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REVIEW ARTICLE

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Genomic biomarkers to guide precision radiotherapy in prostate cancer

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Abstract

Our ability to prognosticate the clinical course of patients with cancer has historically been limited to clinical, histopathological, and radiographic features. It has long been clear however, that these data alone do not adequately capture the heterogeneity and breadth of disease trajectories experienced by patients. The advent of efficient genomic sequencing has led to a revolution in cancer care as we try to understand and personalize treatment specific to patient clinico-genomic phenotypes. Within prostate cancer, emerging evidence suggests that tumor genomics (e.g., DNA, RNA, and epigenetics) can be utilized to inform clinical decision making. In addition to providing discriminatory information about prognosis, it is likely tumor genomics also hold a key in predicting response to oncologic therapies which could be used to further tailor treatment recommendations. Herein we review select literature surrounding the use of tumor genomics within the management of prostate cancer, specifically leaning toward analytically

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validated and clinically tested genomic biomarkers utilized in radiotherapy and/or adjunctive therapies given with radiotherapy.

KEYWORDS
biomarkers, genomics, prostate cancer, radiotherapy

1 | INTRODUCTION

In the United States, prostate cancer (PCa) represents the most common solid organ malignancy among men accounting for nearly 250,000 new cases and over 30,000 deaths in 2021.[1] Given the high incidence of disease, it is therefore unsurprising the significant heterogeneity in disease course and outcomes of men diagnosed with PCa. Although many with PCa experience a highly curable and indolent disease course, a subset of patients have more aggressive disease biology with progression to metastatic disease, castration-resistance, and ultimately death.[2] The D'Amico prostate cancer risk stratification for localized disease strove to classify this spectrum by incorporating clinical and pathologic factors, and has subsequently guided the management of localized PCa for decades.[3] Despite this landmark achievement characterizing the behavior of localized PCa, there is still wide variability not fully explained by clinical factors alone.

Historically, oncologists have been limited to using clinical features such as radiographic and histopathologic findings to infer the disease course despite recognizing the complex and diverse genetic and molecular alterations involved in tumorigenesis. With the identification of driver mutations and subsequent development of targeted therapies, a more personalized approach to treatment became possible.[4–8] The advent of affordable and efficient next-generation sequencing (NGS) allowed for whole-genome, whole-exome, limited panel, transcriptome, and epigenetic sequencing to become increasingly utilized.[9] These monumental advancements in sequencing technology over the past two decades allowed for a more nuanced understanding of the tumor biology of an individual and has opened countless doors for greater precision in clinical oncology. NGS has not only allowed for more rapid identification of specific targetable driver mutations, but also for uncovering the milieu of genomic alterations that may be leveraged as prognostic and more importantly predictive biomarkers to help guide treatment decisions.[10–12]

With an eye toward PCa, tumor genomics hold potential to demystify the continued heterogeneous disease course observed among men and provide greater insight into predicting response to the various available treatments. Herein we review current select literature of genomic markers, somatic, and when applicable germline, for radiotherapeutic efficacy across all stages of PCa from localized disease to lethal metastatic castration-resistance. Given the considerable breadth of the topic, we apologize in advance that we cannot include all of the excellent research in this area, but we chose specifically to lean toward analytically validated genomic biomarkers tested for predictive radiotherapy efficacy and/or adjunctive therapies given with radiotherapy

2 | PAN-CANCER GENOMIC BIOMARKERS OF RADIATION SENSITIVITY

Determining the proper radiation dose has commonly been identified through dose escalation/de-escalation trials based on histology. With the adoption of tumor genomic profiling, developing an assay to predict tumor specific radiation sensitivity has garnered greater interest. Initial in vitro work by Torres-Roca et al.[13] developed and validated a radiation sensitivity classifier that predicts the survival fraction of various cancer cell lines to 2 Gy dependent upon gene expression profiles of three novel genes (RbAp48, RGS19, and R5PIA). Follow-up work validated a clinical radiosensitive index (RSI) modeled as a function of expression of 10 genes extracted from an interaction network across 48 cancer cell lines. This RSI was found to be significantly different in responders versus nonresponders in patients with rectal and esophageal cancer treated with radiation.[14] This radiation sensitivity index has further demonstrated utility in glioblastoma,[15] breast,[16] pancreatic,[17] and endometrial[18] cancer.

