Prostate cancer genomics: comparing results from three molecular assays

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Introduction: *OncotypeDx, Prolaris, and Decipher have each been validated to predict outcomes and guide treatment for patients with clinically localized prostate cancer, but they have yet to be compared to one another. Here we assess the correspondence between the results of each.*

Materials and methods: *We performed a retrospective chart review to identify patients who underwent at least two of the three genomic tests at Hartford Hospital between 2014 and 2017. We used test-specific definitions of a favorable prediction for each to compare the percent agreement between each pair. Results were also compared to treatment recommendations based on current National Comprehensive Cancer Network (NCCN) guidelines. We compared pair-wise agreement using Cohen's kappa (K).*

Results: *Twenty-two patients received at least two different genomic tests. For 12 patients who received both the Decipher and Prolaris, % agreement and K were 66.7 and 0.31 (p = .276), respectively. For 8 patients who received both Prolaris and Oncotype DX, % agreement and K were 75 and 0.39 (p = .168), respectively. Two patients received both Decipher and Oncotype DX, yielding 50% agreement and an incalculable K. For Prolaris versus NCCN, % agreement and K were 75 and .21, respectively (p = .117; n = 20). For Decipher versus NCCN, % agreement and K were 60 and .15, respectively (p = .268; n = 15). For Oncotype DX versus NCCN (n = 10), agreement was 50%, K was incalculable.*

Conclusions: *Notable differences exist in prognostic outcomes obtained from OncotypeDx, Prolaris, and Decipher.*

Key Words: prostatic neoplasms, genomics, Decipher, Prolaris, Oncotype Dx

Introduction

The American Cancer Society estimates 164,690 new cases of prostate cancer and 29,430 deaths from the disease in 2018.[1] Standard of care is controversial, especially given the heterogeneous nature of this disease, and up to 98.9% of patients are alive at 5 year follow up.[2] A recent multi-center randomized control trial revealed no significant difference in 10 year mortality outcomes between radical prostatectomy, radiation therapy, and active surveillance, suggesting that aggressive therapy may be over-utilized.[3] Furthermore, although the prostate-specific antigen (PSA) screening tool has been associated with a significant decrease in prostate cancer mortality, it has consequently led to over-treatment and over-diagnosis for some patients. It is therefore imperative to develop new tools to better stratify patients according to the safest and most effective treatment strategy possible. Recently, the advent of molecular analytics has provided a means to better classify prostate tumors and their prognosis according to their genetic profile. Three unique tests (OncotypeDx, Prolaris, and Decipher) have now been validated and approved to predict outcomes and guide treatment for patients with clinically localized prostate cancer.

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OncotypeDx. The OncotypeDx assay (Genomic Health, Inc., Redwood City, CA, USA) predicts risk of high grade or non-organ–confined disease and incorporates the patient's National Comprehensive Cancer Network (NCCN) risk group (very low, low, intermediate, high and very high).[4] It was established using samples of prostate tumors from prostatectomy and biopsies, which provide a multigene-expression–based signature known as the Genomic Prostate Score (GPS). In a validating study, 39% of genes analyzed predicted clinical recurrence and 27% of genes predicted aggressive disease after controlling for confounders, including Gleason score.[5] A panel of 17 genes representing multiple cellular pathways are now combined in an assay designed to aid physicians and patients in making appropriate treatment decisions (i.e., active surveillance (AS) versus immediate treatment). Ten year prostate cancer mortality and metastasis rates after surgery have recently been added as outcomes but were not available during the time period of this study.

Prolaris. The Prolaris assay (Myriad Genetics, Inc., Salt Lake City, UT, USA) utilizes RNA cell cycle progression data as opposed to multi-gene analysis. A 46 gene signature generates the Cell Cycle Progression (CCP) score, for which a single unit increase is significantly associated with a 2.08 increase in the hazard ratio for death from prostate cancer. Combining the CCP score with the CAPRA score increases the area under the curve (AUC) and the predictive value of the test.[6] The Prolaris test predicts the 10 year prostate cancer mortality for patients delaying initial curative therapy.[7] The 10 year prostate cancer metastasis rate after definitive therapy was recently added as a predictive outcome but was not available during the time period of this study.

