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INVITED REVIEW

Prostate Cancer

Clinically available RNA profiling tests of prostate tumors: utility and comparison

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In the postscreening era, physicians are in need of methods to discriminate aggressive from nonaggressive prostate cancer (PCa) to reduce overdiagnosis and overtreatment. However, studies have shown that prognoses (e.g., progression and mortality) differ even among individuals with similar clinical and pathological characteristics. Existing risk classifiers (TMN grading system, Gleason score, etc.) are not accurately enough to represent the biological features of PCa. Using new genomic technologies, novel biomarkers and classifiers have been developed and shown to add value to clinical or pathological risk factors for predicting aggressive disease. Among them, RNA testing (gene expression analysis) is useful because it can not only reflect genetic variations but also reflect epigenetic regulations. Commercially available RNA profiling tests (Oncotype Dx, Prolaris, and Decipher) have demonstrated strong abilities to discriminate PCa with poor prognosis from less aggressive diseases. For instance, these RNA profiling tests can predict disease progression in active surveillance patients or early recurrence after radical treatments. These tests may offer more dependable methods for PCa prognosis prediction to make more accurate and personal medical decisions.

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INTRODUCTION

Prostate cancer (PCa) has become the second leading cause of cancer-related death among men, with an estimated 914 000 new cases and 258 000 deaths worldwide every year.[1] This makes PCa a major public health problem worldwide.

The introduction of prostate-specific antigen (PSA) testing has provided a method for early detection of PCa and has been associated with a decline in PCa mortality; however, it has also been associated with a widespread problem of overdiagnosis and overtreatment of the non-aggressive PCa.[2] To solve this problem, active surveillance (AS) is recommended for patients with PCa cases that are at low-risk of progressing.[3] However, studies have found that the accuracy of available risk assessment tools (based on clinical information, tests such as PSA, Gleason score of biopsy, etc.) should be challenged.[4] For example, a proportion of up to 60% of patients with preoperational low-risk PCa were found to have higher grades of disease after surgery.[5–7] This raises concerns of potential for missed-treatment using AS for patients with high-grade diseases in which curative treatment would be necessary. However, the prognosis of patients after radical treatments varies widely. For instance, studies have shown that approximately 70% of patients who undergo radical prostatectomy, who are at high-risk for aggressive disease (with a high Gleason score, extraprostatic extension, seminal vesicle invasion, or having positive lymph node) would not die of PCa after 15 years.[8] In addition, several studies have suggested that patients with adverse pathology outcomes may be cured by surgery alone and that adjuvant therapy would not be necessary for all of them.[9,10]

To address the issue of being unable to accurately predict PCa prognosis, novel biomarkers have been shown to determine whether PCa is aggressive and to predict poor prognosis.[11–13] In addition, new approaches that utilize new genomic technologies can assess to genetic alterations and epigenetic events. Among them, RNA testing (gene expression analysis) is considered highly useful, for reflecting not only genetic variations but also epigenetic regulations. Several RNA tests have been approved for clinical use in prostate cancer and have been found to add value to clinical and pathological risks for prostate cancer progression. In this review, we focus on the value of commercially available RNA profiling tests in precision medicine practice for PCa.

COMMERCIALLY AVAILABLE RNA PROFILING PANELS FOR PROSTATE CANCER

Oncotype Dx

Oncotype Dx Prostate Cancer Assay is a multigene expression assay based on a real-time polymerase chain reaction (RT-PCR) technique developed by Genomic Health Inc., Redwood City, CA, USA. The assay measures expression of 17 genes using approximately 1 mm of fixed paraffin-embedded (FPE) prostate biopsy tissue. After assessing gene expression, a Genomic Prostate Score (GPS) is calculated. Among these 17 genes, 12 are cancer-related, representing a stromal response pathway (*BGN*, *COL1A1*, and *SFRP4*), an androgen signaling pathway (*AZGP1*, *KLK2*, *SRD5A2*, and *FAM13C*), a cellular organization pathway (*FLNC*, *GSN*, *TPM2*, and *GSTM2*) and a proliferation pathway (*TPX2*). The remaining five genes are housekeeping genes, including *ARF1*, *ATP5E*, *CLTC*, *GPS1*, and *PGK1*. Previous studies suggest that this assay could accurately predict PCa recurrence after radical prostatectomy (RP) or PCa progression in active surveillance (AS) patients, which could help make the decision

