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Title: Genomic classifiers in personalized prostate cancer radiotherapy approaches – a systematic review and future perspectives based on international consensus

Short Running Title: Genomic Classifier Prostate Cancer Radiation

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Data Availability Statement
The results of the systematic review are included in the manuscript. All data generated during the DELPHI consensus are included in the manuscript and supplementary material. The corresponding author is available for any further questions on the data.

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Abstract

Background:

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 exists for patients treated with definitive radiotherapy (RT) or RT in oligo-/metastatic disease stages. In order to guide future perspectives of GCs for RT, we conducted (i) a systematic review on the evidence of GCs for patients treated with RT and (ii) 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.

Methods:

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. 31 and 30 experts answered round 1 and round 2, respectively. Questions with ≥ 75% agreement were considered as relevant and included into the qualitative synthesis.

Results:

Evidence for GCs as predictive biomarkers is mainly available to the postoperative RT setting. Validation of GCs as prognostic markers in the definitive RT settings is emerging. Experts used GCs in PCa patients with extensive metastases (30%), in postoperative settings (27%) and newly diagnosed PCa (23%). 47% 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/de-intensification in various disease stages.

Conclusions:

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.

1. 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 diagnosed with all stages of PCa [2, 3]. Radiotherapy (RT) plays a central role in the management of PCa patients and can be applied in a curative setting or as part of a palliative treatment concept. However, current risk stratification systems are imperfect — the use of novel prognostic or 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 [4, 5]). Additionally, the PAM50 classifier has been demonstrated to differentiate between luminal and basal PCa, with luminal B tumours being associated with favorable response to postoperative 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 exists 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 is to (i) summarize the role of GCs for PCa patients in all disease stages treated with RT, since this is aspect has not previously been highlighted and (ii) point out relevant clinical and translational issues for future fields of research. We therefore conducted (i) a systematic review and (ii) a survey of experts and key opinion leaders using the DELPHI method. See Figure 1 for a summarizing overview.

2. Methodology

2.1 Systematic Review

Studies eligible for inclusion were original articles on GC in PCa in the setting of RT, comprising primary definitive, post-operative, as well as metastasis-directed (MDT) RT. In general, 3 types of manuscript were included: (A) manuscripts on oncologic outcomes after RT, (B) the role of GCs in RT decision process and (C) correlation studies between other biomarkers and GCs. Inclusion criteria were: A1) patients treated with RT (definitive, postoperative, MDT); A2) clinical results with the following endpoints: clinical recurrence (CR), biochemical recurrence (BR), distant metastases (DM), prostate-cancer specific mortality (PCSM), overall survival (OS). A3) Articles with retrospective and prospective data were allowed (n patients > 50); B1) Translational work addressing correlation of GCs with imaging, biomarkers or biological features (radioresistance, androgen signaling etc); C1) Impact of GCs in RT treatment decision processes. Exclusion criteria were: 1) articles not written in English 2) non-original articles. SKBS and CZ performed a PubMed/Medline, EMBASE and Cochrane Library database search for the 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 (Radiotherapy"[8]) 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')

Mapped terms ''genomic classifier'' mapped to 'genomic classifier'.

In case of discrepant findings (n=3), a third reviewer (CeDr) provided a final decision. The time period considered in this review was from June 6th 2013 until December 1st 2021. One hundred twenty-six articles were identified and 32 duplicates removed. After applying inclusion and exclusion criteria, 26 studies were included for qualitative review according to PRISMA [9] (Figure 2). 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 the December 31st 2021. No additional studies matching in- and exclusion criteria were found. During the peer-review process an update of the literature search was performed:5 more studies and one more clinical trial were included by considering a time period from June 6th 2013 until December 1st 2022.

2.2 **Ongoing clinical trials**

In order to provide an overview of clinical trials implementing GCs in treatment decision, 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. SKBS 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.

2.3 **Expert opinion**

The multidisciplinary team of expert professionals included radiation oncologists, urological oncologists and pathologists. Experts were characterized by long-time

experience in care and/or clinical trials of PCa patients, 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. Since predictive biomarkers are ultimately warranted to guide personalized treatments, we focused on the putative capability of GCs to identity patients who might benefit from a certain treatment. In round 1 (R1) preliminary results of literature search and key questions were prepared by SKBS and CZ and emailed 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 additional 9 invitations, of which 4 replied. In total 31 experts answered R1 (response rate: 56%). After completion of R1, SKBS and CZ consolidated questionnaires and prepared round 2 (R2), in which participant's feedback and questions that did not reach consensus (defined as 50-75% of votes) were included. These results were prepared by SKBS and CZ and distributed to all participants (n=31). 30 experts provided answers in R2 (response rate: 97%). Finally, only questions with ≥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 information.

3. Results

3.1 GC in the Literature – methodological aspects

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 whilst 5 studies analyzed GC in prospectively collected patient cohorts. Only two studies performed an external validation [11][36]. With 20 (65%) studies, the Decipher test was used in the vast majority [10-29].

