomics Resource for Intelligent Discovery; HR = hazard ratio; ICS = immune content score;</p> <p>MDT = metastases directed therapy; MFS = metastases-free survival; OS = overall survival; PCa = prostate cancer; PCSM = prostate cancer specific mortality; PFS = progression-free survival; PORTOS = Post-Operative Radiation Therapy Outcome Score; RCT = randomized controlled trial; RP = radical prostatectomy; RT = radiation therapy; SRT = salvage radiation therapy; TCGA = The Cancer Genome Atlas; US = United States.</p>					

Lee et al¹² observed a C-index of 0.84 in an external validation of this model. The group by Den et al^{13,14} evaluated the prognostic role of the Decipher score for DM prediction in the postoperative setting and observed a HR of 1.61 (95% CI, 1.2-2.15) and of 0.78 (95% CI, 0.64-0.91) in multicentric and monocentric retrospective cohorts, respectively. Both studies suggested that patients with low GC scores are best treated with SRT, whereas those with high GC scores benefit from adjuvant RT. Similar results for DM prediction after postoperative RT were observed by other studies incorporating Post-Operative Radiation Therapy Outcomes Score (PORTOS),³⁵ the genomic expression of stromal infiltration markers,³⁴ and the clinical genomic risk.³⁶ Feng et al¹⁵ showed a significant effect of the Decipher score on DM (HR, 1.17; 95% CI, 1.05-1.32) and PCSM (HR, 1.39; 95% CI, 1.20-1.63) in the prospective Radiation Therapy Oncology Group 9601 trial cohort treated with SRT ± ADT. Dal Pra et al¹⁶ examined the prognostic effect of the Decipher score in the Swiss Group for Clinical Cancer Research 09/10 study collective, which was treated with SRT for recurrent PCa after surgery and observed an HR of 2.21 (95% CI, 1.41-3.47) for BR.

GC in the literature: GCs for outcome prediction in RT for oligometastatic PCa

Deek et al³⁸ analyzed the effect of genetic features on outcomes in a pooled cohort of the STOMP and ORIOLE trial. Patients without a high-risk mutational status experienced favorable progression-free survival rates (HR, 0.57; 95% CI, 0.32-1.03). The authors observed a potential larger benefit for MDT in patients with high-risk mutations.

GC in the literature: GCs for treatment decision making

Eight studies evaluated the effect of the 22-gene Decipher score on postoperative treatment decision making and showed that high GC risk scores were associated with intensification of treatment in terms of admission of ADT, RT dose, and expansion of RT fields, independent from clinicopathologic factors.¹⁷⁻²⁴ Five studies assessed treatment recommendations before and after addition of GC score information in patients treated with RP and adverse pathologic features such as pT3 stage and positive margins.¹⁷⁻²¹ Post-Decipher recommendations changed in up to 40%²¹; the number needed to test for a change in recommendation varied between 3 and 4.^{17,18} Badani et al²² showed similar results in a retrospective cohort of low-, intermediate-, and high-risk patients according to D'Amico risk classification. Furthermore, implementation of GC testing and its results in clinical practice decreased cancer-specific anxiety^{17,19} and decisional conflict scores.^{19,20} Nguyen et al²³ assessed the treatment recommendations from 20 United States board certified urologists and 26 radiation oncologists with high rates of recommendation

change, identifying the GC risk score as the strongest influencing factor. Lobo et al²⁴ developed a Markov model for postoperative treatment decisions and for cost effectiveness, which demonstrated improved cost effectiveness and quality adjusted life years.²⁵

GC in the literature: GCs in correlation with other biomarkers

In addition to the 22-gene Decipher score, the Genomics Resource for Intelligent Discovery (GRID) database provides comprehensive transcriptomic profiles and thus enables additional genomic studies. Ben-Salem et al³⁹ analyzed androgen receptor (AR) target genes in the GRID database and validated their results in smaller cohorts and could identify a baseline heterogeneity in AR action and found that specific up- or downregulation of AR genes was associated with treatment response prediction. Two studies additionally assessed the immune content score (ICS) derived from immune cell-specific genes.^{26,40} Yamoah et al²⁶ showed that patients with high Decipher GC and ICS scores have a higher risk of DM and PCSM and are associated with genes correlated to radiosensitivity. Awasthi et al⁴⁰ assessed difference in immune-specific genes between African American and European American patients and identified that PCa of African American patients exhibits higher ICS scores, lower DNA damage repair, and higher radiosensitivity.

