Contemporary Role of the Decipher® Test in Prostate Cancer Management: Current Practice and Future Perspectives

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We performed a systematic literature search to identify original articles and editorials about the Decipher® Prostate Cancer Test (GenomeDx Biosciences, San Diego, CA) to provide an overview of the current literature and its present role in urologic clinical practice. The Decipher test, which uses the expression of 22 selected RNA markers (from a total of over 1.4 million), showed a very high discrimination in predicting clinical metastasis (0.75-0.83) and cancer-specific mortality (0.78) in external validation studies, outperforming all routinely available clinicopathologic characteristics. Further, the timing of postoperative radiotherapy (adjuvant vs salvage) may be guided based on Decipher scores. The Decipher test was also the only independent predictor of clinical metastasis in patients with biochemical recurrence after surgery. The Decipher Genomic Resource Information Database (GRID) is a novel research tool that captures 1.4 million marker expressions per patient and may facilitate precision-guided, individualized care to patients with prostate cancer. In this era of precision medicine, Decipher, along with the Decipher GRID platform, is a promising genomic tool that may aid in managing prostate cancer patients throughout the continuum of care and delivering appropriate treatment at an individualized level.

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KEY WORDS

Decipher® Prostate Cancer Test• Prostate cancer • Genomic classifier • Neoplasm recurrence • Local/surgery • Treatment outcome

In the United States, approximately 220,800 men are diagnosed with prostate cancer (PCa) and more than 27,000 men die from the disease annually.[1] The optimal management strategy for this tumor is a subject of continuous debate. Physicians face many challenges in treating PCa, primarily because of the apparent heterogeneity of the disease, which acts differently in each patient. Although there is a concern of overdiagnosis and overtreatment of many men with low-risk tumors, many others with high-risk tumors are likely undertreated. Moreover, in cases in which active treatment is indicated, the optimal initial treatment strategy and the most appropriate sequence of treatments are not always clear. Likewise, the most appropriate management strategy for patients with metastatic and castration-resistant disease is a subject of controversy and continuous research.

These uncertainties in treating PCa are mainly derived by our inability to accurately identify the natural history and aggressiveness of the tumor at an individualized level. To address this issue, many PCa classification systems have been proposed, such as TNM staging, Gleason score grading, D'Amico risk stratification,[2] the University of California, San Francisco-Cancer of the Prostate Risk Assessment (CAPRA) score, and many others.[3-5] Although these models have improved our ability to evaluate and predict the aggressiveness of PCa, their performance in many cases is still suboptimal.[6] This may stem from the fact that these models rely heavily on the macro- and microscopic features of the tumor, which can be misleading. Further, current risk prediction methods are limited because they are unable to distinguish individual risk for patients who present with similar pathology. To overcome this limitation, genomic markers have been proposed as a complementary tool to these models. These markers offer the advantage of capturing information that is beyond the reach of the routinely available clinical and pathologic characteristics of the disease, such as tumor stage, grade, and prostate-specific antigen (PSA) value. This will likely revolutionize the way we approach PCa, and allow us to conquer new territories in our continuous fight against this disease.

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The objective of this review is to assess the role of one of the most promising genomic biomarkers, Decipher® (GenomeDx Biosciences, San Diego, CA), in staging/grading and managing PCa.

Methods

We performed a literature search in December 2015 using the MEDLINE, Embase, and Web of Science databases to identify original articles and editorials addressing the role of Decipher in PCa. Only English-language articles were included. The following limits were used: humans, sex (male). Keyword combinations included *prostate*, *Decipher*, and *genomic classifier*. The combination "*prostate* AND *Decipher*" resulted in 51 articles, and the combination "*prostate* AND *genomic classifier*" resulted in 34 articles. All titles were screened, and studies were excluded if obviously irrelevant. In case of doubt concerning the eligibility of a study, abstracts—and if necessary, the full text—were examined. Additional references were identified from the reference lists of these articles. Moreover, a complete list of the abstracts that were accepted or presented at international meetings, and those that are in press but not yet published in peer-reviewed journals, was obtained by directly contacting GenomeDx Biosciences.

What Is the Decipher Prostate Cancer Test?