In 24 (77%) studies RP specimens were used to obtain tissue for genomic analyses [10-24, 26, 28, 30-36]. In one study (3%) the Decipher test was applied to both RP-

and biopsy-specimens [26], whilst six studies (19%) solely used biopsy specimens for further analyses [27-29, 37-39]. Most studies (n=18, 58%) investigated the associations between GCs and oncological outcomes such as DM (n=12, 39%) [12-14, 26-32, 38, 39], prostate cancer specific mortality (PCSM) (n=3, 10%) [14, 28, 38], overall survival (OS) (n=1, 3%)[14], clinical recurrence (CR) (n=3, 10%) [10, 11, 15] and biochemical recurrence (BR) (n=6, 19%) [13, 15, 27, 33, 37, 38]. The other studies reported on the role of GCs on treatment decision making (n=9, 29%) [16-24] or correlated GCs with other biomarkers (n=4, 13%) [25, 34-36].

All studies included in this review reported on the role of GC as prognostic biomarkers for PCa patients. To correctly assess the predictive value of a biomarker in a study, at least two comparison groups must be available (in the best case, two treatment arms in a RCT) [40]. This pre-requirement was not fulfilled by any study in this review. However, five studies suggested a predictive role for GC in the setting of adjuvant RT after surgery and one study supposed a predictive role of GC in the response to androgen deprivation therapy (ADT) in the definitive RT setting [11-13, 30, 31, 39].

3.2 GC in the Literature – GCs for outcome prediction in RT for primary localized PCa

In total seven studies included 1551 patients treated with definitive RT [26-29, 37-39]. Tosoian et al. performed a retrospective analysis of 405 men with high-risk PCa, of which 80 were treated with definitive RT +/- ADT. A subset analysis showed that GC was an independent prognosticator for patients treated with RT (HR 1.61, 95%CI 1.08–2.40,) [26]. Berlin et al. 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) [27]. Nguyen et al. investigated retrospectively the Decipher biopsy test as a prognosticator for DM and PCSM in intermediate- and high-risk patients treated with RP or RT +/- 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) [28]. Another study by Nguyen et al. 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 [29]. Tward et al. showed that a clinical cell-cycle risk score (CAPRA score + Prolaris GC) prognosticated DM with a HR per unit score of 2.22 (95%CI: 1.71-2.89) after dose-escalated RT +/- ADT in intermediate- and high-risk patients [39]. Additionally, the authors suggested a multimodality threshold defining men in which adding ADT may not significantly reduce their risk of DM. Freedland et al. included patients with low-, intermediate- and high-risk PCa and evaluated the prognostic utility of the Polaris score for BR after primary RT +/- ADT. In the multivariate analysis the GC was a significant predictor for BR (HR 2.11, 95%CI: 1.05-4.25) [37]. Comparable results in a similar collective were observed by the study from Janes et al. 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) [38].

3.3 GC in the Literature – GCs for outcome prediction in RT for postoperative PCa

In total 10 studies (ART or SRT: n=7, SRT: n=3) with 9792 patients evaluated the role of GC in the postoperative RT setting [10-15, 30-33]. Dalela et al. [11] 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. Lee et al. observed a C-Index of 0.84 in an external validation of this model [10]. The group by Den et al. 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 [12, 13]. Both studies suggested that patients with low GC scores are best treated with SRT, whereas those with high GC scores benefit from ART. Similar results for DM prediction after postoperative RT were observed by other studies incorporating PORTOS [31], the genomic expression of stromal infiltration markers [30] and the clinical genomic risk [32]. Feng et al. showed a significant impact of the Decipher score on DM (HR, 1.17 95%CI: 1.05 – 1.32) and PCSM (HR 1.39, 95%CI1.20 – 1.63) in the prospective RTOG 9601 trial cohort treated with SRT +/- ADT [14]. Dal Pra et al. examined the prognostic impact of the Decipher score in the SAKK09/10 study collective which was treated with SRT for recurrent PCa after surgery and observed a HR of 2.21 (95%CI: 1.41 – 3.47) for BR [15].

3.4 GC in the Literature – GCs for outcome prediction in RT for oligometastatic PCa

Deek et al. analyzed the impact of genetic features on outcomes in a pooled cohort of the STOMP and ORIOLE trial [41]. 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.

3.5 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 clinicopathological factors [16-23]. Five studies assessed treatment recommendations before and after addition of GC score information in patients treated with RP and adverse pathological features such as pT3 stage and positive margins [16-20]. Post-Decipher recommendations changed in up to 40% [20], the number needed to test for a change in recommendation varied between 3 and 4 [16, 17]. Badani et al. showed similar results in a retrospective cohort of low-, intermediate- and high-risk patients according to D'Amico risk classification [21]. Furthermore, implementation of GC testing and its results in clinical practice decreased cancer specific anxiety [16, 18] and decisional conflict scores [18, 19]. Nguyen et al. assessed the treatment recommendations from 20 US board certified urologists and 26 radiation oncologists with high rates of recommendation change, identifying the GC risk score as the strongest influencing factor [22]. Lobo et al. developed a Markov Model for decision of postoperative treatment decision [23] and for cost effectiveness, which demonstrated improved cost effectiveness and quality adjusted life years (QALYs) [24].