Ongoing prospective clinical trials

In total, 9 studies were identified via ClinicalTrials.gov incorporating GC and RT treatment. Additionally, 5 studies were included based on the recommendations of the authors of this work. Eight and 1 studies incorporate GCs in the primary and salvage PCa setting, respectively. See Table 2 and Supplementary Material Appendix E3 for synthesis of ongoing clinical trials.

Survey

Thirty experts answered R2 of the modified Delphi survey. Half of the participating experts reported on using GCs in clinical practice, mostly in extensive metastatic disease (30%) and postoperative settings (27%). See Fig. 3 for details.

See Fig. 4 and Table 3 for the detailed results of the expert survey concerning the clinical and research settings, respectively. Considering patients with primary PCa, the majority (97%) of experts were convinced that GCs could be implemented as a dedicated feature into PCa risk group stratification systems in the future. Consensus was reached that additional tools for risk stratifications are needed across NCCN risk groups (low/favorable intermediate-risk: 83%; unfavorable intermediate-risk: 100%; high-risk: 100%) and

Table 2 Summary of ongoing prospective clinical trials for prostate cancer RT applying GCs

Ongoing trials				
Trial number	Study type	Patient characteristics	Applied GC	Treatment decision based on GC
NCT04513717 (NRG-GU009)	Parallel phase 3, randomized	NCCN high risk	Decipher	Escalation or de-escalation of systemic therapy
NCT05100472 (SHORTER)	Phase 2, nonrandomized	NCCN high risk	Decipher	ADT de-escalation
NCT05050084 (NRG-GU10)	Parallel phase 3, randomized	NCCN unfavorable intermediate risk	Decipher	Escalation or de-escalation of systemic therapy
NCT04025372 (INTREPID)	Phase 2, randomized	NCCN intermediate risk	Decipher	N/A (GC is required and serves as stratification variable)
NCT05169970	Phase 2, nonrandomized	NCCN unfavorable intermediate risk	Decipher	Inclusion of elective pelvic lymphatics in RT field
NCT02783950 (G-Minor)	Randomized, parallel assignment	RPE with pT3 or positive margins	Decipher	Adjuvant treatment decision (RT or ADT)
NCT04984343 (FORT)	Phase 2, randomized	NCCN low and intermediate risk	Decipher	N/A (GC >0.6 serves as inclusion criterion)
NCT04396808	Crossover assignment, randomized	NCCN low and intermediate risk	Decipher, Prolaris, and Oncotype DX	N/A (effect of GC on treatment decision)
NCT02723734 (VANDAAM)	Cohort	NCCN low and intermediate risk	Decipher	N/A (effect of GC on outcome prediction)
NCT03495427 (subgroup of VANDAAM)	Cohort	NCCN low and intermediate risk	Decipher	N/A (concordance between GC and PSMA-PET)
NCT03371719 (NRG-GU006)	Phase 2, randomized	SRT	PAM50 gene expression	N/A (gene expression clustering)
NCT03770351	Cohort	NCCN low and intermediate risk	Decipher ProstateNext	N/A (effect of GC on outcome prediction)
NCT03141671	Phase 2, randomized	SRT	Decipher	N/A (high-risk Decipher score as inclusion criterion)
NCT04134260	Phase 3, randomized	SRT	Decipher PAM50 gene expression	N/A (effect of GC on outcome prediction)

Abbreviations: ADT = androgen deprivation therapy; GC = genomic classifier; N/A = not applicable; NCCN = National Comprehensive Cancer Network; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RPE = radical prostatectomy; RT = radiation therapy; SRT = salvage radiation therapy.

that GCs are likely to be a useful tool in this setting (low/favorable intermediate-risk: 83%; unfavorable intermediate-risk: 90%; high-risk: 93%). Experts were convinced that GCs might be applied as a predictive biomarker and to determine optimal treatments across various risk groups, including administration and duration of ADT, intensification of systemic therapies, or addition of radiation to elective pelvic nodes.