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regarding further treatment (e.g., adjuvant therapy after RP, radical treatment for patients undertaking AS).[14,15]

During discovery period, 727 genes were first evaluated in 441 patients (111 of whom had a clinical recurrence and 45 of whom died of PCa) who underwent RP from 1987 to 2004 at the Cleveland Clinic in Cleveland, Ohio, USA. The associations of these genes with Gleason score (GS) patterns and PCa recurrence after surgery were investigated. Eighty-one of 727 genes with the highest differential expression ($P < 0.10$) were included in further analysis under the following criteria: (1) added value to American Urological Association (AUA) risk stratification system and Cancer of the Prostate Risk Assessment Score (CAPRA-S); (2) were significantly associated with PCa death and adverse pathology at RP; (3) represented carcinogenesis pathways, or *ER* and *AR*. The associations of these 81 genes with GS and PCa recurrence were evaluated in a 167 biopsy population, confirming that 58 genes involved in six biological pathways were significantly associated with aggressive disease. Finally, 12 cancer-related genes and five housekeeping genes were used to build a scoring model of GPS based on consistency of the testing.[14]

A summarization of Oncotype Dx studies is shown in **Table 1**. Oncotype Dx has been shown to add value to the prediction of PCa recurrence after RP. In the 167 biopsy population, investigators found that GPS was an independent predictor when adjusted for AUA group. In the low-risk AUA group, the 10-year risk of clinical recurrence was 7.0% for patients with high GPS, which was 3 times higher than that of the patients with low GPS. In the AUA high-risk group, in which patients are considered to have a high probability of recurrence, the 10-year recurrence rates varied from 6.2% to 28.6% for patients with different levels of GPS.[14] In a validation study that consisted of 395 patients who met AS criteria but underwent RP, GPS was able to discriminate high-grade from low-grade prostate cancer in various clinical risk groups including CAPRA-S and National Comprehensive Cancer Network (NCCN) risk groups.[14] This indicates that the Oncotype Dx GPS might also be able to predict adverse pathology and high-risk prostate cancer in an AS population and may be able to supplement other clinical and pathological information to develop personalized AS plans for PCa. Further analysis showed that combining CAPRA-S and GPS might bring even more benefit, leading to fewer unnecessary treatments without increasing the number of high-risk PCa cases left untreated.[14] Another validation study was performed with a median follow-up of 5.2 years by Cullen *et al.* The study indicated that GPS had prediction value for time to biochemical recurrence (BCR) of PCa, time to metastasis and adverse pathology after RP (GS pattern ≥4) when adjusting for NCCN risk group.[15] In addition, the distributions of GPS were similar in different races such as African American and Caucasian.[15] Therefore, researchers suggested that the Oncotype Dx GPS could predict cancer recurrence after RP and PCa progression for AS patients and could help further inform personalized medical decision making to RP patients and AS patients.

Prolaris

It has been shown that the expression of cell cycle progression (CCP) genes varies among different types of cells and reflects the pattern of mitosis.[16] Cancer cells, especially aggressive cancer cells, will transcribe more CCP genes than normal cells due to continuous proliferation. Thus, CCP gene expression could reflect tumor biology (i.e., the more aggressive the tumor is, the more CCP genes are expressed), which may be useful for predicting the outcomes of cancers. This has been demonstrated in other types of malignancies, as well.[17–19] The Prolaris PCa test (Myriad Genetics Inc., Salt Lake City, UT, USA) was designed based on this theory to test the expression of 31 CCP genes (*FOXM1*, *CDC20*, *CDKN3*, *CDC2*, *KIF11*, *KIAA0101*, *NUSAP1*, *CENPF*, *ASPM*, *BUB1B*, *RRM2*, *DLGAP5*, *BIRC5*, *KIF20A*, *PLK1*, *TOP2A*, *TK1*, *PBK*, *ASF1B*, *C18orf24*, *RAD54L*, *PTTG1*, *CDCA3*, *MCM10*, *PRC1*, *DTL*, *CEP55*, *RAD51*, *CENPM*, *CDCA8*, and *ORC6L*) and 15 housekeeping genes using quantitative RT-PCR. After testing, a CCP score is calculated for predicting cancer recurrence, metastases, PCa-specific mortality in RP patients, and PCa progression in AS patients.[19–23]