3.6 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 al. 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

[34]. Two studies additionally assessed the immune content score (ICS) derived from immune cell-specific genes [25, 35]. Yamoah et al. 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 [25]. Awashti et al. assessed difference in immune specific genes between African-American (AAM) and European-American (EAM) patients and identified that PCa of AAM patients exhibit higher ICS scores, lower DNA damage repair and higher radiosensitivity [35].

3.7 Ongoing prospective clinical trials

In total nine studies were identified via “clinicaltrials.gov” incorporating GC and RT treatment. Additionally, five studies were included based on the recommendations of the authors of this work. Eight and one studies incorporate GCs in the primary and salvage PCa setting, respectively. See Table 2 and supplementary material for synthesis of ongoing clinical trials.

3.8 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 Figure 3 for details.

Please see Figure 4 and Table 3 for the detailed results of the expert survey concerning the clinical and research setting, respectively. Considering primary PCa patients, 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 that GCs are likely to be 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 are needed and 89% believed that GCs might be a useful tool in this scenario. Relevant questions identified by experts were administration of adjuvant vs early-salvage RT, administration and duration of ADT and additional pelvic irradiation in salvage RT.

MFS was considered as the most appropriate endpoint to evaluate the role of GCs in clinical studies for non-metastasized 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 androgen receptor 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 of 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 is explainable by regional differences in the distribution of facilities capable to perform GC tests and

reimbursement issues. However, our work shows, that the potential clinical utility is 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 utilized GC in PCa patients 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 de-intensification. Predictive biomarkers are warranted in order 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 dedicated treatment arm of a RCT. Additionally, only two of the studies included external validation cohorts, which underlines the need of 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 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 seven studies including in total 1551 patients in which GCs were analyzed as a prognosticator of DM and BR after definitive RT [26, 27, 29, 37-39]. See Figure 5 for details. We did not include the study by Ngyuen et al. in Figure 4, since no individual data on the prognostic value of GCs in the cohort of patients

treated only with RT are presented [28]. 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 III studies, such as the NRG/RTOG 9202, 9314, 9902, 0126 and STAMPEDE trials, which have been presented at the ASTRO 2021, ASCO GU 2022 and ESMO 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 PSMA-PET and multiparametric magnetic resonance imaging (MRI), and treated with modern radiation approaches, including stereotactic body radiotherapy (SBRT) or brachytherapy (BT). 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. [39] Feng et al. [14] and Ben-Salem et al. [34], GC scores might help to stratify patients that benefit the most from concomitant ADT, define the optimal duration of ADT, as well as identify those that may benefit from systemic treatment intensification in definitive RT settings. Consequently, consensus was reached 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 androgen receptor signaling were considered to be a relevant translational research field. Additional predicative markers are urgently needed addressing this vague clinical issue in order 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 de-intensification 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, EQD2 α/β=1.6 Gy). Dose escalation improves BR-free survival and can be performed via BT [45] or focal boosting [46]. Kishan et al. analyzed the genomic heterogeneity of patients with Grade group 4-5 who underwent prostatectomy within the GRID database and could identify four distinct clusters, of which one was enriched with genes related to cell cycle and proliferation and was associated with worse DM-free survival [47]. Furthermore, GRID analysis revealed PCa subtypes with increased genomic radiosensitivity [25, 35], therefore GC scores might be utilized to identify patients with radioresistent 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 radio-resistance. On the basis of a high fractionation sensitivity of PCa [48], moderately hypofractionated RT (MHRT) [49, 50] and ultra-hypofractionated RT or SBRT [51, 52] have been analyzed in randomized controlled trials and were demonstrated to have comparable relapse rates to conventionally fractionated RT. The consideration that genomic alterations might influence the individual α/β-value [48] and that GCs might thus be used to predict

whether a specific fractionation scheme is beneficial, was not considered to be relevant by experts (≤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 al. reported in a congress abstract that Patients with high PORTOS score that received 70Gy SRT dose to the fossa had better 5-year clinical progress-free survival (94% vs. 49%, p=0.006) compared to patients that received the 64Gy dose [53].