Using the gene-expression based RSI and a linear quadratic model, which is used to estimate biologic effective dose of varying radiation fractionation schemes, Scott et al.[19] derived a genome-based model for adjusting radiotherapy dose (GARD) and calculated a GARD score for 8271 tumors across 20 disease sites. The GARD was then validated in a clinical cohort of glioblastoma, breast, pancreatic, and lung cancer. GARD values across these samples ranged from 1.66 to 172.2 with a higher GARD representing a greater biologic effect to radiation. Among the 186 patients with PCa treated with 70 Gy there was significant heterogeneity within GARD values particularly skewed toward higher values. This indicates PCa may be particularly well suited for dose de-escalation dependent upon tumor gene expression and radiation fraction size. Within a pan-cancer analysis, GARD (as a continuous variable) was demonstrated to be associated with overall survival (OS) which was dependent upon whether the patient received radiation therapy (RT).[20] Although RSI/GARD have not yet been utilized in a randomized clinical trial, it has been identified as trial ready by the European Organisation for Research and Treatment of Cancer.[21]

Radiation is believed to exert its biologic effect predominately through the generation of free radicals leading to DNA double strand breaks (DSB). Given this mechanism of action, several mutations in DNA damage response (DDR) pathways, specifically those involved in

DSB repair, have been implicated in response to radiation. The Ataxia Telangiectasia-Mutated (ATM) protein is linked to DDR as it is recruited to assist in DSB repair by the MRE11-RAD50-NBSS1 (MRN) complex and has been implicated in several malignancies.[22] Within a pan-cancer assessment of patients with either *ATM* loss of function or variant of unknown significance, loss of function was associated with significantly improved 2-year local progression following radiation (13.2% vs. 27.5%).[23] Despite this preliminary evidence for radiation sensitivity in context of *ATM* disruption, the Ataxia Telangiectasia and Rad3-related gene *(ATR)* is able to partially compensate for *ATM* loss of function due to redundant overlapping function.[24,25] This has led to interest in utilizing ATR inhibition as a radiosensitizer among patients with DDR mutations.[24–26] Pathogenic mutations within *BRCA1/2* (involved in homologous recombination repair [HRR]) have similarly been implicated in several malignancies and have demonstrated increased dependency upon poly(ADP-ribose) polymerase (PARP) for DNA repair,[27] including in PCa,[28] likely due to defects in homologous recombination leading to a synthetic lethal relationship.[29] This has led to the utilization of PARP inhibition for use as a radiosensitizer in BRCA deficient tumors.[30,31] Although uncommon in PCa, several mutations have also been identified that appear to confer radioresistance across several malignancies including *NRF2*, *BRAF*, and *EGFR* and may hold promise as targeted radiosensitizers through molecular antagonists.[32–36]

3 | MOLECULAR SUBTYPES WITHIN PCa

Given the parallels of breast and PCa as hormone driven malignancies, the notion of molecular subtyping, pioneered within breast cancer, has recently been applied to PCa.[37,38] The PAM50 algorithm is a clustering-based genomic classifier (GC) based on the expression of a set of 50 genes categorizing patients into "luminal" and "basal" molecular subtypes. Zhao et al.[39] applied this PAM50 classifier to 3782 localized PCa samples which segregated three distinct molecular subtypes including luminal A, luminal B, and basal type. Similar to breast cancer, luminal subtypes have increased hormone receptor expression and downstream signaling. This study further identified luminal B PCa to demonstrate the worst clinical prognosis and was the only subtype to be significantly associated with postoperative response to androgen deprivation therapy (ADT). The presence of these molecular subtypes has subsequently been identified in patients with metastatic castration-sensitive[40] and -resistant PCa.[41] Within castration-resistant disease, luminal type tumors have demonstrated significantly better survival following treatment with androgen-signaling inhibitors while basal tumors (encompassing 90% of small cell/neuroendocrine PCa) do not benefit in relative comparison.[41] Given the very recent application of molecular subtyping of PCa, there is a paucity of data on how these subtypes may influence response to RT. Within breast cancer, Lalani et al.[42] evaluated whether molecular subtypes exhibited differential response to radiation by fractional dose. This study did not identify any significant interaction between subtype and fractionation regimen. It is not currently known whether molecular subtypes experience differential response to total dose of radiation or to the radiosensitizing effects of ADT.