A total of 126 CCP genes chosen from the Gene Expression Omnibus database were evaluated. According to the database, genes with the highest differential expression (compared to the mean expressions of the 126 CCP genes) were selected, and further evaluated in multivariable analyses. Thirty-one of the 126 CCP genes were ultimately selected for having robust and independent abilities to measure levels of cell proliferation. In addition to these CCP genes, 15 housekeeping genes were included in the panel.[19]

Several studies have evaluated the clinical utility of Prolaris (**Table 2**). For patients that underwent RP, CCP score had better prediction abilities for BCR and PCa-specific mortality than any other clinical or pathological variables. One study found that 10-year BCR rates and PCa-specific mortality rates significantly increased if the patient had a higher CCP.[19] For patients who received other radical therapies (e.g., external beam radiation therapy), CCP score was considered an independent risk factor of both BCR and PCa-specific mortality when adjusting to other clinical variables.[20,23] The predictive value of Prolaris CCP scores was even further improved when combined with clinical variables, such as CAPRA-S risk group.[20] In addition, the most recent study indicated that CCP could predict

Table 1: Summary of Oncotype Dx PCa assay studies

Study	*Number of cases*	*Tissue*	*Endpoint*	*Results*	*Conclusion*
Klein *et al.*[14]	167	Biopsy	Adverse pathology after RP; clinical recurrence after RP	GPS was significantly associated with clinical recurrence after RP when adjusting AUA risk group	GPS may conduct personalized medical decision on RP patients (whether or not should the patient receive early adjuvant therapy after RP) and AS patients (predict the probability of adverse pathology that will suggest the necessity of early intervention)
	395	Biopsy	Adverse pathology after RP	GPS could well predict adverse pathology after RP when adjusting CAPRA-S and NCCN risk group The addition of GPS to CAPRA-S could improve AUC in ROC analysis and net benefit in decision-curve analysis	
Cullen *et al.*[15]	431	Biopsy	BCR; metastatic recurrence; adverse pathology after RP	GPS had prediction value for time to biochemical recurrence of PCa (BCR), time to metastases and adverse pathology after RP (GS pattern ≥4) when adjusting NCCN risk group The distributions of GPS were similar in different ancestors (African American and Caucasian)	

AS: active surveillance; AUA: American Urological Association; AUC: area under the receiver operating curve; BCR: biochemical recurrence; CAPRA-S: Cancer of the Prostate Risk Assessment Score; GPS: Genomic Prostate Score; NCCN: National Comprehensive Cancer Network; ROC: receiver operating curve; RP: radical prostatectomy; PCa: prostate cancer; GS: Gleason score