GCs 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 II 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 PCa patients who 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]. Since PSMA-PET was used in none of the identified studies, there are many open questions to what extent GC and advanced imaging methods give complementary or redundant information addressing outcome prediction or decision management. Expert's answers were inconsistent with 45% agreeing that image features might be utilized to predict GC scores in R1 and 61% agreeing that GC might be useful to predict imaging results in R2. Only one 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, which excellently predicted a Decipher score of ≥0.60 (AUC=0.84). These promising results should be validated in larger patient cohorts. Considering the possible capability to depict intratumoral molecular characteristics on PSMA-PET [58, 59], 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- [60, 61] or primary- directed therapies [62]. Stopsack et al. reported on specific genomic features associated with poor survival in metastatic PCa, which might be used to intensify systemic therapies or develop targeted therapies [63]. The pooled analysis of the STOMP and ORIOLOE trial links outcome after MDT to mutational burden in oligometastatic PCa patients, encouraging that further research will possibly add value to define patients with “genomic” low- and high metastatic burden and guide treatment in these stages. Consequently, consensus was reached that GCs might be helpful as a predictive factor for progression-free survival/ prostate cancer specific survival after MDT or systemic therapies or the combination of both in oligometastatic, oligorecurrent or oligoprogressive patients. In 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 tumours and metastases should be assessed in future.

A factor that should not be underestimated is decisional conflict and patient’s anxiety. Luckily, patients with PCa have multiple treatment options in the primary, postoperative and metastatic setting [64, 65]. Likely, the implementation of GCs as a tool to guide treatment decision will not only be beneficial in patients aiming for RP

[16-22] 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 a surrogate end point in the era of molecular imaging [66]. We want to highlight, that most of the available prospective data on GCs still only exists for the Decipher GC. The PORTOS signature complies with high methodological standards since a statistical analysis of treatment interaction and an external validation was performed in the study by Zhao et al. [31].

However, due to the lack of prospective data, external validation and its benefit on long-term outcomes GCs are still not recommended for routine use [67]. 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 PCa patients.

We want to acknowledge the limitations of this work. Due to a lack in 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 RT [43] or salvage RT [53] .

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 its 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 its 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, which can help to design studies capable to validate GCs as predictive biomarkers and thus ultimately guide personalized treatments. The authors want to emphasize that the development and establishment of tumor biomarkers for PCa patients is complex. Thus, a dedicated system for biomarker study design, conduct, analysis, and evaluation that incorporates a hierarchal level of evidence should be applied. The presented expert consensus might help to guide future research perspectives.

Data availability

The results of the systematic review are included in the manuscript. All data generated during the DELPHI consensus are included in the manuscript and supplementary material. The corresponding author is available for any further questions on the data.

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Figure legend

Figure 1: Summarizing overview

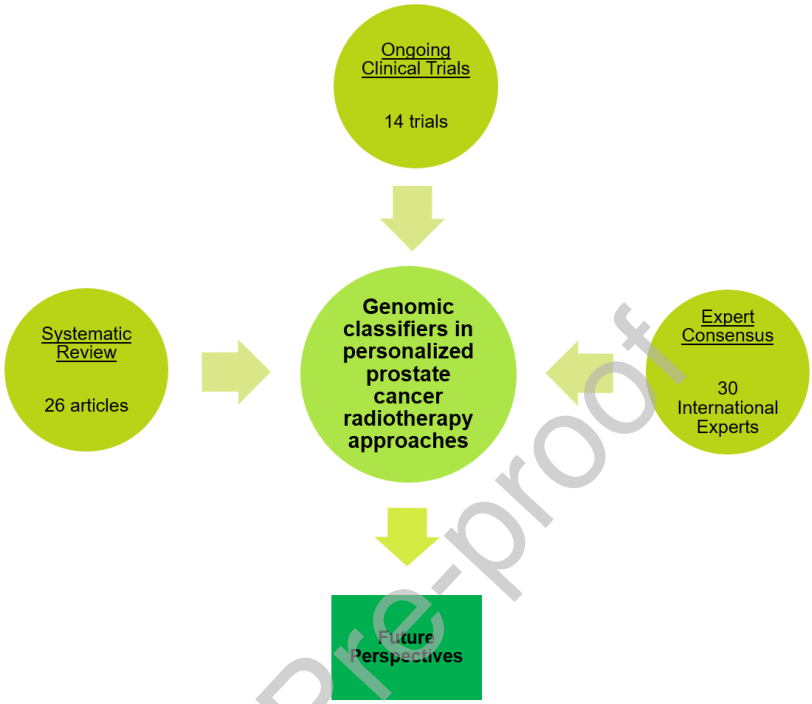

Figure 2: PRISMA Flow diagram of the systematic database search and excluded records. Abbreviations: GC=genomic classifier, RT=radiotherapy