4 | LOCALIZED PCa

4.1 | Genomic biomarkers within localized PCa at initial diagnosis

Within localized PCa, several commercially available genomic biomarkers have been developed aiming to improve risk stratification over clinical factors alone. The Decipher prostate biopsy (Veracyte) represents the most ubiquitous and well validated GC. Decipher is a commercially available 22-gene GC that utilizes a whole-transcriptome oligonucleotide analytically validated microarray platform. A random forest algorithm identified the expression of 22 RNA biomarkers related to androgen receptor (AR) signaling, cell proliferation, differentiation, motility, and immune modulation that comprises the GC.[43] Although initially intended for use after radical prostatectomy, the Decipher prostate biopsy has been approved in the United States for use in the entire spectrum of localized disease. Providing a score ranging from 0 to 1, it provides an estimated risk of adverse pathologic features at RP (Grade group 3–5, pT3b-T4, lymph node involvement) as well as 5- and 10-year risk of distant metastasis and 15-year PCa specific mortality. A summary of current data and future trials for the Decipher genomic score within localized PCa can be found in Figure 1. The Oncotype Dx (Exact Sciences) genomic prostate score test is a 17-gene reverse transcription-polymerase chain reaction assay that has been clinically validated to predict the likelihood of adverse pathology (Gleason grade group >3 and/or ≥T3a), distant metastases, and prostate-cancer specific mortality. This assay measures 12 cancer-related genes across four biologic pathways including stromal response, androgen signaling, cellular organization, and proliferation along with five reference genes[44–46] providing likelihood of adverse pathology at radical prostatectomy. The Prolaris test (Myriad Genetics) evaluates total RNA expression levels of 31 cell cycle progression genes and reports a CCP score that estimates 10-year disease specific mortality.[47,48]

Currently, for patients with very low- or low-risk PCa, active surveillance is the favored option given the side effects from radical treatment and without affecting prostate-cancer specific survival.[49] Although most men undergoing active surveillance can be effectively treated with either radical prostatectomy or RT if they experience disease progression, there is potentially an increased risk of development of distant metastasis compared to those undergoing upfront treatment which cannot be identified with clinical features alone.[49] Hyung et al. demonstrated that among men with very low-, low-, or favorable intermediate risk PCa, the Decipher biopsy GC can predict for adverse pathologic features (Gleason primary pattern 4 or 5, pTb or greater, or LN involvement) with an odds ratio of 1.29 (95% CI: 1.03–1.61) per 10% increase in score and demonstrated a negative predictive value of 96% when Decipher score was ≤0.2.[50]

