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Genomic testing for localized prostate cancer: where do we go from here?

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Structured Abstract

Purpose of Review—The goal of this article is to discuss current genomic testing options in localized prostate cancer.

Recent Findings—There are multiple genomic tests currently available for men with localized prostate cancer. Prolaris, OncotypeDx and Decipher can all be tested using biopsy tissue. Prolaris and Decipher are also available for men undergoing radical prostatectomy to predict subsequent disease progression.

Summary—The Prolaris cell cycle progression score measured on biopsy predicts the risk of prostate cancer death in 10 years with conservative management; whereas, the primary endpoint for the OncotypeDx genomic prostate score is the risk of adverse pathology at radical prostatectomy. Decipher measures genome wide RNA expression and its Genomic Classifier signature was initially designed to predict the risk of metastasis for men with adverse pathology at radical prostatectomy, and more recently a biopsy version was released. Recently, Decipher signatures predicting prostate cancer cell lineage and post-operative radiation sensitivity have also been described. Any of these tests can be used by men with localized prostate cancer to provide additional prognostic risk stratification to aid in treatment decisions.

Keywords

prostate cancer; markers; Prolaris; OncotypeDx; Decipher

Introduction

Patients diagnosed with localized prostate cancer may face multiple management decisions, including initial treatment selection and in some cases, the decision whether to undergo secondary therapy. Current methods of risk classification based on PSA, clinical stage and biopsy histopathology have significant limitations. Misclassification is possible with a

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potential impact on management decisions. To provide men with additional information on risk stratification, several genomic tests are now available. The purpose of this article is to provide a summary of the Prolaris, OncotypeDx and Decipher tests.

Prolaris

Prolaris is a panel of cell cycle progression (CCP) genes measuring cancer proliferation. The primary endpoint of this test is the 10-year risk of prostate cancer death with conservative management. Using Cuzick et al. examined the paraffin specimens from 349 men diagnosed with prostate cancer in 1990–1996 who were managed conservatively.[1] After adjusting for with PSA and Gleason score, CCP score was a significant predictor of prostate cancer death (HR 1.65, 95% CI 1.31–2.09).

The Prolaris test measured on biopsy has also been shown to predict outcomes after radical treatment. Freedland et al. reported on 141 men diagnosed with prostate cancer from 1991–2006 who received external beam radiation.[2] CCP score was a significant predictor of biochemical recurrence (HR 2.11, 1.05–4.25, $p=0.034$) after adjusting for PSA, Gleason score, positive cores, and use of hormonal therapy. There was also a statistically significant relationship with prostate cancer death on univariate analysis but the number of events was small. Similarly, Bishoff et al. showed that biopsy CCP scores were a significant predictor of biochemical recurrence after radical prostatectomy (HR 1.47, 95% CI 1.23–1.76) in a multi-institutional cohort.[3] It was also a significant predictor of metastatic disease on univariate analysis. Another recent study by Oderda et al. examined biopsy CCP scores in 52 Italian men treated by radical prostatectomy. Mean Prolaris scores were -1.2 , -0.444 , and 0.208 in low, intermediate, and high-risk patients. Prolaris was a significant predictor of high-risk disease (OR 5.73, 95% CI 1.65–19.85) on multivariable analysis adjusting for CAPRA scores.[4] Prolaris was also significantly associated with biochemical recurrence on univariate but not multivariate analysis, although there were only 15 events.

Clinical utility studies have also been performed using surveys to ask clinicians whether the results would lead to a change in practice. For example, Shore et al. surveyed 15 urologists about the influence of Prolaris results in 294 different cases, and they reported that approximately 1/3 of the results would potentially lead to changes in practice.[5] Another study by Crawford et al. reported changes from interventional to non-interventional management, and vice versa due to Prolaris results.[6] Less is known about the long-term impact of changing initial management decisions on the basis of genomic test results, or how these tests fit in a context with widespread multiparametric MRI use.

Finally, Prolaris has also been studied in men who have already undergone surgery using the radical prostatectomy specimen. Cooperberg et al. reported on Prolaris in 413 surgically treated patients, of which 19.9% experienced biochemical recurrence.[7] Each unit increase in CCP score was associated with a significantly risk of biochemical recurrence (HR 1.7, 95% CI 1.3–2.4) after adjusting for the CAPRA-S post-surgical risk classification. For men who are post radical prostatectomy, the Prolaris report provides the 10-year risk of biochemical recurrence which could be used to inform decisions regarding secondary therapy.