Considering metastatic disease, 100% of experts agreed that additional tools for improved risk stratification are needed, and 76% believed that GCs might be a useful tool in this scenario. Relevant scenarios identified by experts were administration of MDT and the combination of MDT and systemic therapies.

Considering the postoperative setting, 97% of experts agreed that additional tools for improved risk stratification

Experts' current use of genomic classifiers in clinical practise

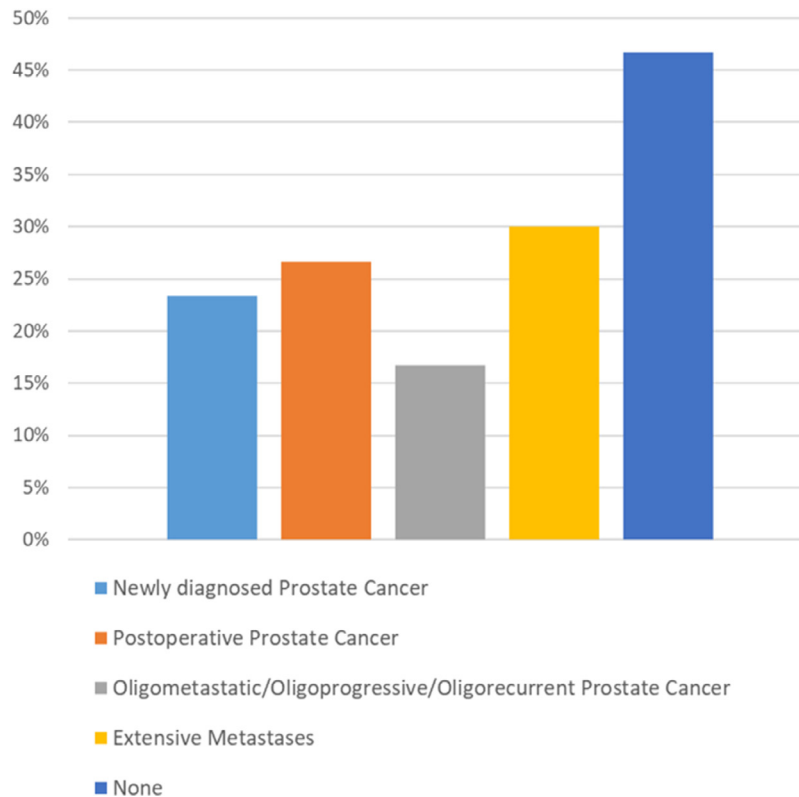


Fig. 3. Clinical applications of genomic classifiers in various prostate cancer (PCa) stages.

are needed, and 89% believed that GCs might be a useful tool in this scenario. Relevant issues identified by experts were administration of adjuvant versus early-salvage RT, administration and duration of ADT, and additional pelvic irradiation in salvage RT.

Metastases-free survival (MFS) was considered as the most appropriate endpoint to evaluate the role of GCs in clinical studies for nonmetastasized PCa. Consensus that GCs might be relevant in translational research fields was reached, in strategies to cope with intertumoral heterogeneity (between the primary and metastatic lesions), alteration in AR signaling, and decision making for physicians.