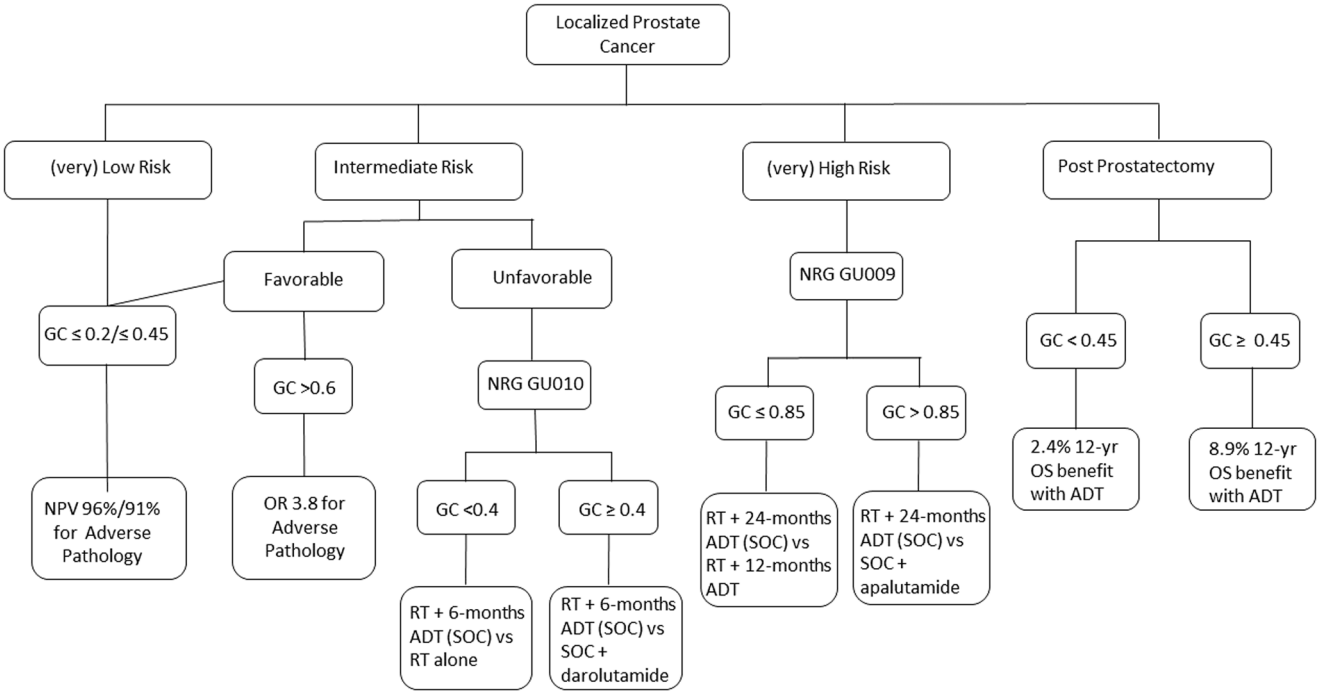


FIGURE 1 Decipher genomic classifier within localized prostate cancer. ADT, androgen deprivation therapy; GC, genomic classifier; NPV, negative predictive value; OR, odds ratio; OS, overall survival; RT, radiation therapy; SOC, standard of care.

This can therefore aid in selecting the appropriate population who can be safely be monitored on active surveillance and conversely which low-risk patients should be recommended for upfront treatment. Herlemann et al.[51] further demonstrated that among men with favorable intermediate-risk disease, in which active surveillance is controversial, only those with Decipher high-risk tumors (score > 0.6) had increased risk of adverse pathology upon radical prostatectomy. This suggests GCs may be integrated into identifying patients with favorable intermediate-risk disease in whom active surveillance is potentially appropriate. Taken together, these studies demonstrate the utility of GC to appropriately select patients for active surveillance, however there remains no consensus on what the threshold score should be and thus mutual decision making between the patient and physician is prudent.

In addition to augmenting our identification of low-risk patients, the GC has identified patients at higher risk of developing metastatic disease following radical treatment. Jairath et al.[52] reported a systematic review of studies evaluating the Decipher GC on biopsy tissue including 18 studies with 19,223 patients ranging from single and multicenter retrospective studies, as well as analyses of prospective clinical trials and prospective registry studies. These studies consistently demonstrated increased risk of development of metastatic disease with a multivariate hazard ratio (HR) ranging from 1.33 to 1.72 (per 10% increase in Decipher score) across low-, intermediate-, and high-risk disease treated with either radical prostatectomy or RT+/- ADT while clinical and pathologic features were inferior.[53–58] Additionally, the incorporation of the GC to the regression models based on either National comprehensive cancer network (NCCN) risk grouping, CAPRA,[59] or Stephenson[60] models demonstrated significantly improved AUC and C-index metrics.[53–57]

Currently, several ongoing prospective clinical trials are aiming to incorporate the GC for greater precision in the management of localized PCa (Table 1). NRG GU009 and GU010 are two parallel phase III randomized clinical trials aiming to deintensify or intensify high- and unfavorable intermediate-risk PCa, respectively, based on GC risk. GU009 will randomized 2478 patients with high-risk PCa and those with: (i) low/intermediate GC risk (score ≤ 0.85) to either standard of care with RT+ 24 months ADT versus RT+ 12 months ADT (deintensification arm); or, (ii) high GC risk (score > 0.85) to either same standard of care versus the addition of apalutamide (intensification arm). GU010 will randomize 2050 patients with unfavorable intermediate-risk PCa and those with: (i) low GC risk (score < 0.4) to either standard of care with RT+ 6 months ADT versus RT alone (deintensification arm); or, (ii) higher GC risk (score ≥ 0.4) to same standard of care versus the addition of darolutamide. The genomics in Michigan to Adjust Outcomes in Prostate cancer (G-Major) trial is a randomized trial enrolling 900 patients with newly diagnosed favorable intermediate-risk PCa to either standard of care versus integration of GC to further guide management. The investigators hypothesize a greater proportion of patients will be managed with active surveillance within the GC arm.

Outside of the commercially available GC discussed above, several individual and multigene signatures have additionally been implicated in more aggressive localized PCa and radiation resistance though most lack the robust analytical and clinical validation of the work discussed above. Mutations within tumor suppressor genes

TABLE 1 Select ongoing trials evaluating genomic biomarkers to guide management within prostate cancer.