Table 2: Summary of Prolaris studies

Study	*Study population*	*Tissue**	*Endpoint*	*Results*	*Conclusion*
Cuzick *et al*.[19]	366 RP patients treated without neoadjuvant therapies before surgery	RP tissue	BCR (PSA >0.3 ng ml^{-1}); PCa-specific mortality	Median follow-up time: 9.4 years; CCP score could independently predict BCR: 10-year BCR rates for patients with CCP score >2, 1 <CCP score ≤2, 0 <CCP score ≤1 and CCP score ≤0, were 83.3%, 61.9%, 44.5%, and 23.7%, respectively, CCP score could independently predict PCa-specific mortality (HR=2.99, *P*=0.0007)	CCP score from Prolaris PCa test is significantly associated with BCR (in patients received RP), metastasis (in patients received RP) and PCa-specific mortality (in patients received AS or RP). These indicate that CCP may help make or change clinical decisions
	337 patients with localized PCa diagnosed by TURP (age <76 years old), met watchful waiting criteria	TURP tissue	PCa-specific mortality	Median follow-up time: 9.8 years; CCP score could predict PCa-specific mortality: 10-year PCa-specific mortality rates for patients with CCP score >2, 1< CCP score ≤2, 0< CCP score ≤1 and CCP score ≤0, were 78.3%, 34.6%, 13.1%, and 2.2%, respectively	
Cuzick *et al*.[21]	349 PCa patients received conservative treatment (watchful waiting, active surveillance, etc.)	Biopsy tissue	PCa-specific mortality	Median follow-up time: 11.8 years; CCP score was an independent risk factor for PCa-specific mortality: 10-year death rates differ in patients with different level of CCP score, which is 19.3% (CCP score <0), 19.8% (CCP score 0–1), 21.1% (CCP score 1–2), 48.2% (CCP score 2–3), and 74.9% (CCP score >3), respectively	
Cooperberg *et al*.[20]	413 RP patients	RP tissue	BCR (two PSA ≥0.2 ng ml^{-1} or received any salvage treatment)	CCP score was significantly associated with BCR (*P*=0.001), even when stratified into different CAPRA-S group (*P*=0.003 when CAPRA-S is 0–2; *P*=0.01 when CAPRA-S ≥3) The combination of CCP and CAPRA-S had added predictive value upon CAPRA-S alone (*P*<0.001)	
Freedland *et al*.[23]	141 PCa patients received external beam radiation therapy	Biopsy tissue	BCR; PCa-specific mortality	CCP score was significantly associated with BCR (multivariable *P*=0.034) and PCa-specific mortality (*P*=0.013)	
Bishoff *et al*.[22]	582 PCa patients diagnosed by biopsy	Biopsy tissue	BCR; metastasis	In multivariate analysis, CCP score was found to be a strong predictor of BCR (HR: 1.47, *P*=4.7×10^{-5}) and metastases (HR: 4.19, *P*=8.2×10^{-6})	

*Dissection of the formalin-FPE tissue to obtain cancer tissue sections by instructions from pathologists. BCR: biochemical recurrence; CAPRA-S: Cancer of the Prostate Risk Assessment Score; CCP: cell cycle progression; HR: hazard ratio; RP: radical prostatectomy; TURP: transurethral resection of prostate; PSA: prostate-specific antigen; PCa: prostate cancer

metastasis after RP (HR: 4.19, $P = 8.2 \times 10^{-6}$).[22] CCP also predicted prognosis of AS (or "watchful waiting") patients. In a watchful waiting cohort where patients were occasionally diagnosed with PCa via TURP, investigators found that CCP score (from TURP tissue) was able to predict PCa mortality after a median follow-up time of 9.8 years. They found that 10-year PCa-specific mortality rates for patients with CCP score >2, 1< CCP score ≤2, 0< CCP score ≤1 and CCP score ≤0, were 78.3%, 34.6%, 13.1% and 2.2%, respectively.[19] A similar result was also observed in another cohort after a median follow-up time of 11.8 years, where patients were diagnosed with low clinical risk PCa via biopsy and received conservative treatments (e.g., watchful waiting, active surveillance, etc.).[21] Thus, studies have suggested that CCP score from the Prolaris PCa test added predictive value for PCa prognosis for clinical and pathological risk factors in both RP patients and AS patients.

Decipher

Decipher is a genetic classifier that uses an RNA profiling panel of 22 genetic markers. Before testing, microdissection of the formalin-FPE tissue from RP should be performed to obtain tissue sections with highest Gleason grade. Total RNA is extracted and tested using the Decipher panel. The panel is designed to evaluate the expression of various genetic markers associated with specific of biological processes, including cell proliferation and differentiation processes (*LASP1*, *IQGAP3*, *NFIB*, and *S1PR4*); cell structure, adhesion, and motility processes (*THBS2*, *ANO7*, *PCDH7*, *MYBPC1*, and *EPPK1*); the immune response process (*TSBP*, *PBX1*); cell cycle progression and mitosis processes (*NUSAP1*, *ZWILCH*, *UBE2C*, *CAMK2N1*, and *RABGAP1*); and other unknown functional processes (*PCAT-32*, *GLYATL1P4/PCAT-80*, and *TNFRSF19*); as well as three unidentified segments. The genetic markers are located in or near the gene segments (e.g., intron, exon, 3'UTR, and noncoding transcript). A genetic classifier (GC) score is then calculated, which may predict PCa metastasis and cancer-specific mortality after RP. The panel was developed by GenomeDx Biosciences Inc., Vancouver, BC, Canada.[24] Previous studies have indicated that GC score may be able to predict early metastasis and cancer-specific mortality after RP, which leads to the potential to provide earlier intervention for these patients.[24–30]