Decipher. The Decipher assay (GenomeDx Biosciences, San Diego, CA, USA) predicts the rates of high grade disease (grade groups 3, 4, 5) at surgery as well as the 5 year prostate cancer metastasis rate and 10 year prostate cancer specific mortality rate after surgery. Lastly, the Decipher prostate cancer assay yields the risk of early metastases within 5 years after surgery or within 3 years after biochemical recurrence and the risk of mortality within 10 years after surgery. Twenty-two genes representing cell cycle proliferation, adhesion and motility, immune modulation, and androgen signaling are analyzed, generating a Decipher score ranging from 0-1.[8] In a recent validation study this assay outperformed each of the NCCN clinical risk groups, Gleason score, and preoperative PSA in the risk-stratification of patients using prostate biopsy specimens. In fact, every 10% increase in the biopsy Decipher score was associated with a 1.72 increase in the hazard ratio for patients with prostate cancer.[9]

Although these prognostic tools have been validated individually, they have yet to be compared to one another. In this study, we assess the correspondence between the results of each. We examined how often each assay supported AS when an option based on NCCN risk stratification. Finally, for patients who ultimately underwent surgery, we compared the rates of favorable/unfavorable assay outcomes with outcomes based on pathology.

Materials and methods

We performed a retrospective chart review to identify patients at Hartford Hospital who had prostate biopsy or post-prostatectomy specimen evaluations using at least two of three genomic assays (Decipher, Prolaris, or OncotypeDx) between 2014 and 2017. Results from the three assays were abstracted from Hartford Hospital's electronic medical records or from the medical charts.

A favorable prediction for each genomic test was defined as follows: Decipher and Prolaris: ≤ 3% likelihood of 10 year prostate cancer mortality; Oncotype DX: > 70% likelihood of organ confined, grade group 1 or 2 disease at surgery (as determined through pathology). Patients with favorable results were considered to meet active surveillance (AS) criteria by genomic standards. These predictions were also compared to the appropriateness of AS based on NCCN guidelines, which include favorable intermediate risk patients. We calculated the percent (%) agreement between each pair and we used Cohen's kappa (κ)[10] to obtain the proportion of agreement *over and above* chance, with moderate agreement being defined as $\kappa \geq .6$. SPSS version 21 was used for statistical analyses.

Patient demographics, including age and race; treatment information, and clinical biopsy and pathological stage and grade were collected from our IRB approved Prostate Cancer Registry. The hospital's electronic medical records were used to supplement missing data and to confirm or correct any questionable data points in the data set.

Results

A total of 22 patients received at least two different genomic tests: 12 received both Decipher and Prolaris, 8 received Prolaris and Oncotype DX and 2 received both Decipher and Oncotype DX. Demographic and clinical measures are presented in Table 1. Overall, 17 patients met NCCN criteria for very low or low risk, 3 met criteria for favorable intermediate risk and 2 met criteria for unfavorable intermediate risk.

TABLE 1. **Demographics and clinical characteristics (n = 22)**

Age at biopsy (median; IQR)	61.50 (58.0-69.3)
PSA (ng/mL)((median; IQR)	4.85 (4.0-6.2)
Gleason grade group (n, %)	
1	17 (77.3)
2	5 (22.7)
cTNM (n,%)	
T1c	17 (77.3)
T2a	4 (18.2)
T2c	1 (4.5)

PSA is the prostate-specific antigen measure that prompted the biopsy leading to genomic testing

Table 2 presents agreement statistics between each genomic test and NCCN risk group. Table 3 presents agreement statistics between the three assays. Results from surgical pathology were available for 8 patients. Table 4 presents the agreement between the results of each test and results from surgical pathology.