Trial name	Full/formal name of trial	Common name	Setting	Phase	Number of participants	Status (March 2022)
NRG GU009 NCT04513717	Two Studies for Patients With High Risk Prostate Cancer Testing Less Intense Treatment for Patients With a Low Gene Risk Score and Testing a More Intense Treatment for Patients With a High Gene Risk Score	PREDICT-RT	Upfront localized	III	2478	Recruiting
NRG GU010 NCT05050084	Two Studies for Patients With Unfavorable Intermediate Risk Prostate Cancer Testing Less Intense Treatment for Patients With a Low Gene Risk Score and Testing a More Intense Treatment for Patients With a Higher Gene Risk Score	GUIDANCE	Upfront localized	III	2050	Recruiting
NCT04396808	Genomics in Michigan to Adjust Outcomes in Prostate Cancer or Men With Newly Diagnosed Favorable Risk Prostate Cancer	G-Major	Upfront localized	III	350	Recruiting
NRG GU006 NCT03371719	Biomarker Trial of Apalutamide and Radiation for Recurrent Prostate Cancer	BALANCE	Recurrent	II	311	Active, not recruiting
EA8183 NCT04484818	Testing the Addition of Darolutamide to Hormonal Therapy Androgen Deprivation Therapy after Surgery for Men With High-Risk Prostate Cancer	ERADICATE	Postprostatectomy	III	810	Recruiting
NCT02783950	Genomics in Michigan Impacting Observation or Radiation	G-Minor	Postprostatectomy	N/A	356	Active, not recruiting

have been shown to promote metastatic progression.[61–63] Chipidza et al.[64] identified and validated a *TP53* mutational signature that was associated with an approximate 20%–30% absolute decrease in 5-year metastasis-free survival. Somatic *HOXB13* mutations have also been evaluated within localized disease. HOXB13 protein interacts with the AR and contributes to the regulation of AR-transcriptomes important for PCa growth.[65] Weiner et al.[66] demonstrated that patients with localized PCa with the highest quartile of *HOXB13* expression demonstrated significantly worse metastasis-free survival compared to the lowest quartile with adjusted HR ranging 1.46–1.8. *BRCA* germline mutations have also been implicated in more aggressive localized PCa, demonstrating more advanced disease at diagnosis and worse metastasis free- and cause-specific survival.[67,68] More generally, Fraser et al.[69] demonstrated that within localized nonindolent PCa, although there appears to be lack of clinically actionable single nucleotide variants, the presence of numerous genomic alterations portends worse clinical outcomes.

A multigene DNA-based 100-locus copy number alteration genomic signature stratified patients with localized PCa into low- and high-risk of recurrence.[70] It is comprised of 276 genes and was developed using a ~27,000 probe array comparative genomic hybridization platform. To better translate to the clinic, the signature has been refined to a 31-locus biomarker that can be assessed on the analytically validated and FDA approved NanoString CNV platform.[71] Both 100- and 31-locus biomarkers reflect genomic instability and were shown to have high prognostic value in >500 PCa patients. A more recent signature comprising expression of 28-hypoxia based genes has shown to be independently prognostic for relapse and metastasis in 11 cohorts of low- to high-risk PCa patients with localized disease treated with surgery or radiotherapy (definitive and postoperative cohorts).[72] Improved prognostication may be achievable by combining the 28-hypoxia gene expression signature and indicators of genome instability such as with the 31-locus biomarker,[72] but these specific strategies need prospective validation. Several other biologic pathways have also been generally implicated with increased radiation resistance including altered DNA damage repair and increased activation of *PI3K-Akt-mTor* pathway.[73–76] Although the genomic biomarkers described previously have been shown to be highly prognostic, unfortunately, there are currently no clinically validated predictive genomic biomarkers to predict response to definitive RT within localized PCa.

4.2 | GC in the postprostatectomy setting

Following radical prostatectomy, three randomized clinical trials demonstrated immediate postprostatectomy RT improved biochemical progression-free survival (PFS) in patients with adverse pathologic features including positive margins, extracapsular extension, or seminal vesicle invasion.[77–79] Given the added morbidity associated with postprostatectomy RT, several trials were performed evaluating adjuvant versus early salvage RT (esRT; defined as prostate specific antigen [PSA] 0.1–0.2).[80–82] The ARTISTIC meta-

analysis of these trials demonstrated no improvement in event free survival with adjuvant RT compared with early salvage.[83] Given these findings, NCCN guidelines currently allow for consideration of adjuvant RT+/- ADT for patients with adverse pathologic features versus esRT. The Decipher GC has the potential for identifying patients who are at highest risk for disease progression and therefore may have the greatest benefit to aggressive management.