A nested case–control study was performed in a subset of the population from the Mayo Clinic Radical Prostatectomy Tumor Registry from 1987 to 2001 who received RP for primary PCa as first-line treatment. A total of 639 patients were included, of which 545 patients had available samples. One hundred ninety-two patients without evidence of disease progression after at least 7 years of follow-up were identified as the control group. The remaining 353 patients had biochemical recurrences or metastases during follow-up and were identified as the case group. The investigators tested the tissue samples using an exon transcriptome chip containing approximately 1.4 million selection regions including coding and noncoding regions. Initially, 18 902 differentially expressed RNA regions were observed. Using logistic regression and random forest machine learning algorithm methods, a final set of 22 markers were selected to calculate GC scores.[24]

The major findings from studies of Decipher are shown in **Table 3**. Studies have indicated that GC scores from Decipher could predict BCR and metastasis after RP. In a retrospective case–control study based on a population of 192 BCR/metastasis patients and 353 patients without BCR/metastasis, GC had a better predictive utility for BCR/metastasis (AUC = 0.75) than other clinical or pathological variables. Investigators also found that GC had better predictive value than other existing biomarkers (e.g., PCA3, PSA, PSMA, ERG, etc.).[24] In studies that investigated high-risk patients who received RP, the 5-year

Table 3: Summary of decipher studies

Study	*Study population*	*Tissue*	*Endpoint*	*Results*	*Conclusion*
Erho *et al*.[24]	192 with BCR/ metastasis versus 353 without BCR/ metastasis	RP tissue*	BCR/metastasis; PCa-specific survival; overall survival	GC (from Decipher) could independently predict BCR/ metastasis (multivariate logistic regression OR=1.36, P<0.001; AUC=0.75, higher than other clinical or pathological variables) PCa-specific survival: low GC 6.9 years versus high GC 2.9 years (P=0.003) Overall survival: low GC 4.98 years versus high GC 2.5 years (P=0.03) GC had better prediction utility for clinical outcomes than other biomarkers	GC can well predict PCa metastasis and PCa-specific mortality and may conduct personalized early intervention (adjuvant therapy or salvage therapy) for high-risk patients after RP to reduce metastasis rate and improve survival
Ross *et al*.[26]	85 BCR patients after RP	RP tissue*	Metastasis after BCR	GC could well predict metastasis after BCR Low GC with 8% metastasis versus high GC with 40% metastasis (P=0.001) AUC=0.82, highest than other clinical or pathological variables	
Karnes *et al*.[27]	219 locally advanced PCa after RP[a]	RP tissue*	Metastasis after RP	GC could well predict metastasis after RP for patients with locally advanced PCa AUC was 0.79 for predicting 5-year metastasis after RP 5-year metastasis rates were 2.4% for patients with low GC, 6.0% for intermediate GC and 22.5% with high GC (P=0.001)	
Cooperberg *et al*.[25]	185 high-risk PCa after RP[b]	RP tissue*	PCa-specific mortality	28/185 had PCa-specific mortality. AUC was 0.78 for predicting PCa-specific mortality. The combination of GC and CAPRA-S could improve the prediction utility. Patients with high GC and high CAPRA-S had a cumulative incidence of 10-year PCa-specific mortality of 45%	
Ross *et al*.[28]	260 patients received RP	RP tissue*	Regional or distant metastasis; BCR; PCa-specific mortality.	99/260 experienced metastasis GC was significantly associated with BCR, metastasis and PCa-specific mortality (P=0.01) 10-year metastasis rates were 12% for patients with low GC and 47% for patients with high GC GC had added value for predicting metastasis upon Eggener and CAPRA-S risk groups	
Klein *et al*.[29]	169 patients received RP[c]	RP tissue*	Rapid metastasis (progress to metastatic disease within 5 years after RP)	GC from decipher was a significant predictor for rapid metastasis (OR=1.48, P=0.018) in multivariable analysis, had highest AUC of 0.77	
Den *et al*.[30]	139 patients with pT3 or positive margin after RP and received radiation therapy thereafter	RP tissue*	Biochemical failure (like BCR, but with subsequent PSA ≥0.4 ng ml^{-1}) and metastasis	GC had added value for predicting biochemical failure and metastasis when being combined with clinical risk prediction tools. 8-year biochemical failure rates for patients with low (GC <0.4), intermediate (0.4≤ GC ≤0.6), and high GC (GC >0.6) were 21%, 48%, and 81% (P=0.0001), respectively. 8-year metastasis rates were 0%, 12%, and 17%, respectively (P=0.032)	