Discussion

This work incorporated a systematic review and a modified Delphi survey to assess the role of GC in PCa RT and to define future directions. Despite the fact that 47% of the participants in the survey do not use GC in clinical routine, the vast majority agreed that GC should be incorporated in RT strategies in all PCa disease stages in the future. Differences in clinical utilization of GC are explainable by regional differences in the distribution of facilities capable of performing GC tests and reimbursement issues. However, our work

shows that the potential clinical utility of GCs is expected to be relevant. In line with a previous systemic review and meta-analysis,⁷ our current synthesis shows that the Decipher test is the most commonly used GC in patients with PCa, and the highest level of evidence for the Decipher GC exists in the setting of risk stratification, outcome prediction, and treatment guidance after RP.⁷

Prognostic biomarkers are helpful tools to identify patients who are at high or low risk of recurrence and thus are candidates for treatment intensification or deintensification. Predictive biomarkers are warranted to truly guide personalized treatments. All studies demonstrate the prognostic value of the GCs, but due to the methodological design of the studies, no clear conclusions regarding the predictive value of GCs can be drawn. None of the studies assessed the predictive capacity of a GC within a dedicated treatment arm of an RCT. Additionally, only 2 of the studies included external validation cohorts, which underlines the need for more high-quality studies. Therefore, the results of the expert consensus may help to guide clinical decision making, the design of future clinical trials, and translational research. Fortunately, some of the presented clinical questions are addressed by currently ongoing clinical trials. However, we want to mention that these studies are designed to evaluate the prognostic capability of GCs in