The Decipher Prostate Cancer Test is a genomic test that serves as a prognostic marker of cancer control outcomes in patients who have undergone radical prostatectomy (RP). Based on the expression pattern of 22 RNA markers in the RP specimen, it allows postsurgery risk stratification of patients to predict likelihood of metastases and cancer-specific mortality, determine the need for adjuvant versus salvage therapy based on a discrete cut-off score, and, in patients who have already had a biochemical recurrence (BCR), guide the treatment decision for early/multimodal salvage therapy versus salvage therapy alone.[51] A detailed methodology describing the development and validation of Decipher has been previously described.[7] Briefly, a cohort of 545 PCa patients treated with RP between 1987 and 2001 at the Mayo Clinic (Rochester, MN) was used. These patients were divided into training

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(n = 359) and validation (n = 186) cohorts. In the development cohort, the expression of over 1.4 million RNA features was assessed. This included the vast majority of known protein coding genes, as well as non-coding RNAs. The ability of these features to predict clinical metastasis was tested in several steps of analyses. First, *t* tests for complexity reduction yielded 18,902 differentially expressed features between cases and control subjects. Further selection of these differentially expressed features by regularized logistic regression reduced the list to a total of 43. As a final step, these 43 differentially expressed features were further filtered to only those that demonstrated to improve a random forest-based performance metric. This resulted in a final set of 22 markers corresponding to RNAs from coding and non–protein-coding regions of the genome, which formed the novel Genomic classifier (GC), the Decipher Prostate Cancer Classifier Test. The outcomes of this classifier were continuous, with a variable score range from 0 to 1, in which a higher score indicates a higher probability of clinical metastasis. The performance of this tool was tested in the validation cohort (n = 186) showing a high discrimination accuracy (0.75), which significantly outperformed the discrimination accuracy of clinical and pathologic features alone (0.69). Likewise, the novel GC outperformed 17 other previously developed genetic signatures in predicting clinical metastasis (discrimination 0.54-0.68).

The Role of the Decipher Prostate Cancer Test in Clinical Practice

Decipher Prostate Cancer Test Results Obtained From Pathologic RP Specimen

Most currently available reports addressing the role of the Decipher Prostate Cancer Test are based on the results obtained from the pathologic specimen of the prostate gland, which is available only after surgery. These studies help answer many clinically relevant questions.

Postoperative Risk Stratification in Patients Treated With RP. After its initial development,[7] the validity of the novel GC model was tested in a large cohort that originated at the Mayo Clinic.[7] This cohort consisted of 256 PCa patients with a high risk of metastasis, defined as a PSA value ≥ 20 ng/mL, a pathologic Gleason score ≥ 8, a pathologic T3b stage, or a Mayo Clinic nomogram score ≥ 10.[8] All these men were treated with RP between 2000 and 2006. The discrimination of the GC in this cohort was 0.79 (95% confidence interval [CI], 0.68-0.87), outperforming all clinical variables (discrimination 0.49-0.65). Incorporating all clinical variables into the GC marginally increased the discrimination to 0.82 (95% CI, 0.72-0.88). GC score deciles were then incrementally collapsed to create three GC risk groups (GC < 0.4, GC 0.4-0.6, and GC > 0.6). Progression-free probability estimates and cumulative incidence plots revealed that 60% of patients had a GC < 0.4 with only a 2.4% 5-year cumulative incidence of metastasis. In contrast, 21% and 19% of patients had a GC score of 0.4 to 0.6, and > 0.6, respectively. These patients had a 6% and 22.5% 5-year cumulative incidence of metastasis, respectively ($P < .001$). Later, these cutoffs were recalibrated and optimized using a number of metrics; calibration in-the-large, calibration slope, goodness-of-fit, and a modified Hosmer-Lemeshow test. Cutpoints of the recalibrated score were identified using resampling and maximizing the partial likelihood of a Cox model. Based on this approach, optimized categories of Decipher were < 0.45, 0.45 to 0.60, and > 0.60.[9]