Among the commercially available genomic biomarker test, the Decipher GC has been validated in the postprostatectomy setting and provides prognostic information regarding 5- and 10-year risk of clinical metastases and 15-year PCa specific mortality. Feng et al.[84] demonstrated the Decipher GC was independently associated with distant metastases (HR: 1.17, 95% CI: 1.05–1.32), PCa specific mortality (HR: 1.39, 95% CI: 1.20–1.63), and OS (HR: 1.17, 95% CI: 1.06–1.29) in patients treated on RTOG 9601 (salvage RT ± anti-androgen therapy in recurrent PCa). Interestingly, this study also identified the benefit of ADT on 12-year OS was nearly threefold greater in patients with intermediate/high- (8.9% 12-OS benefit) versus low-risk (2.4% 12-OS benefit) GC. This is particularly noteworthy as there continues to be controversy over which patients should be offered ADT along with salvage RT in the postprostatectomy setting, especially those eligible for low presalvage RT, PSA, or esRT.[85–87]

Given the current uncertainty in the management of postprostatectomy patients with adverse pathologic features, prospective studies have aimed to evaluate the integration of genomic biomarkers, such as the Decipher GC, into management decisions. Marascio et al.[88] evaluated two prospective registries (clinical utility cohort and clinical benefit cohort) of PCa patients treated between 2014 and 2019 with adverse features following prostatectomy. Within the clinical utility cohort, GC testing altered treatment recommendations in 39% of patients. Within the clinical benefit cohort, patients with high GC risk experienced significantly improved 2-year PSA recurrence with adjuvant RT (3% vs. 25%). Additionally, patients with low or intermediate risk score demonstrated similar 2-year PSA recurrence (0% vs. 2.8%). Further prospective studies similarly demonstrated the utility of the GC in guiding treatment decisions with a number needed to treat ranging from 1.5 to 4 patients to change management, most commonly in patients with high GC risk.[89,90] Given the complex interaction between clinical, radiographic, and genomic data there is further interest in applying machine learning methods to integrate these features for improved clinical predictions.[91,92]

The Postoperative Radiation Therapy Outcomes Score (PORTOS) is a predictive signature of distant metastases risk after RT developed incorporating expression of 24 genes implicated in DNA damage repair and response to radiation. In a validation cohort of 330 patients, those treated with radiotherapy had a decreased incidence of distant metastases within the high PORTOS group (4% vs. 35%, HR: 0.15, $p = 0.002$) but not the low PORTOS group (32% vs. 32%, HR: 0.92, $p = 0.76$) with a significant interaction.[93] PORTOS represents the only clinically validated biomarker predictive for response to RT in the postprostatectomy setting.

Similar to the upfront setting, several randomized clinical trials are currently enrolling to further appreciate precisely how to apply these genomic data (Table 1). NRG Oncology GU006 (Balance) is a 324 patient phase II randomized trial biomarker stratified by the PAM50 classifier of salvage RT+/- the next-generation anti-androgen apalutamide. The Eradicate trial is currently recruiting and intends to randomize 810 patients treated with radical prostatectomy with high GC score (≥0.6) to either 12 months of ADT+/- darolutamide. The genomics in Michigan impacting observation or Radiation (G-Minor) trial will randomize 356 patients treated with radical prostatectomy with adverse pathologic features and undetectable postoperative PSA to either receive Decipher GC versus standard of care and evaluate the proportion of patients that receive adjuvant therapy within each group.

Although not ready for clinical use, several emerging biomarkers are being evaluated outside of the commercially available genomic tests. Brady et al.[94] demonstrated decrease/loss of erythroblast transformation-specific-related gene expression levels are associated with immediate biochemical progression following radical prostatectomy with decrease/loss of phosphatase and TENsin homolog deleted on chromosome 10 expression demonstrating a trend toward immediate biochemical progression. Circulating tumor DNA (ctDNA) is also being evaluated in predicting rapid progression after prostatectomy though data are conflicting. Lau et al.[95] demonstrated patients with tumor variants in ctDNA after prostatectomy had rapid disease recurrence and progression compared to those where variants were not detected. Detection of *TP53* mutations in ctDNA also demonstrated significantly shorter metastasis-free survival. To the contrary, Hennigan et al.[96] demonstrated ultra-low-pass whole-genome sequencing was unable to detect ctDNA in plasma of patients after RP before PSA biochemical recurrence.