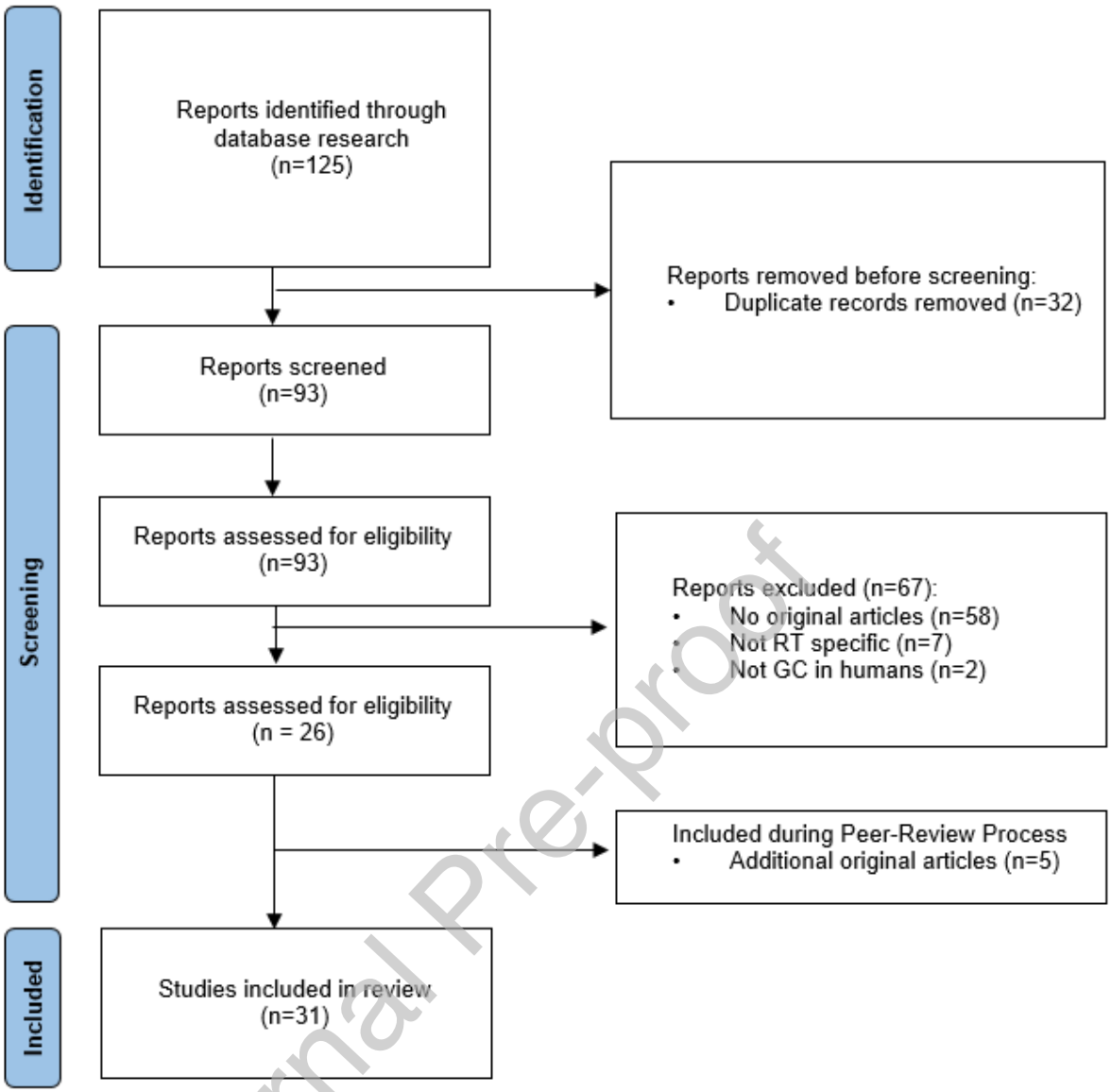

Figure 3: Clinical applications of genomic classifiers in various prostate cancer (PCa) stages.