In a subsequent study, Klein and colleagues[10] tested the ability of GC in predicting early metastasis, which was defined as metastasis within 5 years after surgery. The authors used a cohort of 169 men treated with RP, between 1987 and 2008, in the Cleveland Clinic (Cleveland, OH). All of the PCa patients met the following criteria: (1) preoperative PSA > 20 ng/mL, stage pT3, positive surgical margin, or pathologic Gleason score ≥ 8; (2) pathologic node-negative disease; (3) undetectable post-RP PSA; (4) no neoadjuvant or adjuvant therapy; (5) a minimum of 5-year follow-up for those who remained metastasis free; and (6) adequate tumor cell content for extracting RNA. Decipher discrimination (c-index) to predict early metastasis was 0.77 (95% CI, 0.66-0.87), which outperformed individual clinicopathologic variables including pathologic Gleason score (c-index 0.71; 95% CI, 0.59-0.84), pathologic CAPRA score (CAPRA-S)[11] (c-index 0.72; 95% CI, 0.60-0.84), and the Stephenson nomogram[5] (c-index 0.75; 95% CI, 0.65-0.85). The highest c-index was obtained by the combination of Decipher plus the Stephenson nomogram (c-index 0.79; 95% CI, 0.68-0.89). Among patients with low-risk Decipher scores, 95% had early metastasis-free survival versus 82% for those with high-risk scores. In multivariable analyses, Decipher was the only independent predictor of early metastasis (hazard ratio [HR] 1.48; 95% CI, 1.07-2.05; $P = .018$). In a similar report, Cooperberg and colleagues[12] examined Decipher ability to predict cancer-specific mortality (CSM), using a cohort similar to the one used in a previous report.[7] When

compared with individual clinicopathologic variables, Decipher had the highest discrimination with a c-index of 0.78 (95% CI, 0.68-0.87). When both Decipher and CAPRA-S were merged in one model using Cox regression, the final model discrimination (0.78) was not significantly higher from the individual models; however, decision curve analysis showed that the merged model had a higher net benefit compared with Decipher or CAPRA-S alone.

Recently, Ross and associates[13] examined the performance of Decipher in 260 PCa patients treated with RP alone (until metastasis, or end of follow-up) in the Johns Hopkins Medical Institutions (Baltimore, MD), between 1992 and 2010. All these men met the following criteria: (1) CAPRA-S score $\geq$ 3; (2) pathologic Gleason score $\geq$ 7; (3) post-RP PSA nadir $<$ 0.2 ng/mL; and (4) sufficient tissue and clinical data for analysis. Patients were excluded if they had nodal/metastatic disease prior to surgery, received neoadjuvant therapy, or received radiation and/or hormonal therapy before clinical evidence of metastasis. This cohort represented the natural history of the disease from surgery to metastasis, or end of follow-up. In this report, Decipher was a significant predictor of BCR, metastasis, and CSM, but not overall mortality. At 10-year follow-up after RP, the cumulative incidence of metastasis was 12%, 31%, and 47% ($P < .01$) among patients with low ($<$ 0.45), intermediate (0.45-0.60), and high ($>$ 0.60) Decipher scores, respectively. In multivariable analysis predicting metastasis, the statistically significant factors were Gleason score 9 (HR 4.6; 95% CI, 2.5-8.5), seminal vesicle invasion (HR 2.63; 95% CI, 1.4-4.8), lymph node invasion (HR 3.8; 95% CI, 2.1-6.8), and Decipher score (HR 1.3; 95% CI, 1.1-1.5). When modeled with either CAPRA-S or the Eggener risk model,[4] Decipher was independently associated with metastasis (both $P < .01$). Combining Decipher with the Eggener risk model or CAPRA-S improved the prognostic discrimination of these models with areas under the curve (AUCs) of 0.86 and 0.87, respectively. The discrimination of Decipher, the Eggener model, and CAPRA-S individually in predicting metastatic disease at 10 years after RP was 0.76, 0.76, and 0.77, respectively.

Taken together, these reports show that Decipher adds important prognostic information to the routinely available clinicopathologic variables. This can greatly improve the accuracy of predicting patient outcomes, and can significantly improve the clinical decision-making process in the setting of multimodal treatment for patients with adverse pathologic characteristics after surgery or with Gleason grade $\geq$ 7. Finally, Glass and coworkers[14] observed similar favorable performance characteristics with Decipher when examined in a population-based cohort. This confirms the generalizability of the Decipher performance beyond the limits of single institutional databases.