5 | METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER (mCSPC)

5.1 | Genomic biomarkers within oligometastatic castration-sensitive prostate cancer (omCSPC)

Management of mCSPC is largely focused on hormonal and systemic therapies with RT historically playing a palliative role as needed.[97–100] This paradigm was challenged by the results of the STAMPEDE Arm H trial which evaluated radiotherapy to the primary tumor within de novo metastatic PCa.[101] This phase III trial of 2061 patients randomized to either standard of care systemic therapy or the addition of primary radiotherapy demonstrated an improvement in failure-free survival and OS in patients with "low-burden" but not "high-burden" disease. Radiation as metastasis directed therapy (MDT) has also garnered further interest among patients with oligometastasis, typically defined as three to five (or fewer) metastases on conventional imaging.[102–108]

Several prospective randomized trials within varying histologies have demonstrated that MDT improves PFS and OS in

oligometastatic disease.[102,104,105,109] Within metachronous omCSPC specifically, MDT has demonstrated prolonged time to initiation of ADT and PFS compared to observation, with no decrement to quality of life.[102,103] Our group previously reported the ORIOLE trial,[102] a randomized phase II trial of 54 patients with omCSPC (≤3 lesions) not on ADT, randomized to either stereotactic ablative body radiotherapy (SABR) versus observation (2:1 randomization). At 6 months, the proportion of patients experiencing progression was lower in the SABR arm compared to the observation arm (19% vs. 61%, $p = 0.005$). This finding translated into median PFS not yet reached for the SABR arm and 5.8 months in the observation arm (HR 0.30, $p = 0.002$). On the ORIOLE trial, saliva, plasma, and matched leukocyte DNA samples were collected in all patients at baseline and mutations in specific genes where analyzed from ctDNA using the cancer personalized profiling by deep sequencing (CAPP-Seq) method.[110] Using this method, we developed a high-risk mutational signature composed of truncating/pathogenic mutations encompassing *ATM*, *BRCA1/2*, *RB1*, or *TP53*. Among patients with detectable ctDNA or germline mutations, those without a high-risk mutation, PFS was significantly longer among participants receiving SABR than among those in the observation arm. However, in those with a high-risk mutation, no difference in PFS was observed between the SABR and observation group, suggesting genomic profiles can provide predictive information regarding response to SABR MDT. Work is currently ongoing to validate this potentially predictive genomic signature using the STOMP trial[103] (Deek et al., unpublished communication).

To further expand upon these findings, our group investigated high-risk mutations within the spectrum of mCSPC by grouping patients into four categories: biochemical recurrence (micrometastases), metachronous oligometastatic disease, metachronous polymetastatic disease, and de novo metastatic disease.[111] Driver mutations in high-risk genes were significantly different across metastatic categories and increased in frequency across the spectrum from biochemical recurrence, to polymetastatic and de novo metastatic disease for several genes and pathways. Mutations in DDR genes (incidence rate ratio [IRR] 1.61; $p < 0.001$), and *TP53* (IRR 1.45; $p = 0.004$) were associated with increasing number of metastatic lesions. Along with the specific high-risk mutations detailed above, additional work in this space may hold potential in further classifying omCSPC patients.[111–124]

6 | METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Within mCRPC much more is understood about the genomic landscape[115,125,126] however the role of RT has thus far been limited as improvements in outcomes have been driven by advancements in systemic therapy and increasingly immunotherapy.[127–129] Outside of palliation, the integration of systemic radioisotope therapies such as radium-223 and PSMA targeted radioligand therapy have expanded the utilization of radiation in mCRPC.

6.1 | Genomic predictors of synthetic lethal response to radium-223

Radium-223 is an alpha-particle-emitting bone-targeted therapy that demonstrated consistent improvement in pain and OS in patients with mCRPC harboring bone disease.[130,131] Alpha particles emitted at the site of disease have high linear energy transfer, resulting in the deposition of energy in the immediate vicinity of the radionuclide decay. This highly localized radiotherapy selectively targets the bone microenvironment and metastatic tumor cells, causing what is suspected to be irreparable DNA, DSB, and very locally restricted cytotoxic effects.[132]

Germline mutations in DDR genes are present in 8%–12% of mCRPC, whereas the previously estimated prevalence was 4%–5% in localized disease.[133,134] In addition, somatic aberrations in genes linked to DNA repair are seen in 20%–25% of mCRPC patients.[135] Corroborating studies have shown that both germline and somatic HRR gene mutations are seen in up to one-third of patients with mCRPC.[136] Synthetic lethality described previously, are observed in tumors with defects in mechanisms of DNA repair that are theoretically more susceptible to therapies that cause DNA damage, such as DSBs. The high prevalence of DDR mutations in mCRPC has led to their validation as prognostic[67,68,137,138] and predictive biomarkers.[135,139]