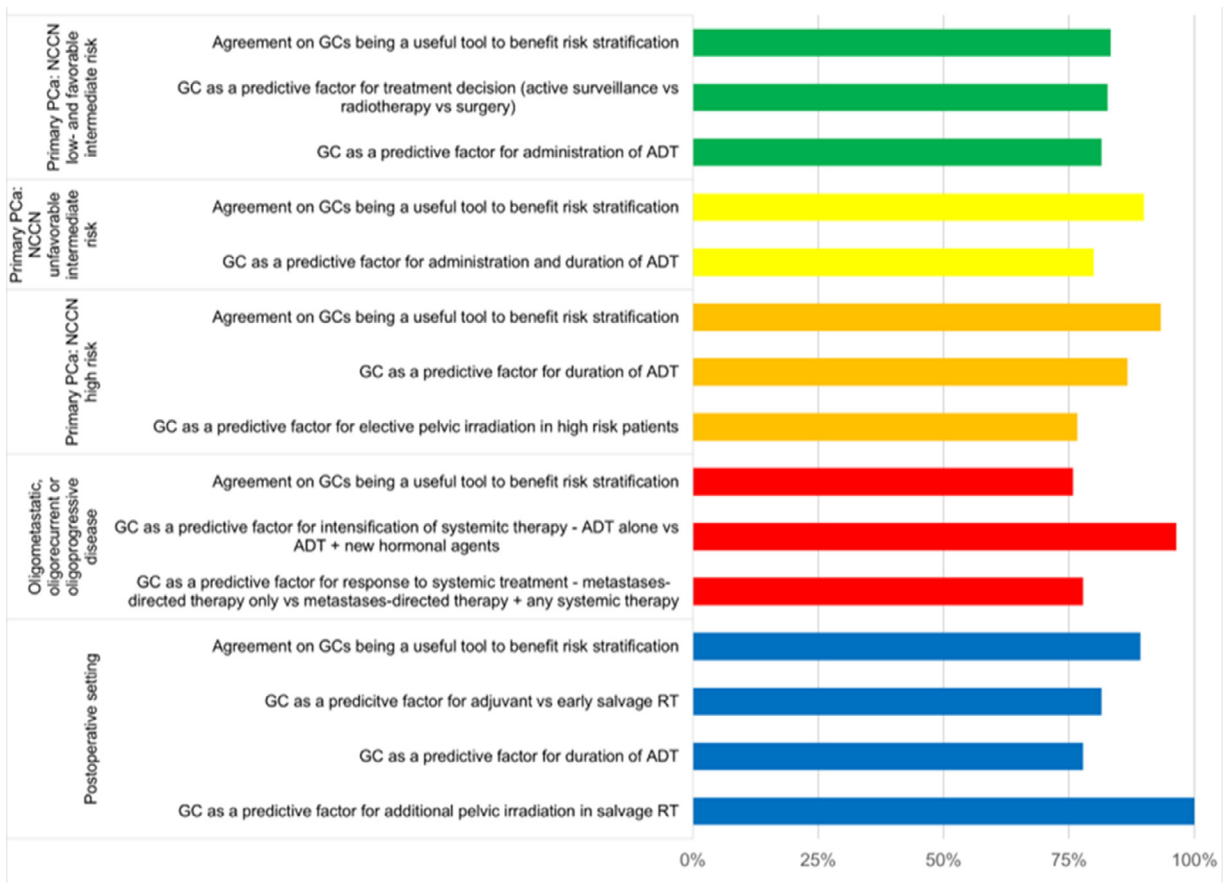


Fig. 4. Consensus answers: Bars show agreement on genomic classifiers (GCs) being a useful tool to improve risk stratification across National Cancer Comprehensive Network (NCCN) risk groups, recurrent and metastatic disease, and in postoperative settings or as a predictive factor for various parameters across risk groups and disease stages. In this context, “predictive factor” intends to represent the ability of GCs to identify patients who might benefit from a certain treatment. Abbreviations: ADT = androgen deprivation therapy; PCa = prostate cancer; RT = radiation therapy.

these new clinical scenarios, which might form the basis for future studies addressing the predictive capabilities. Despite the absence of prospective and externally validated studies addressing predictive values of GC in patients treated with definitive RT, we could identify 7 studies including in total 1551 patients in which GCs were analyzed as a prognosticator of DM and BR after definitive RT (see Fig. 5 for details).^{27–33} We did not include the study by Nguyen et al²⁹ in Fig. 4 because no individual data on the prognostic value of GCs in the cohort of patients treated only with RT are presented. This moderate sample size contrasts the larger number of GC analyses in patients treated with RP (n = 9792) but demonstrates similar results, with the Decipher GC score being an independent prognosticator after both treatments. Furthermore, additional information will be provided by forthcoming studies, validating the Decipher GC in phase 3 studies, such as the NRG/Radiation Therapy Oncology Group 9202, 9314, 9902, 0126, and STAMPEDE trials, which have been presented at the American Society for Radiation Oncology 2021, American Society for Clinical Oncology Genitourinary Cancers Symposium GU 2022, and European Society for Medical Oncology 2022 annual

congresses.^{42–44} Thus, performing GC tests on biopsy cores yields promising results to predict PCa aggressiveness, suggesting implementation in risk and treatment stratification after definitive RT. Confirming these results, expert consensus was reached that GCs are a promising tool to improve PCa risk stratification in the primary PCa setting. However, we demonstrate a lack of data for RT, pointing out the need for additional studies, including validation of GCs in patient cohorts staged with state-of-the-art imaging, such as prostate-specific membrane antigen (PSMA)–positron emission tomography (PET) and multiparametric magnetic resonance imaging (MRI), and treated with modern radiation approaches, including stereotactic body RT or brachytherapy. Future studies should clarify whether the applied biopsy method (MRI-fusion vs MRI-guided vs no implementation of MRI information) influences the GC results.

Extrapolating the results of Tward et al,³³ Feng et al,¹⁵ and Ben-Salem et al,³⁹ GC scores might help to stratify patients who benefit the most from concomitant ADT, define the optimal duration of ADT, and identify those that may benefit from systemic treatment intensification in definitive RT settings. Consequently, consensus was reached

Table 3 Expert consensus on endpoints to be addressed in clinical studies on GC and translational research fields