Oncotype Dx

The OncotypeDx prostate biopsy test calculates a genomic prostate score (GPS) based on genes from 4 different pathways involved in prostate cancer: stromal response, androgen signaling, proliferation, and cellular organization. The primary endpoint of this test is to predict the risk of adverse pathology at radical prostatectomy. Unlike Prolaris and Decipher, OncotypeDx was designed for use with biopsy tissue and does not have a commercially available test for post-prostatectomy risk stratification.

The initial study by Klein et al. defined the 17-gene panel for use in the OncotypeDx GPS, then tested this in the biopsies of 395 men with low- to intermediate-risk prostate cancer.[8] A 20-unit increase in GPS was associated with a significantly increased risk of high-grade and/or high-stage disease (OR 2.1, 95% CI, 1.4–3.2), after adjusting for the CAPRA score. Adding in a GPS measurement improved the discrimination of adverse pathology compared to that of the CAPRA risk classification alone (AUC 0.67 vs. 0.63).

Cullen et al. subsequently validated the OncotypeDx biopsy test in independent populations of men from military hospitals.[9] On multivariable analysis adjusting for NCCN risk group, a 20 unit increase in OncotypeDX genomic prostate score associated with 3.3× increased risk of adverse pathology at RP and 2.7× increased risk of BCR.

Recently, these studies were combined in a patient-specific meta-analysis by Brand et al., which was used to update the reporting based on 732 total patients.[10] The overall median score was 27 (range 1–74). Using NCCN risk groups alone had an AUC of 0.64 for adverse pathology which increased to 0.70 adding GPS. Instead using the CAPRA risk classification had an AUC of 0.68 alone which increased to 0.73 with the addition of the GPS.

Clinical utility studies indicate that OncotypeDx results may also influence decisions about patient management. Badani et al. reported that the GPS was discordant to the NCCN risk category in 39% of patients, and that 18% of recommendations between active surveillance and treatment changed as a result of OncotypeDx.[11] Clinicians also reported that the results increased their confidence in decisions. Subsequently, Whalen et al. reported follow-up of 50 men from the clinical utility study treated by radical prostatectomy, with an AUC of 0.92 for favorable pathology.[12] In order to achieve >90% accuracy for the likelihood of favorable pathology, they suggested using cutoffs of 76% and 68% for low- and intermediate-risk patients, respectively.

Decipher

The Decipher test is a clinical grade high density micro array encompassing 1.4 million probes that detect coding and non-coding RNA expression levels across the genome.[13] The test can be run on small amounts of routinely collected formalin fixed paraffin embedded tissue including prostate biopsy tissue and that from radical prostatectomy. Genomic signatures on this platform have been developed, locked and validated, with most of the evidence to date describing the Genomic Classifier signature that was developed to predict metastatic progression of localized disease.[13] The expansiveness of the platform allows for the development and refinement of prognostic signatures as well as for the

development of predictive signatures for treatment response, as well as for the molecular characterization of tumor subtypes.[14–16]

The Decipher Genomic Classifier consists of 22 RNA expression based genomic markers that are prognostic for metastatic progression and relate to cellular differentiation, cell cycle progression, cellular adhesion and motility, androgen signaling and immune modulation. The classifier score is reported in a range from 0 to 1 and is calibrated, with each 0.1 increase in score representing a 10% increase in metastatic risk. The score is reported and additionally patients are categorized into low (0–0.44, average 0.45–0.59, and high 0.6–1 genomic risk). This score was initially developed and validated on radical prostatectomy tissue but more recently has been evaluated in prostate biopsy samples. An initial validation series included 219 high risk men who had undergone radical prostatectomy at the Mayo clinic. Here the Decipher Genomic Classifier was independently predictive of metastasis and prostate cancer specific mortality with hazard ratios of 7.3 and 11, respectively, when moving from low to high genomic risk on multivariable analysis.[17, 18] The ability of Decipher to be prognostic for metastatic progression in the post-prostatectomy setting was further validated and demonstrated similar results when performed on a natural history cohort of 260 men with NCCN intermediate or high risk prostate cancer from the Johns Hopkins Medical Institute, and in an additional cohort from the Cleveland Clinic.[19, 20] Recently Spratt and colleagues reported a retrospective meta-analysis of the Genomic Classifier in 855 patients who had undergone radical prostatectomy, had known clinical outcomes and underwent Decipher testing.[21] The Decipher Genomic Classifier was independently prognostic of metastasis across multiple patient subgroups (i.e., high versus low Gleason scores, PSA levels and various clinical stages) and had a C-index for prediction of metastasis of 0.81 when considered with clinical and pathological variables.