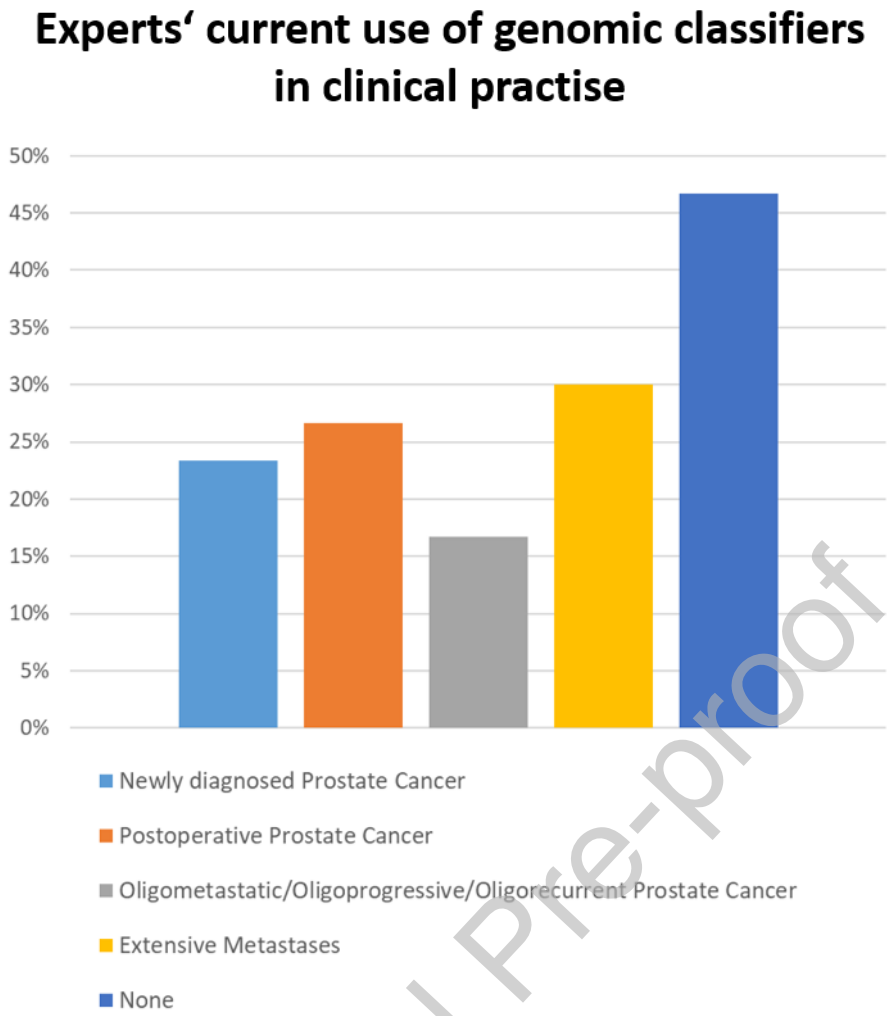

Figure 4 Consensus answers: Bars show agreement on genomic classifiers (GC) being a useful tool to improve risk stratification across national cancer comprehensive network (NCCN) risk groups, recurrent and metastatic disease and in postoperative settings or as a predictive factor for various parameters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

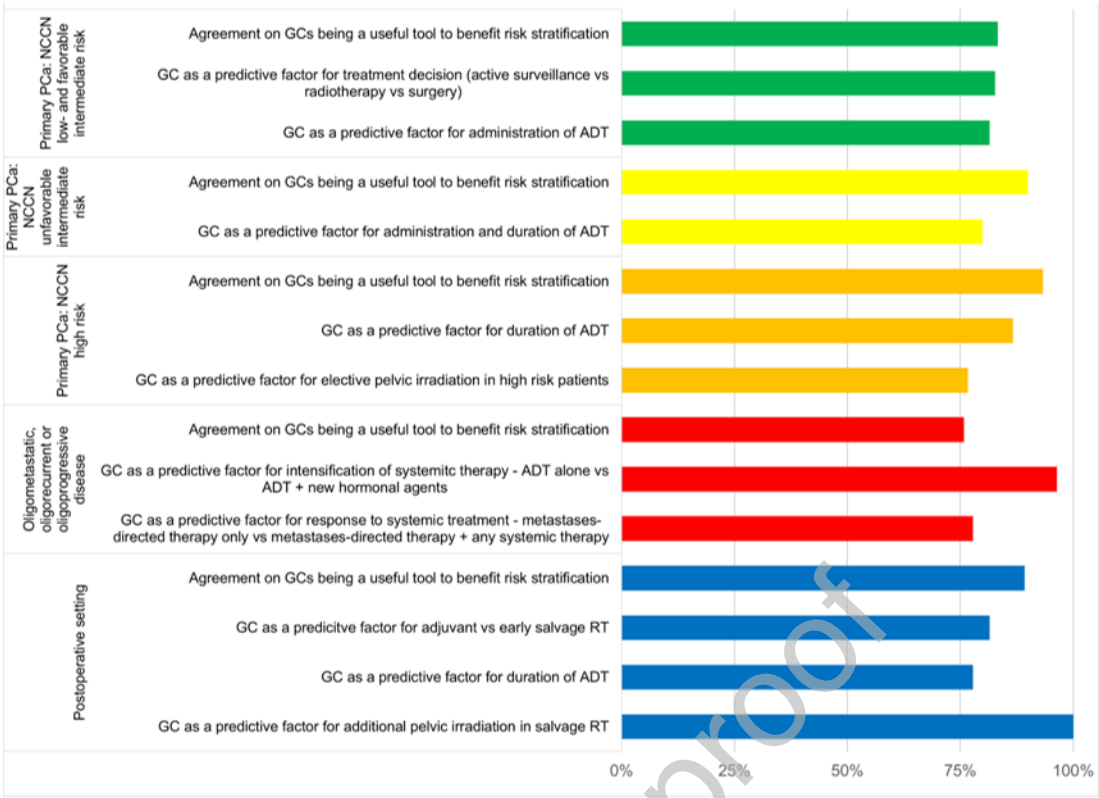

Figure 5: For each study assessing definitive radiotherapy, the hazard ratio (HR) and 95% confidence intervals on multivariate analysis of genomic classifiers predicting distant metastases and biochemical recurrence is shown. For the Decipher score (Studies by Ngyuen et al., Berlin et al. and Toisan et al.) HR per 0.1 unit increase is shown. For the Oncotype DX Prostate Score (Study by Janes et al.) HR per 20 unit increase is shown. For the Cell Cycle Progression score (Studies by Freedland and Tward et al.) HR per 1 unit increase is shown.