Prostate Cancer Risk Group or Stage	Question	Percentage of answers
Primary PCa: NCCN low/favorable intermediate risk	Which of the following endpoints do you consider relevant to be addressed with GCs as predictors for treatment?	
	MFS	82.8%
Primary PCa: NCCN unfavorable intermediate risk	Which of the following endpoints do you consider relevant to be addressed with GCs as predictors for treatment?	
	MFS	96.6%
	Time to distant metastases	82.1%
Primary PCa: NCCN high risk	Which of the following endpoints do you consider relevant to be addressed with GCs as predictors for treatment?	
	MFS	96.6%
	PCSS	79.3%
	Time to distant metastases	93.1%
Oligometastatic, oligoprogressive, or oligorecurrent disease	Which of the following endpoints do you consider most relevant to be addressed with GCs as predictors for treatment management?	
	PCSS	82.8%
	Time to castration resistance	75.9%
	PFS	75.9%
Translational research fields	Which of the following translational research fields do you consider as relevant to be addressed in future research incorporating GCs?	
	Strategies to cope with intertumoral heterogeneity in case GCs are obtained from biopsy cores in metastatic disease (evaluation of intertumoral heterogeneity between primary and metastases)	75.0%
	Alteration in androgen signaling	75.0%
	Decision making for physicians	85.7%

Abbreviations: GC = genomic classifier; MFS = metastases-free survival; NCCN = National Comprehensive Cancer Network; PCa = prostate cancer; PCSS = prostate cancer-specific survival; PFS = progression-free survival.

by experts that GCs are promising tools to improve recommendations for administration of systemic therapies in the primary setting across all NCCN risk groups, including duration of ADT and addition of new hormonal agents, particularly in high-risk patients. Furthermore, alterations in AR signaling were considered to be a relevant translational research field. Additional predicative markers are urgently needed addressing this vague clinical issue to guide personalized treatment decisions. Four ongoing prospective trials will contribute to this field of research by stratifying patients according to genomic risk groups into intensification or deintensification of systemic treatments and thus optimize therapies based on GCs.

Treatment intensification in the setting of definitive RT can also be achieved by dose escalation in all primary PCa risk stages (delivered dose to the tumor >80-90 Gy, Equivalent dose in 2Gy fractions $\alpha/\beta = 1.6$ Gy). Dose escalation improves BR-free survival and can be performed via

brachytherapy⁴⁵ or focal boosting.⁴⁶ Kishan et al⁴⁷ analyzed the genomic heterogeneity of patients with grade group 4 to 5 who underwent prostatectomy within the GRID database and could identify 4 distinct clusters, of which 1 was enriched with genes related to cell cycle and proliferation and was associated with worse DM-free survival. Furthermore, GRID analysis revealed PCa subtypes with increased genomic radiosensitivity,^{26,40} therefore GC scores might be used to identify patients with radioresistant or radiosensitive PCa and thus guide treatment decision in terms of (focal) dose escalation and the optimal dose in the primary setting. However, these aspects were not considered relevant by experts, with approximately 50% agreement that GCs might be useful to identify patients who benefit from focal dose escalation due to increased radioresistance. On the basis of a high fractionation sensitivity of PCa,⁴⁸ moderately hypofractionated RT^{49,50} and ultrahypofractionated RT or stereotactic body RT^{51,52} have been analyzed in RCTs and were