For 12 patients who received both the Decipher and Prolaris, % agreement and κ were 67% and 0.31 (p = .276), respectively. For 8 patients who received both Prolaris and Oncotype DX, % agreement and κ were 75% and 0.39 (p = .168), respectively with Prolaris tending to favor AS over surgery. Two patients received both Decipher and Oncotype DX, yielding 50% agreement and an incalculable κ. NCCN guidelines included AS as an option for 21 out of 22 patients. For Prolaris versus NCCN, % agreement and κ were 75%

TABLE 2. **Agreement with National Comprehensive Cancer Network risk categories**

Test	n	% agree	kappa	p value
Prolaris	20	75%	0.21	0.117
Decipher	15	60%	0.15	0.268
Oncotype DX	10	50%	-	-

TABLE 3. **Agreement between tests**

Tests	n	% agree	kappa	p value	Δ Definition favorable test
Decipher vs. Prolaris	12	67%	0.31	0.276	62%
Prolaris vs. Oncotype DX	8	75%	0.39	0.168	89%
Decipher vs. Oncotype DX	2	50%	-	-	50%

TABLE 4. **Agreement between each test and results of surgical pathology**

Patient	Gleason group	Stage	Margin	Oncotype	Prolaris	Decipher
1	2	T3aN0	Negative	Unfavorable	-	Unfavorable
2	2	T2cN0	Negative	Unfavorable	-	Favorable
3	2	T3bN1	Positive	-	Unfavorable	Favorable
4	2	T2cN0	Negative	-	Favorable	Favorable
5	2	T2cN0	Positive	-	Favorable	Unfavorable
6	2	T3bN0	Negative	-	Favorable	Favorable
7	3	T3bN0	Negative	-	Unfavorable	Favorable
8	4	T3bN0	Positive	-	Unfavorable	Unfavorable

and .21, respectively (p = .117; n = 20). For Decipher versus NCCN, % agreement and κ were 60% and .15, respectively (p = .268; n = 15). For Oncotype DX versus NCCN (n = 10), agreement was 50%, κ was incalculable.

Discussion

For many years, clinicians have used some combination of clinical stage, PSA, Gleason score, and tumor volume to make treatment recommendations. These clinical factors have been incorporated into risk groups (e.g., NCCN,[4] CAPRA,[6] AUA[11]), tables and nomograms (e.g., Partin,[12] MSKCC[13]) to better stratify patients and aid in treatment recommendations. However, significant heterogeneity exists between patients who seem to be similar clinically. To meet these challenges, the goal of all genomic/molecular testing is to better stratify prostate cancer patients and aid in treatment recommendations.

Our data indicate that notable differences exist in favorable prognostic outcomes obtained from Oncotype Dx, Prolaris, and Decipher. Comparisons of the three assays included in this report are complicated because the assays do not provide the same predictive measures. For example, both Prolaris and Decipher provide a 10 year risk of mortality but these predictions are based on different initial treatment decisions. Prolaris and OncotypeDX each provide a percentile risk score within risk group but the risk groups differ slightly (e.g., AUA guidelines have 3 risk groups, NCCN guidelines have 5) and they differ on where the thresholds for stage are located. Nevertheless, we anticipated that the three assays would yield comparable results. Rather, it seems that for a patient struggling to make a decision between AS and definitive treatment, assay X might point toward AS while assay Y might point toward definitive treatment, complicating the decision process instead of clarifying it.

There are several obvious criticisms of this study. First, multiple tests were performed solely upon patient request. Clearly a randomized, prospective trial would be needed to better address how well the results of these various assays correspond. As with most tests and medications addressing similar cohorts, there is little commercial drive to perform such studies.

Second, we do not know the degree to which financial barriers precluded patients from undergoing these genomic tests. To our knowledge, Medicare did not deny coverage of any ordered genomic tests as all met NCCN standards for ordering. Commercial coverage varied considerably among our patients. This is also our experience for a single test ordered for appropriate clinical indications. In the face of denial, the current financial plans employed by the test manufacturers are such that they are affordable to most patients. However, it is certainly true some patients do not move forward with genomic testing after discussing finances with the caring urologist, but we do not track this data.

Third, as all of these assays yield different predictive outcomes, comparing the results is difficult. Even when the outcomes appear similar, the patient cohorts that were used to validate them are very different. For instance, both Prolaris and Decipher report 10 year prostate cancer specific mortality. However, in the Prolaris cohort, patients initially deferred definitive treatment though a significant number received treatment during the 10 year span. The Decipher cohort had all undergone radical prostatectomy.