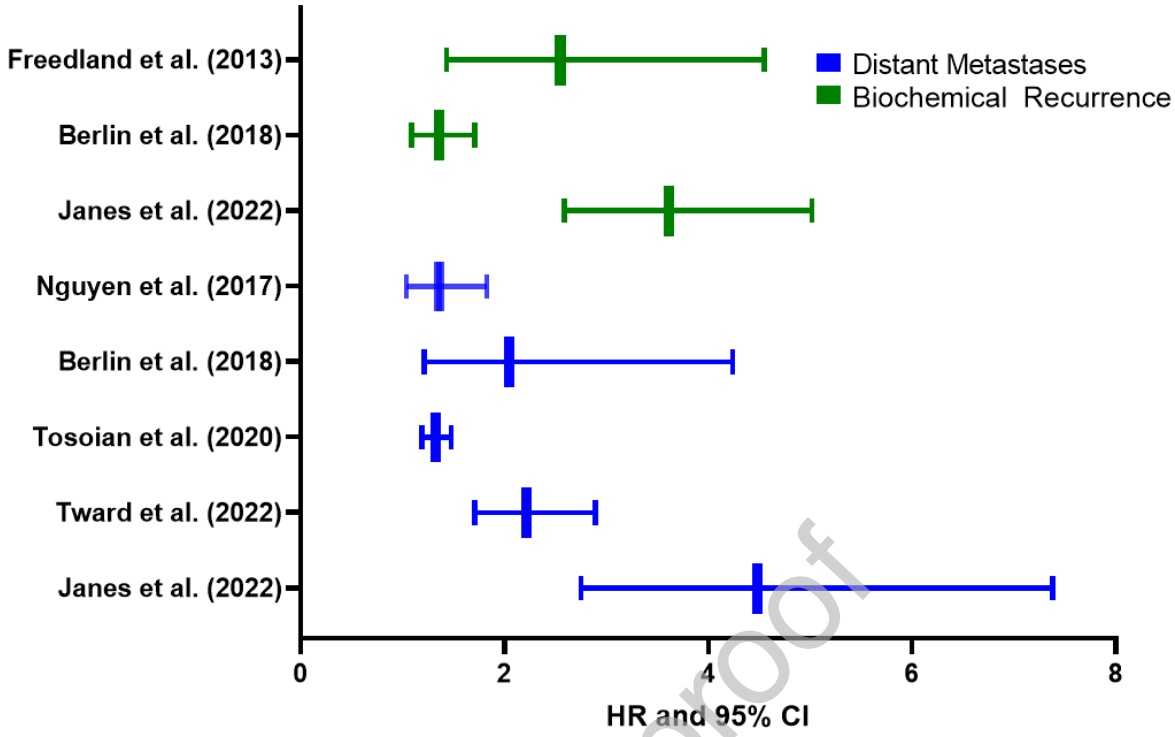

Table legend

Table 1: List of included articles on GC in prostate cancer in the setting of radiotherapy structured after prognostic and predictive oncological endpoints, decision making and other biomarker studies. The second column includes endpoints and the third column identifies whether patients were primarily treated with RP or RT.

Abbreviations:

CR=clinical recurrence, GC=genomic classifier, DM=distant metastases, ART=adjuvant radiotherapy, BR=biochemical recurrence, RP= radical prostatectomy, PCSM=prostate cancer specific mortality, OS=overall survival, SRT= salvage radiotherapy, ADT=androgen deprivation therapy, RT = radiotherapy, AAM = Afro-American Men, EAM=European American Men, MDT= metastases directed therapy, PFS= progression free survival, PCa=prostate cancer, HR=Hazard Ratio, C-Index=concordance index, TCGA=The Cancer Genome Atlas, PORTOS=Post

Operative Radiation Therapy Outcome Score, CAPRA=Cancer of the Prostate Risk Assessment

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

Table 3: Expert consensus on endpoints to be addressed in clinical studies on GC and translational research fields. Abbreviations: PCa=prostate cancer, NCCN=national comprehensive cancer network, GC=genomic classifier, MFS=metastases-free survival, PCSS=prostate cancer specific survival, PFS=progression free survival

Table 1:

Studies analyzing oncological endpoints - Primary localized PCa					
Author	**Genomic classifier / function**	**Endpoint(s)**	**Treatment**	**Cohort Details: Number of patients (n)/study design/validation**	**C-Index/Hazard Ratio (HR) with 95% confidence interval (CI)/$P_{interaction}$ (if analyzed)**
Tosoian et al. [26]	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. [27]	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. [28]	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. [29]	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. [37]	Prolaris / prognostic	BR	Definitive RT +/- ADT	n=141 Retrospective Monocentric No dedicated external validation	HR for BR: Per one unit change in score: 2.11 (1.05-4.25)
Janes et al. [38]	Ocotype 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. [39]	Clinical cell-cycle risk score (CAPRA score +	DM	Definitive dose-escalated RT	n=741 Retrospective Multicentric No dedicated external validation	HR for DM = 2.22 (1.71 – 2.89)