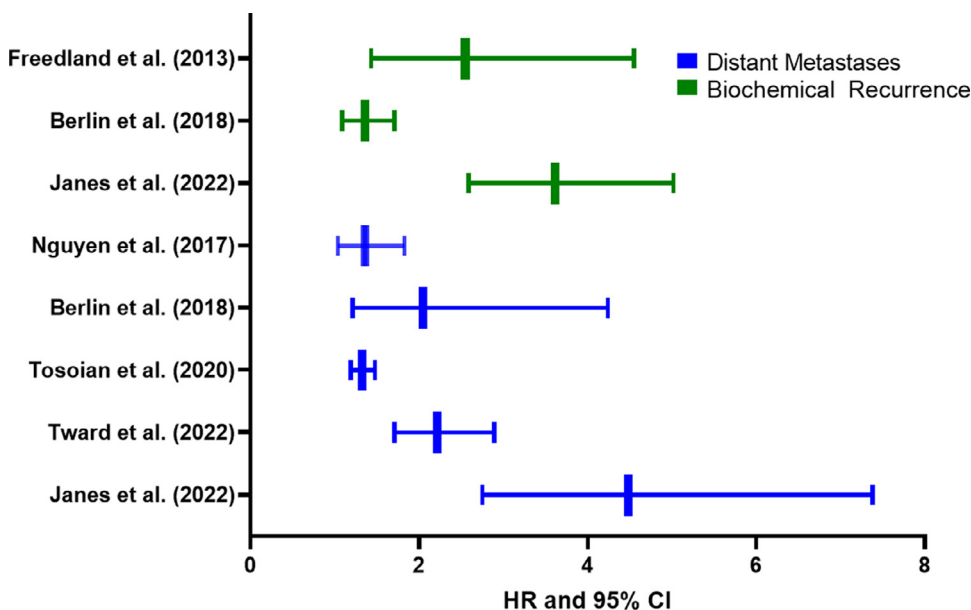


Fig. 5. For each study assessing definitive radiation therapy, the hazard ratio (HR) and 95% confidence intervals on multivariate analysis of genomic classifiers predicting distant metastases and biochemical recurrence are shown. For the Decipher score (studies by Nguyen et al,³⁰ Berlin et al,²⁸ and Tosoian et al²⁷), HR per 0.1-unit increase is shown. For the Oncotype DX Prostate Score (study by Janes et al³²), HR per 20-unit increase is shown. For the Cell Cycle Progression score (studies by Freedland et al³¹ and Tward et al³³), HR per 1-unit increase is shown.

demonstrated to have comparable relapse rates to conventionally fractionated RT. The consideration that genomic alterations might influence the individual α/β -value⁴⁸ and that GCs might thus be used to predict whether a specific fractionation scheme is beneficial was not considered to be relevant by experts ($\leq 37\%$ agreement across NCCN risk groups). Nevertheless, future research might provide new insights into the heterogeneity of PCa and the linkage between the genomic signatures and radiation and fractionation sensitivity. For example, Dal Pra et al⁵³ reported in a congress abstract that patients with high PORTOS score that received 70-Gy SRT dose to the fossa had better 5-year clinical progress-free survival (94% vs 49%, $P = .006$) compared with patients who received the 64-Gy dose.

Genomic classifiers might help to improve risk stratification for treatment escalation or de-escalation in terms of RT to pelvic lymphatics. Prophylactic whole pelvis radiation has recently been shown to improve BR free survival at the cost of late genitourinary toxicities,⁵⁴ thus improved patient selection to prevent overtreatment is needed. Currently, a phase 2 study adapts RT fields based on GC and includes pelvic lymphatics only in GC high-risk patients (NCT05169970). Consensus was reached that GCs might be a useful predictive marker to identify high-risk patients with PCa who would benefit the most from elective pelvic irradiation and alleviate this controversial discussion.

Incorporating recent improvements in diagnostics, in particular PSMA-PET, might further facilitate treatment personalization.^{55,56} Because PSMA-PET was used in none of the identified studies, there are many open questions as to the extent that GC and advanced imaging methods give

complementary or redundant information addressing outcome prediction or decision management. Experts' answers were inconsistent, with 45% agreeing that image features might be used to predict GC scores in R1, and 61% agreeing that GC might be useful to predict imaging results in R2. Only 1 trial analyzed the ability of GC scores to predict PET-positive extraprostatic lesions and found a significant association with pelvic nodal disease.⁵⁷ Interestingly, Hectors et al extracted imaging features from multiparametric magnetic resonance tomography and developed a machine-learning model that excellently predicted a Decipher score of ≥ 0.60 (area under the curve = 0.84).⁵⁸ These promising results should be validated in larger patient cohorts. Considering the possible capability to depict intratumoral molecular characteristics on PSMA-PET,^{59,60} this imaging method should be included for future genomic-imaging correlations.