Finally, none of the assays have a defined cut off, and we feel clinicians are at the early stages of identifying the most appropriate cut off for each. Prior to the availability of genomic studies, most clinicians obtained acceptable rates of adverse pathology for their patients considering active surveillance. We used the Partin tables and the MSKCC nomogram to determine the acceptable cut off points for these genomic assays.

Several questions remain. When using Prolaris, should we use a 3% prostate cancer-specific mortality rate at 10 year follow up? Should we devise a formula incorporating the rates of complications with definitive treatment or should we take into account the risk of death with conservative treatment? When we use Oncotype Dx and Decipher, what is an acceptable risk of adverse pathologic features (80%, 70%, 60%)? For Oncotype Dx, would a GPS score of 20 or 30 be acceptable? For Decipher, should we use a score of 0.45 or 0.60? Further studies are needed to help clinicians determine the most acceptable cut off points for each test. Using a CCR score of 0.8, Lin et al recently demonstrated that patients could be categorized into low and high risk groups for 10 year prostate cancer mortality, which may enable more appropriate selection of patients for AS.[14] If we were to change our cut off points even slightly, we might note that the rates of acceptance change considerably.

Despite these shortcomings, we feel our study illustrates an important point — that the genomic test and the chosen cut off point each may, not infrequently, lead a patient to different treatment decisions. Patients want to take the test that is going to tell them "the right thing to do." Unfortunately, such a test does not exist. However, understanding the differences between these tests and their rates of agreement will enable the clinician to better counsel the patient tasked with making the very difficult decision of whether to choose AS over definitive treatment strategies.

Conclusions

The prognostic outcomes obtained from OncotypeDx, Prolaris, and Decipher differ markedly; interpreting the results of these genomic tests can present significant challenges to both the clinician and patient.

Disclosure

This project did not receive support from funding agencies or industry. JW serves on the Speakers Bureau for Genomic Health and serves as a Consultant for Covidien. None of the other authors have anything to disclose. □

References

1. The American Cancer Society, Inc. Key statistics for prostate cancer. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html. Accessed August 9, 2018.
2. Howlader N, Noone AM, Krapcho M. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/. Accessed July 13, 2018.
3. Hamdy FC, Donovan JL, Lane JA et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375(15):1415-1424.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer. Version 3. 2016 Available from www.nccn.org. Accessed August 8, 2018.
5. Brand TC, Zhang N, Crager MR et al. Patient-specific meta-analysis of 2 clinical validation studies to predict pathologic outcomes in prostate cancer using the 17-gene genomic prostate score. *Urology* 2016;89:69-75.
6. Cooperberg MR, Pasta DJ, Elkin EP et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol* 2005; 173(6):1938-1942.
7. Cuzick J, Stone S, Fisher G et al. Validation of an RNA cell cycle progression score for predicting death from prostate cancer in a conservatively managed needle biopsy cohort. *B J Cancer* 2015;113(3):382-389.
8. Klein EA, Santiago-Jimenez M, Yousefi K et al. Molecular analysis of low grade prostate cancer using a genomic classifier of metastatic potential. *J Urol* 2017;197(1):122-128.
9. Klein EA, Haddad Z, Yousefi K et al. Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. *Urology* 2016;90:148-152.
10. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas* 1960;20:37-46.
11. Sanda MG, Cadeddu JA, Kirkby E et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. part I: risk stratification, shared decision making, and care options. *J Urol* 2018;199(3):683-690.
12. Tosoian JJ, Chappidi M, Feng Z et al. Prediction of pathological stage based on clinical stage, serum prostate-specific antigen, and biopsy Gleason score: Partin Tables in the contemporary era. *BJU Int* 2017;119(5):676-683.
13. Prostate Cancer Nomograms: Post-Radical Prostatectomy | Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/nomograms/prostate/post-op. Accessed August 9, 2018.
14. Lin DW, Crawford ED, Keane T et al. Identification of men with low-risk biopsy-confirmed prostate cancer as candidates for active surveillance. *Urol Oncol* 2018;36(6):310 e317-310 e313.