*Microdissection of the formalin-FPE tissue to obtain tissue sections with highest Gleason grade; [a]PSA >20 ng ml^{-1}, pathologic GS ≥8, stage pT3b, or Mayo Clinic nomogram score ≥10; [b]PSA >20 ng ml^{-1}, pathologic GS ≥8, or stage pT3b; [c]PSA >20 ng ml^{-1}, pathologic GS ≥8, or stage pT3b, pathologic node negative, undetectable post-RP PA, no neoadjuvant or adjuvant therapy; minimum of 5-year follow-up. AUC: area under the receiver operating curve; BCR: biochemical recurrence; CAPRA-S: Cancer of the Prostate Risk Assessment Score; GC: genomic classifier; OR: odds ratio; RP: radical prostatectomy; PCa: prostate cancer

metastasis rates differed among patients with low GC (<0.4, 2.4%), intermediate GC (0.4–0.6, 6%), and high GC (>0.6, 22.5%); therefore, GC was found to be a significant predictor for metastasis.[27,29,30] Ross *et al*. also observed that the 10-year metastasis rate increased for patients with higher GC (GC <0.45, 10-year metastasis rate = 12%; GC >0.5, 10-year metastasis rate = 47%).[26,28] GC could also predict PCa-specific mortality and overall survival. Erho *et al*. found that RP patients with GC ≤0.5 had a longer median PCa-specific survival (6.9 *vs* 2.9 years, P = 0.003) and overall survival (4.98 *vs* 2.5 years, P = 0.03) than patients with GC >0.5.[24] The prediction ability (assessed using AUC) of CG for PCa-specific mortality was 0.78.[25] In addition, a study found that patients with high GC and high CAPRA-S have a cumulative 10-year PCa-specific mortality of up to 45%.[25] Taken together, these findings indicate that Decipher GC scores have the potential to predict PCa metastasis and PCa-specific mortality, allowing for early adjuvant or salvage therapy for high GC patients after RP to improve individual prognoses.

CONCLUSIONS

Uses of three commercially available RNA-based testing panels are summarized in **Table 4**. Although these RNA profiling panels have shown promising results in regards to clinical utility, several limitations are worth noting: (1) the current studies are retrospective with relatively small sample sizes, so larger-scale prospective randomized trials are necessary for validation; (2) RNA quality varies among panels (e.g., microdissection is needed for Decipher [some medical center may not have the equipment], while for Prolaris, tissue extraction relies on the instruction from pathologist, which will lead to heterogeneity of the testing results); and (3) the relatively high prices (~$1500–2000 US dollars per test if not covered by insurance) limit potential use of the panels, and it will be necessary to further evaluate their cost-effective values.

Table 4: Uses of different commercially available RNA testing panel

	Decipher	*Oncotype Dx*	*Prolaris*
Cancer recurrence after RP (BCR)	-	Yes	Yes
Metastasis after RP	Yes	-	Yes
PCa-specific mortality after RP	Yes	-	Yes
PCa progression (PCa-specific mortality) in AS population	-	Yes	Yes

AS: active surveillance; BCR: biochemical recurrence; RP: radical prostatectomy; PCa: prostate cancer

Nevertheless, these commercialized RNA profiling tests provide physicians and patients with more choices for more personalized treatment rather than following one-size-fits-all clinical guidelines. Further investigations are necessary to evaluate the clinical values of these RNA-based tests (e.g., whether they can truly predict prognoses in prospective, large-scale studies; the cutoff value of the genetic classifiers) and benefits (whether they can reduce overtreatment of nonaggressive PCa and increase early treatment of aggressive PCa, as well as their medical cost-effective values).

COMPETING INTERESTS

There is no competing financial interest.

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