Combination of genomic signatures and PSMA-PET-based staging of tumor localization could be of particular interest in oligometastatic and oligorecurrent disease stages, enabling identification of patients who benefit from metastasis-^{61,62} or primary- directed therapies.⁶³ Stopsack et al⁶⁴ reported on specific genomic features associated with poor survival in metastatic PCa, which might be used to intensify systemic therapies or develop targeted therapies. The pooled analysis of the STOMP and ORIOLOE trial links outcome after MDT to mutational burden in patients with oligometastatic PCa, encouraging that further research will possibly add value to define patients with "genomic" low and high metastatic burden and to guide treatment in these stages. Consequently, consensus was reached that GCs might be helpful as a predictive factor for progression-free

survival/PCa-specific survival after MDT or systemic therapies or the combination of both in oligometastatic, oligorecurrent, or oligoprogressive patients. On the contrary, implementation of GC as a predictor for primary-directed therapies was not considered relevant in this setting. Additionally, experts agreed that strategies to cope with intertumoral heterogeneity between primary tumors and metastases should be assessed in the future.

A factor that should not be underestimated is decisional conflict and patient anxiety. Luckily, patients with PCa have multiple treatment options in the primary, postoperative, and metastatic setting.^{65,66} Likely, the implementation of GCs as a tool to guide treatment decision will not only be beneficial in patients aiming for RP^{17–23} but also for RT concepts, an opinion that is confirmed by the expert consensus.

Further clinical trials are needed to tackle the scarcity of studies addressing the predictive value of GC in RT, and therefore accurate definition of study endpoints is warranted. Experts reached consensus that the validated surrogate parameter MFS is an appropriate endpoint across all NCCN risk groups. However, future research will assess the role of MFS as a surrogate endpoint in the era of molecular imaging.⁶⁷

We want to highlight that most of the available prospective data on GCs still only exist for the Decipher GC. The PORTOS signature complies with high methodological standards because a statistical analysis of treatment interaction and an external validation were performed in the study by Zhao et al.³⁵

However, because of the lack of prospective data, external validation, and information on the benefit on long-term outcomes, GCs are still not recommended for routine use.⁶⁸ Nevertheless, most of the presented studies included multicenter cohorts, partly from RCTs, and potentially some of the ongoing studies will provide data to support broader use of these assays to enable improved treatments for patients with PCa.

We want to acknowledge the limitations of this work. Because of a lack of evidence for the role of GC in the primary PCa RT setting, the discussion is mainly based on extrapolation from data obtained from RP cohorts. However, we brought together an internationally recognized expert panel to optimize conclusions and to highlight future directions in GC research for RT patients. Finally, it is important to mention that implementation of GC in PCa is a fast-moving field and conclusions will need to be iterated in light of rapidly evolving evidence. For example, several studies reported their results in current congresses analyzing the role of GC in the context of primary-definitive RT⁴³ or salvage RT.⁵³

Conclusion

In summary, this work confirms the value of GCs and in particular of the Decipher GC as a prognostic biomarker in

patients undergoing RP and their predictive value for postoperative RT. Additionally, we summarize the scarce but promising evidence that GCs might be equivalently useful in the setting of definitive RT. Nevertheless, we highlight that GCs currently do not comply with their great potential to function as predictive markers and thus guide personalized treatment decisions. In this regard, we await the highly anticipated prospective clinical trials, which will further inform the role of GCs in the setting of RT, and present an expert consensus that can help to design studies capable of validating GCs as predictive biomarkers and thus ultimately guide personalized treatments. The authors want to emphasize that the development and establishment of tumor biomarkers for patients with PCa is complex. Thus, a dedicated system for biomarker study design, conduct, analysis, and evaluation that incorporates a hierarchical level of evidence should be applied. The presented expert consensus might help to guide future research perspectives.

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