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Risk Stratification in Patients With BCR After Treatment With RP. Patients presenting with BCR after RP continue to present a management dilemma for many clinicians. Treating all of these individuals with salvage radiotherapy (sRT) and/or systemic therapy will result in overtreatment and unnecessary morbidity.[15-17] On the other hand, evidence demonstrates that treatment will improve cancer control outcomes in some of these individuals.[18,19] To help guide the decision to employ salvage treatment in patients with BCR, Ross and colleagues[20] examined the ability of Decipher to predict clinical metastasis in these individuals. For the purpose of this study, the authors examined the data of 85 men with high-risk PCa, who had BCR after treatment with RP at the Mayo Clinic, between 2000 and 2006. Among men with Decipher $\geq$ 0.4, 73% experienced metastasis (sensitivity 0.73, specificity 0.74). Furthermore, 40% of men in this group developed metastasis within 3 years of BCR, compared with fewer than 10% of men in the low-risk group (Decipher $<$ 0.4). The discrimination of Decipher in this cohort was 0.82 (95% CI, 0.76-0.86), outperforming all clinical variables, including PSA doubling time at an AUC of 0.69 (95% CI, 0.62-0.78). Although the discrimination of clinicopathologic features taken individually or combined in the Stephenson nomogram could be improved by the addition of the Decipher score, the discrimination of the Decipher score was not improved by adding standard clinicopathologic features, or by adding the Stephenson nomogram. Decipher was the only significant predictor of metastasis in a multivariable model using clinical information present at the time of BCR (HR of 1.40 for every 10% increase in score; 95% CI, 1.12-1.74; $P = .003$). PSA doubling time (a variable that is not available at the time of BCR) was a predictor of metastasis in both univariable and multivariable analysis. However,

even after adjusting for PSA doubling time, the Decipher score remained an independent predictor of metastatic progression with an HR of 1.49 (95% CI, 1.23-1.81; $P < .001$) for every 10% increase in score. Likewise, decision curve analysis showed that Decipher had the highest net benefit across a wide range of risk. These results suggest that Decipher can be used to better identify men requiring intensification or earlier initiation of treatment at the time of BCR, and also can identify men at lower risk of metastasis who may forego concurrent hormonal therapy.

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Indications for Adjuvant/sRT Treatment After RP. In patients with adverse pathologic characteristics on RP, adjuvant radiotherapy (aRT) can significantly improve cancer control outcomes.[21-24] Despite the availability of level I evidence in this area, the use of aRT in contemporary patients is still limited.[25,26] Surgeons are reluctant to recommend aRT for two primary reasons: (1) this treatment modality has a negative impact on functional outcomes[27]; and (2) almost 50% of patients with advanced pathologic characteristics will not develop biochemical failure, even without any adjuvant treatment.[21-24] This implies that providing aRT to all men with adverse pathologic features after surgery will result in substantial overtreatment. An alternative would be to provide sRT in patients with documented BCR. However, to date, there is no level I evidence to support such a practice, and the benefit of sRT (if any) is not necessarily comparable with that of aRT. To address this dilemma, novel biomarkers can be used to improve patient selection for RT after surgery. This has the potential of decreasing the overtreatment rate, without compromising cancer control outcomes in individuals with aggressive disease. In this context, Den and associates[28] tested the role of Decipher in predicting clinical metastasis among 188 PCa patients with pT3 disease, and/or positive surgical margins, who were treated with RP and postoperative RT at Thomas Jefferson University Hospital (Philadelphia, PA) and the Mayo Clinic between 1990 and 2009. In this cohort, the cumulative incidence of metastasis at 5 years after RT was 0%, 9%, and 29% for low, average, and high Decipher scores, respectively ($P = .002$). Within the low Decipher score (< 0.4), there were no reductions in the cumulative incidence of metastasis for patients who received aRT compared with sRT ($P = .79$). Conversely, for patients with higher Decipher scores (≥ 0.4), cumulative incidence of metastasis at 5 years was 6% for patients treated with aRT compared with 23% for patients treated with sRT ($P = .01$). Cox regression modeling demonstrated an 80% reduction in metastasis risk in the Decipher high-risk patients who received aRT compared with sRT. In a similar report, Den and coworkers[29] showed that, among men with postoperative RT treatment, using the Decipher test could significantly improve the discrimination accuracy in predicting biochemical failure (improved by 8%), and distant metastasis (improved by 10%) as compared with clinicopathologic characteristics alone. This provides evidence that Decipher can be used to guide timing of postoperative RT. Specifically, although patients with low Decipher scores are best treated with sRT, those with high Decipher scores may benefit from aRT.

How Does the Decipher Prostate Cancer Test Affect Clinical Decision Making?