	Prolaris) / prognostic and predictive				
Studies analyzing oncological endpoints – Adjuvant RT or SRT after primary RP					
First author	**Genomic classifier / function**	**Endpoint(s)**	**Treatment**	**Cohort Details: Number of patients (n)/study design/validation**	**C-Index/Hazard Ratio (HR) with 95% confidence interval (CI)/$P_{interaction}$ (if analyzed)**
Lee et al. [10]	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 [11] nomogram	C-index = 0.84
Mahal et al. [30]	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 year MFS for patient with high stromal scores 24% (no ART) vs 68%, p=0.0015 (ART) $p_{interaction}$ = 0.02
Dalela et al. [11]	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. [12]	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. [13]	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. [31]	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. [32]	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)
Studies analyzing oncological endpoints – Salvage RT after primary RP					
First author	**Genomic classifier / function**	**Endpoint(s)**	**Treatment**	**Cohort Details: Number of patients (n)/study design/validation**	**C-Index/Hazard Ratio (HR) with 95% confidence interval (CI)/$P_{interaction}$ (if analyzed)**
Feng et al. [14]	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. [33]	Prolaris / prognostic	BR	SRT after RP	n=47 Retrospective Monocentric No dedicated external validation	Odds ratio for DM or non-response to SRT: Per one unit change in score: 10.4 (2.05-90.1)
Dal Pra et al. [15]	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	High-risk	PFS	MDT (RT or	n=70	HR for PFS:

al. [41]	mutational signature (ATM, BRCA1/2, Rb1, or TP53) / prognostic		surgery) in oligometastatic castration sensitive PCa	Cohort from two prospective trials No dedicated external validation	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	**Genomic classifier**	**Endpoint**			**Primary Treatment**
Gore et al. [16]	Decipher	Postoperative treatment decision			RP
Marascio et al. [17]	Decipher	Postoperative treatment decision			RP
Gore et al. [18]	Decipher	Postoperative treatment decision (ART or SRT)			RP
Michalopoulos et al. [19]	Decipher	Postoperative treatment decision in high risk patients			RP
Badani et al. [20]	Decipher	Postoperative treatment decision in high-risk patients			RP
Badani et al. [21]	Decipher	Postoperative treatment decision			RP
Nguyen et al. [22]	Decipher	Postoperative treatment recommendations from 20 US board certificated urologist and 26 radiation oncologist			RP
Lobo et al. [23]	Decipher	Markov Model for decision of ART vs SRT after RP			RP
Lobo et al. [24]	Decipher	Markov Model for cost effectiveness			RP
Biomarker studies					
First author	**Genomic classifier**	**Endpoint(s)**			
Ben-Salem et al. [34]	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. [25]	Decipher	Transcriptomic interactions between tumor immune content score (ICS) and Decipher GC
Awasthi et al. [35]	Whole transcriptome data from the Decipher GRID registry	Differences of immune-specific genes between AAM and EAM PCa tumor environment
Mahal et al. [36]	Decipher Genomic Resource Information Database	PCSM, all-cause mortality and genomic characterization of PCa patients with low PSA and high grade PCa

Table 2:

Ongoing Trials				
Trial number	**Study type**	**Patient characteristics**	**Applied GC**	**Treatment decision based on GC**
NCT04513717 (NRG-GU009)	Parallel Phase III, randomized	NCCN high-risk	Decipher	Escalation or de-escalation of systemic therapy
NCT05100472 (SHORTER)	Phase II, non-randomized	NCCN high-risk	Decipher	ADT de-escalation
NCT05050084 (NRG-GU10)	Parallel Phase III, randomized	NCCN unfavorable intermediate-risk	Decipher	Escalation or de-escalation of systemic therapy
NCT04025372 (INTREPID)	Phase II, randomized	NCCN intermediate-risk	Decipher	N/A (GC is required and serves as stratification variable)
NCT05169970	Phase II, non-randomized	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 II, randomized	NCCN low- and intermediate-risk	Decipher	N/A (GC>0.6 serves as inclusion criterion)
NCT04396808	Crossover assignment,	NCCN low- and intermediate-	Decipher, Prolaris and	N/A (Impact of GC on treatment

	randomized	risk	Oncotype DX	decision)
NCT02723734 (VANDAAM)	Cohort	NCCN low- and intermediate-risk	Decipher	N/A (Impact 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 II, randomized	SRT	PAM50 gene expression	N/A (gene expression clustering)
NCT03770351	Cohort	NCCN low- and intermediate-risk	Decipher ProstateNext	N/A (Impact of GC on outcome prediction
NCT03141671	Phase II, randomized	SRT	Decipher	N/A (high risk Decipher score as inclusion criterion)
NCT04134260	Phase III, randomized	SRT	Decipher PAM50 gene expression	N/A (Impact of GC on outcome prediction

Table 3:

Primary PCa - NCCN low/favorable	**Which of the following endpoints do you consider relevant to be addressed with GCs as predictors for treatment**	**% of answers**
	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 genomic classifiers 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%