Velho et al.[140] hypothesized that mCRPC patients who harbored either germline and/or somatic HRR mutations may have a greater clinical benefit from radium-223, due to DSBs going unrepaired because of an underlying HRR in the tumor cells. Medical records of 190 mCRPC patients for whom germline and/or somatic DNA sequencing data were available recovered 28 men who had also received standard-of-care radium-223. Of these 28 patients, 10 men (35.7%) had a germline/somatic HRR mutation (3 in *BRCA2*, and 1 each in *ATM*, *ATR*, *CHEK2*, *FANCG*, *FANCI*, *FANCL*, and *PALB2*) and 18 (64.3%) did not have HRR associated mutations. In this exploratory study, bone-metastatic mCRPC patients with inactivating HRR mutations demonstrated significantly improved alkaline phosphatase responses (80% vs. 38%, $p = 0.04$), time to ALP progression (median 10.4 vs. 5.8 months, HR: 6.4, $p = 0.005$), and a trend toward longer OS (median 36.9 vs. 19.0 months, HR: 3.3, $p = 0.11$). Follow-up work by van der Doelen et al.[141] confirmed these findings demonstrating patients with HRR mutations experienced significantly improved OS (36.3 vs. 17.0 months, HR: 2.29, $p = 0.01$). These provocative results and "synthetic lethality" hypothesis between HRR mutations and radium-223 activity is being prospectively tested in a phase II study (NCT04489719).

6.2 | Genomic predictors of response to prostate-specific membrane antigen (PSMA)-targeted radioligand therapy

PSMA is a transmembrane glycoprotein expressed on the surface of PCa that has demonstrated overexpression within both local and

metastatic PCa lesions with high expression independently associated with poor survival.[142–144] (^{177}Lu)-PSMA-617 is a PSMA targeted radioligand that delivers beta-particle radiation. The VISION trial was a phase III trial which randomized 831 patients with mCRPC to either (^{177}Lu)-PSMA-617 or standard of care and demonstrated an improvement in median PFS (8.7 vs. 3.4 months, HR: 0.4, $p < 0.001$) and OS (15.3 vs. 11.3 months, HR: 0.62, $p < 0.001$).[145] Response to (^{177}Lu)-PSMA-617 has previously been associated with detection of AR gene amplification in plasma cell-free DNA. De Giorgi et al.[146] evaluated AR copy number in pretreatment plasma samples and correlated detection of AR gene amplification with early progressive disease on (^{177}Lu)-PSMA-617. Patients who experienced early progressive disease were significantly more likely to have AR gain identified in plasma (OR 16.00, $p = 0.0007$) and patients with plasma AR gain were found to have significantly shorter OS compared to AR-normal patients (7.4 vs. 19.1 months, $p = 0.02$). However, the levels of ctDNA in patient plasma are strongly prognostic,[147,148] so it is difficult to know whether the observed relationship with AR gain detection is independent of the prognostic effect of detecting any ctDNA signal. Mutations in DDR also appear to be implicated in response to PSMA targeted radioligand therapy however preliminary data among small cohorts and case reports[149–151] are conflicting. Conteduca et al.[152] analyzed 25 patients with PSMA targeted radioligand therapy who underwent whole exome sequencing. Patients with *BRCA1/2* mutations were found to have significantly improved PFS whereas those with a *TP53* mutation demonstrated worse PFS. Conversely, Kratochwil et al.[153] identified seven patients with a poor response to PSMA-targeting α-RT who underwent NGS. Six of the seven patients were found to have at least one genetic alteration negatively affecting the DDR pathway leading the authors to hypothesize DDR mutations may confer resistance to PSMA targeted radioligand therapy. Privé et al.[154] demonstrated no difference in PFS between patients with or without DDR mutations in a cohort of 40 patients with mCRPC treated with PSMA targeted radioligand therapy. Future work with a more comprehensive approach to detection of genomic alterations applied to larger and ideally prospectively collected set of cohorts will likely be needed to fully understand these relationships.

7 | CONCLUSIONS

Growing evidence continues to demonstrate the prognostic implications of genomic biomarkers across the spectrum of PCa. Several commercially available genomic biomarkers are currently in use which have consistently demonstrated improved stratification of patients at higher risk of experiencing a more aggressive clinical course. Though the evidence and clinical utility of prognostic genomic biomarkers is mounting, there unfortunately is a scarcity of biomarkers predicting therapeutic response to radiation and/or adjunctive treatments in PCa patients treated with radiotherapy. Consequently, even less is understood about how genomic markers may be predictive of various radiation techniques and dosing however remains an active area of interest. Prospective randomized integral-biomarker radiotherapy trial data utilizing these genomic tests are currently lacking, however, such trials are active and their results should be available in the coming years in the localized space. Integration of tumor genomics into these current and future clinical trials will allow for a more robust identification and utilization of predictive biomarkers and ultimately allow for precision RT in the management of patients across the entire spectrum of PCa.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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