Several reports have shown that Decipher test results have an important impact on decision making in clinical practice. Among 21 fellowship-trained, high-volume urologic oncologists, the Decipher test results changed the aRT treatment decision in 43% of cases, and the sRT treatment decision in 53% of cases. In the adjuvant setting, urologists changed their treatment recommendations from treatment (radiation and/or hormones) to close observation after the Decipher test in 27% of cases. For cases with low Decipher risk (< 3% risk of metastasis), observation was recommended for 79% of the case evaluations after the Decipher test. Similar trends were observed in the salvage setting.[30] Likewise, for urologists in community practice ($n = 15$), over 60% of high-risk patients were reclassified as low risk after review of the Decipher test results. Overall, adjuvant treatment recommendations were modified for 30.8% (95% CI, 23%-39%) of patients.[31]

In a similar context, and using a larger cohort of urologists ($n = 51$), Badani and colleagues[32] showed that 40% of aRT recommendations changed to observation (95% CI, 33%-47%) after Decipher test results were obtained. Of patients originally recommended for observation, 13% (95% CI, 9%-17%) were changed to aRT when Decipher

test results were included in the treatment decision. Patients with low-risk disease according to the Decipher test were recommended for observation 81% of the time, whereas among those with high-risk disease, 65% were recommended for treatment ($P < .001$). Finally, Nguyen and coworkers[33] showed that Decipher results altered 35% and 45% of aRT treatment recommendations made by radiation oncologists and urologists, respectively, and significantly increased interdisciplinary agreement in treatment recommendations.

Based on this cumulative body of evidence, Mohler and coauthors,[34] in the update to the discussion section of the National Comprehensive Cancer Network (NCCN) 2016 Prostate Cancer guidelines, noted "Men with clinically localized disease may consider the use of tumor-based molecular assays. Retrospective case cohort studies have shown that molecular assays performed on biopsy or prostatectomy specimens provide prognostic information independent of NCCN risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression after RP or external beam radiation therapy, and likelihood of developing metastasis after radical prostatectomy or salvage RT."

Decipher Prostate Cancer Test Results Obtained From Prostate Biopsy Specimens

Although preliminary, the results of the Decipher test obtained from prostate biopsy specimens are encouraging. Genome-wide exon arrays yielded data of comparable quality from biopsy and RP tissues. In a report by Knudsen and colleagues,[35] 95% of transcriptomic features detected in RP were detectable in biopsy tissues and demonstrated a high correlation ($r = 0.96$). Likewise, in the same study, the Decipher prognostic test showed a strong correlation between biopsy and RP ($r = 0.70$). The high concordance of tumor-associated gene expression changes between biopsy and RP samples demonstrates the performance of the assay platform with samples from prostate needle biopsies with limited tumor volume.

Further analyses in this area demonstrated that Decipher can be an optimal predictor of multiple important outcomes at the time of prostate biopsy. Lee and colleagues[36] observed that the pathologic Decipher score (obtained from RP specimens) was an independent predictor of lymph node invasion on multivariable analysis. Specifically, patients with a high Decipher score had a 3.1-fold higher lymph node invasion risk than their counterparts with a low Decipher score ($P = .03$). Likewise, the discrimination accuracy of Decipher to predict lymph node invasion was as high as 0.78 (95% CI, 0.71-0.84), which outperformed all other pathologic predictors, such as Gleason score (0.67) and seminal vesicle invasion (0.70). Importantly, in the same cohort, authors found that the concordance between pathologic Decipher and biopsy Decipher scores was as high as 86%. This implies that biopsy Decipher results could be used in the future to decide the probability of lymph node invasion, and hence the necessity of a pelvic lymph node dissection at the time of surgery. In an independent validation of Decipher Biopsy, Klein and colleagues[37] found that, among 57 patients with available biopsy Decipher results, the latter was an independent predictor of clinical metastasis after surgery. Biopsy-based Decipher scores had a c-index of 0.80 (95% CI, 0.58-0.95) for prediction of metastases at 10 years, compared with 0.75 (95% CI, 0.64-0.87) by NCCN risk stratification. Adding Decipher results to NCCN risk stratification improved the c-index to 0.88 (95% CI, 0.76-0.96). On multivariable analysis, biopsy-based Decipher score HR per 10% increase was 1.72 (95% CI, 1.04-2.83). Biopsy-based Decipher score was also a significant predictor of adverse pathology at surgery, with a c-index of 0.71 (95% CI, 0.56-0.86) for presence of primary Gleason ≥ 4 at surgery.