In the post-prostatectomy setting, Decipher has been evaluated for its ability to inform decisions regarding adjuvant and salvage radiation therapy.[22–25] Den and colleagues for instance compared men undergoing adjuvant or salvage radiation therapy after radical prostatectomy and found that those with high genomic risk (prostate classifier scores >0.6) had up to an 80% reduction in metastatic progression if they received adjuvant radiation therapy while no significant reduction was seen in men with low-genomic risk.[25] Dalela and colleagues more recently developed a clinical-genomic nomogram to inform patients regarding adjuvant radiation therapy.[22] They found that patients with two or more of the risk factors of pT3b-T4 disease, Gleason 8–10 prostate cancer, lymph node invasion, or genomic classifier scores >0.6 showed an over 4-fold reduction in metastasis at 10 years if adjuvant radiation was employed. These studies demonstrate that the additional information provided by the genomic classifier allows for more precise point estimates of risk, based on clinical, pathological and genomic features and can help inform patients deciding on adjuvant or salvage therapy.[23] To determine clinical utility in the post-operative setting, PRO_IMPACT is a multi-institutional prospective study to assess clinical decision-making and patient-reported outcomes after Decipher testing (NCT02080689).[26] Use of the Decipher genomic classifier significantly reduced decision-conflict and patient anxiety, and resulted in changes in clinical decision making regarding both adjuvant and salvage radiation therapy (in 18% and 32% of cases respectively).

As mentioned above, Decipher and the Genomic Classifier has also been evaluated for its independent prognostic ability in prostate biopsy tissue using the same markers and coefficients for score calculation as are employed on prostatectomy tissue. In a study by Klein and colleagues examining the Decipher genomic classifier from the biopsies of 57 men who underwent prostatectomy and had long term follow up, the genomic classifier was independently predictive of metastasis and increased the AUC for metastasis prediction from 0.72 for NCCN risk categories alone to 0.88 when combined with genomic testing.[27] Nguyen and colleagues then studied the Decipher genomic classifier in the biopsies of 100 patients undergoing primary radiation therapy for prostate cancer.[28] On multivariable analysis, including clinical pathological variables individually or in nomogram scores like CAPRA, only the genomic classifier score was independently predictive of clinical progression. This highlights the potential importance of genomic testing, particularly in intermediate risk men considering radiation therapy.

When utilized either in the clinical or research setting, the Decipher test acquires genome-wide expression information allowing for the development and use of genomic signatures that are not just prognostic but also can molecularly subclassify tumors and predict treatment response. Locked and calibrated genomic signatures are reported with the genomic classifier as part of the Genomic Resource Information Database (GRID) when Decipher is performed. Recently, Zhao and collaborators developed and validated the Decipher Post-Operative Radiation Therapy Outcomes Score (PORTOS).[16] PORTOS is a 24 gene predictor of response to postoperative radiotherapy. The score is not prognostic of metastatic outcome when no radiation therapy is utilized but is highly predictive of metastatic progression if adjuvant or salvage radiation is used, with high PORTOS scores being associated with a 7-fold reduction in metastatic progression among men receiving post-operative radiation. As PORTOS was developed with gene sets implicated in radiation response it is likely that PORTOS will predict primary response to radiation as well however evaluation of PORTOS from men undergoing primary radiation therapy has yet to be reported on. Zhao and colleagues have also recently reported on the use of Decipher to subtype prostate cancer into luminal and basal types using PAM50 clustering as has been done with breast cancer.[29] Paralleling findings from breast cancer, the Decipher PAM50 classifier subdivided prostate cancer into Luminal A, Luminal B, and Basal subtypes. Luminal A and B subtypes demonstrated far greater amounts of androgen signaling than basal subtypes and when compared to other subtypes, Luminal B cancers appeared to respond favorably to androgen deprivation therapy.

Conclusion

For men with localized prostate cancer making decisions about initial or second-line therapy, there are multiple commercially available genomic tests that can be ordered to provide additional prognostic information. The Prolaris, OncotypeDx and Decipher tests are available for biopsy tissue, and the Prolaris and Decipher tests can be used after radical prostatectomy.

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Key Points

- Prolaris is a panel of cell cycle progression genes, which can be measured using biopsy tissue for men with untreated prostate cancer or using prostatectomy tissue for previously treated patients.
- OncotypeDx is measured on biopsy tissue and predicts the risk of adverse pathology at radical prostatectomy for men with low to intermediate risk prostate cancer.
- Decipher provides genome wide RNA expression information and can be measured using biopsy tissue for newly diagnosed patients or radical prostatectomy tissue for men with adverse pathology facing decisions about secondary therapy.