These reports indicate that biopsy-based Decipher results will likely be a valuable instrument in the pretreatment setting. Many important questions, such as the need for a pelvic lymph node dissection, the necessity of multimodal treatment, and cancer control outcome, can be addressed. Likewise, in the near future, biopsy Decipher could be useful in answering many other important clinical questions, such as the need for neoadjuvant/adjuvant hormonal therapy, and the optimal initial treatment strategy (first-line RP vs first-line RT).

Biopsy-based Decipher predicted metastasis at 10 years with a high discriminatory accuracy of 0.80 (95% CI, 0.58-0.95) and outperformed NCCN risk stratification.

Decipher GRID: a Tool for Advancing Research of Prostate Cancer Genomics

A unique feature of the Decipher test is that it utilizes a genome-wide

RNA expression array to determine tumor aggressiveness. For each patient tested, large amounts of data are generated: approximately 1.4 million expressed markers representing over 46,000 genes and noncoding RNAs (do not encode for proteins). The Decipher Genomic Resource Information Database (GRID™; GenomeDx Biosciences) is a unique genomic resource, a result of every patient profiled in both research studies and clinical Decipher testing. At present, the Decipher GRID contains approximately 3000 genome-wide expression profiles from retrospective validation studies of the Decipher test that have complete clinical, pathologic, treatment, and outcomes data, as well as approximately 5000 de-identified profiles from prospective patients who have clinical and pathologic associated data. This makes the Decipher GRID the world's largest global RNA expression database in urologic oncology, attracting researchers to expand the clinical utility of biomarkers. The Decipher GRID has been utilized to validate and provide clinical characterization of novel discovered coding and noncoding biomarkers such as *SPARCL*,[38] *SChLAP1*,[39] *NEAT1*,[40] *AXIN2*,[41] *ASPN*,[42] and *PCGEM1*.[43] Prensner and colleagues[44] used the Decipher GRID to validate a novel predictor of metastasis, *SChLAP1*, that was discovered from an RNA sequencing platform. This prostate-specific gene was predictive of clinical metastasis with an AUC of 0.68. On multivariate modeling, *SChLAP1* expression was independently predictive of metastasis within 10 years, with an odds ratio (OR) of 2.45 (95% CI, 1.70-3.53). This partnership between academic research and Decipher GRID aims to accelerate the translation of genomic biomarkers into routine clinical practice through a unique approach to data sharing, collaborative research, and user-defined content.

In addition, Decipher GRID is a rich resource for discovering novel prognostic biomarkers, predictive biomarkers, and understanding prostate cancer heterogeneity. Tomlins and colleagues[45] used 1577 samples to discover and characterize prostate cancer subtypes based on *ERG*, *ETV1*, *ETV4*, *ETV5*, and *SPINK1* expression. In this study, Tomlin and colleagues[45] defined four subtypes (ERG^+, ETS^+, $SPINK1^+$, TripleNeg) and found $SPINK1^+$ more common in African American men (OR 16.87; $P < .001$) compared with ERG^+ tumors. Compared with the TripleNeg, ERG^+ was associated with lower preoperative PSA levels (OR 0.47; $P < .001$), lower Gleason grade tumors (OR 0.43; $P < .001$), and nearly twice as likely odds to have extraprostatic extension (OR 1.8; $P < .001$). Using the Decipher GRID, Zhao and associates[46] recently discovered an additional 20 prognostic outlier genes that were associated with tumor migration and invasion. The Decipher GRID has been also used to demonstrate differences in expression of biomarkers between African American and European American men,[47] as well as characterization of genomic differences between anterior compared with posterior anatomic tumor locations.[48]

Recently, the Decipher GRID has been utilized to build an androgen deprivation therapy (ADT) response signature (ARS)[49] and small-cell neuroendocrine signature (SCGS). The ARS was developed using data from 1023 PCa patients and it was predictive of metastasis in cohorts receiving adjuvant ADT (10-year metastasis-free survival c-index of 0.69 [95% CI, 0.59-0.78]). Among ADT-treated patients, those with low ARS scores had a 10-year metastasis-free survival of 87%, compared with 70% in those with high ARS scores ($P < .001$). The SCGS was discovered from small-cell and high-grade adenocarcinoma and validated in multiple data sets of neuroendocrine and metastatic castration-resistant prostate cancer cohorts.[50] Evaluating SCGS in RP samples treated with ADT revealed that patients with high SCGS scores are more likely to fail ADT treatment.

The aforementioned studies are a few examples of the potential that Decipher GRID offers to advance urologic oncology research and precision medicine. The GRID approach seeks engagement from the community of researchers, clinician-scientists, and Decipher users to discover, develop, and validate biomarkers (user-defined content) that can be used to improve care and advance our understanding of urologic oncology.

Present and Future Directions of Decipher GRID

When the Decipher Prostate Cancer Classifier is run for a patient, a rich resource of genomic data is available beyond the markers that make up Decipher, due to the use of whole genome Human Exon Array technology. The Decipher GRID captures 1.4 million expression markers per patient. Access to this broad genomic database provides more information about each individual patient's disease, which could greatly improve precision in delivering care to patients. Currently, Decipher GRID reports on 35 genes related to six pathways, including growth receptors and cell proliferation, invasion and

angiogenesis, androgen signaling, neuroendocrine markers, immune oncology, and molecular subtypes that are implicated in prostate cancer progression. The percentile rank for each gene in a patient is provided with reference to all the prospective patients in the GRID. Additionally, the percentile rank of additional genes of interest for the physicians is provided upon request. This genomic information can guide physicians to avoid unneeded treatment and decide on optimal therapy. Low androgen receptor signaling and high neuroendocrine markers indicate that the patient is more likely to fail any antiandrogen-targeted therapy. Ultimately, the goal of the GRID is to assign patients to open clinical trials targeting genes highly overexpressed in the patient.

Conclusions

Decipher is a trusted long-term partner that helps manage prostate patients throughout the continuum of care. Decipher's technology platform has produced two commercially available tests, the *Decipher Prostate Cancer Classifier Biopsy* and the *Decipher Prostate Cancer Classifier Post-Op*, which provide patients and their physicians valuable information so that they may make the best treatment decisions at the time of biopsy and after RP. Decipher's technology platform is a proven foundation, and through Decipher GRID, can effectively and quickly bring more genomic tests to fruition for managing prostate cancer patients throughout the continuum of care. ■

Dr Abdollah is a GenomeDX Biosciences advisor/consultant, and received an honorarium for this work.

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MAIN POINTS

- The most optimal treatment strategy for patients with prostate cancer (PCa) is a subject of controversy and continuous research. Although overdiagnosis and overtreatment of men with low-risk tumors is a concern, undertreatment of patients with high-risk tumors is also a problem. Moreover, in cases where active treatment is indicated, the initial treatment strategy and most appropriate sequence of treatments is not always clear.
- The uncertainties in treating PCa are mainly derived by the inability to accurately identify the natural history and aggressiveness of the tumor at an individualized level. To address this issue, many PCa risk stratification methods have been proposed based on clinical and pathological characteristics of the disease. Although these models have improved the ability to evaluate and predict the aggressiveness of PCa, their performance in many cases is still suboptimal.
- Current risk stratification methods are limited because they are unable to distinguish individual risk for patients who present with similar pathology. To overcome this limitation, genomic markers have been proposed as a complementary tool to these models. These markers offer the advantage of capturing genomic information specific to each patient's tumor that is beyond the reach of the routinely available clinical and pathologic characteristics of the disease, such as tumor stage, grade, and prostate-specific antigen (PSA) value.
- The Decipher® Prostate Cancer Test (GenomeDx Biosciences, San Diego, CA) is a genomic test that serves as a prognostic marker of cancer control outcomes in patients newly diagnosed with localized PCa at the time of biopsy, as well as patients who have undergone radical prostatectomy. Based on the expression pattern of 22 RNA markers in the biopsy or the radical prostatectomy specimen, it allows risk stratification of patients to predict likelihood of metastases and cancer-specific mortality; helps guide initial treatment strategy in the pretreatment setting; helps determine the need for adjuvant versus salvage radiotherapy based on a discrete cut-off score; and, in patients who have already had a biochemical recurrence, it can guide decisions regarding the need for early/multimodal salvage therapy versus salvage radiotherapy alone.
- Decipher adds important prognostic information to routinely available clinicopathological variables. This can greatly improve the accuracy of predicting patient outcomes, and can significantly improve clinical decision making in the pretreatment setting and the setting of multimodal treatment for patients with postsurgical adverse pathologic characteristics.

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