Update on Biomarkers for Prostate Cancer: Should I Drink the Kool-Aid?

Nathan Perlis, MD MSc

PMH Dialogues 2019 NOTL

Disclosures

- None pertaining to this talk

Overview

- Definition and aim of biomarkers
- Framework for evaluating biomarkers
- Review of main biomarkers used in localized prostate cancer

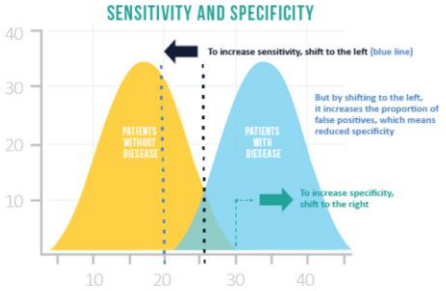
What's a Biomarker

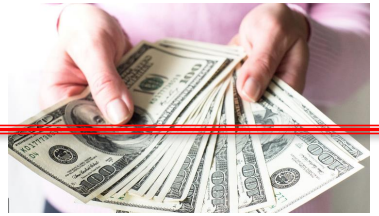
- WHO definition:
  - "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease"

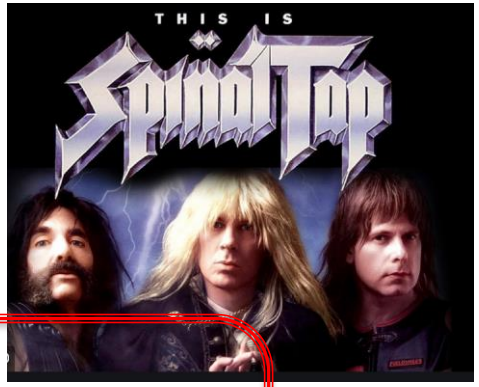
- In prostate cancer the term is often reserved for serum, urine or tissue tests clinically used to help with decision making or for prognostication
  - ? Re-biopsy, ? Add radiotherapy, etc.
  - Estimating survival

Biomarker = Test

- Test characteristics
  - SN, SP, PPV, NPV
- Cost
- Invasiveness
- Practicalities:
  - What does the read-out look like?
  - How will the result change your management?







EUROPEAN UROLOGY 73 (2018) 572–582

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European Association of Urology

Review – Prostate Cancer

Genomic Markers in Prostate Cancer Decision Making

Vito Cucchiara [a], Matthew R. Cooperberg [b], Marc Dall'Era [a], Daniel W. Lin [c], Francesco Montorsi [d], Jack A. Schalken [e], Christopher P. Evans [a,]*

[a] Department of Urology, School of Medicine, University of California, Davis, Sacramento, CA, USA; [b] Departments of Urology and Epidemiology & Biostatistics, University of California, San Francisco, San Francisco, CA, USA; [c] Department of Urology, University of Washington, Seattle, WA, USA; [d] Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy; [e] Department of Urology, Radboud University Medical Center, Nijmegen, The Netherlands

- Prognostic vs Predictive
  - Marginal benefit over PSA/clinical details
- Consider specific disease state where test is intended
  - Susceptibility biomarkers
  - Biomarkers of disease risk
  - Risk stratification biomarkers
  - Biomarkers for prediction of disease response

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PMCID: PMC6515282
PMID: 31013716

A Rich Array of Prostate Cancer Molecular Biomarkers: Opportunities and Challenges

Indu Kohaar,[1,2,*] Gyorgy Petrovics,[1,2,*] and Shiv Srivastava[2]

‣ Author information ‣ Article notes ‣ Copyright and License information Disclaimer

Table 1

Current Food and Drug Administration (FDA) or Clinical Laboratory Improvement Amendments (CLIA) approved blood-, urine-, and tissue-based biomarkers in prostate cancer.

Biomarker Test	Molecular Markers	Available as
Serum-based		
Prostate Serum Antigen (tPSA)	PSA	FDA
PHI (Beckman Coulter Inc., Brea, CA, USA)	Total PSA, fPSA, p2PSA	FDA
4K (OPKO lab, Miami, FL, USA)	Total PSA, fPSA, intact PSA, hK2	CLIA-approved
Urine-based		
PCA3 (Progensa) Hologic, Marlborough, MA, USA	*PCA3*	FDA
ExoDX Prostate (Intelliscore) Exosome Diagnostics Inc., Waltham, MA, USA	Exosomal RNA (*PCA3, ERG*)	CLIA-approved
MiPS (Detroit, MI, USA)	*PCA3* and *TMPRSS2-ERG* mRNA	CLIA-approved
SelectMDX (MDx Health, Irvine, CA, USA)	*HOXC6, DLX1*	CLIA-approved
Tissue-based		
ConfirmMDx (MDxHealth, Irvine, CA, USA)	DNA hypermethylation (*GSTP1; APC; RASSF1*)	CLIA-approved
Prolaris (Myriad Genetics, Salt Lake City, UT, USA)	mRNA expression; 31 genes (cell cycle progression)	FDA
Oncotype Dx (Genomic Health, Redwood City, CA, USA)	mRNA expression; 17 genes	CLIA-approved
Decipher (GenomeDx Biosciences, San Diego, CA, USA)	mRNA expression; 22 genes (cell proliferation, migration, tumor motility, androgen signaling, and immune system evasion)	CLIA-approved
Promark (Metamark, Cambridge, MA, USA)	Protein biomarker test (8 proteins)	CLIA-approved

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- Prognostic vs Predictive
  - Marginal benefit over PSA/clinical details
- Consider specific disease state where test is intended
  - Susceptibility biomarkers (SNPs, rare germline mutations)
  - Biomarkers of disease risk (MiPS, Select MDx, 4K, ExoDX)
  - Risk stratification biomarkers (4K, PHI, PCA3, Confirm MDX, Oncotype DX, Prolaris, Decipher)
  - Biomarkers for prediction of disease response (ARV7, DNA repair)

Urine and Serum tests

PCA3, 4K, Select MDX

- Predictive tests
- Typically used to consider whether or not to biopsy
- May improve long term prognostication

PCA3 Score

- Post DRE Urine
  - Ratio of PCA3 : PSA mRNA

Adult Urology

PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing Repeat Biopsy

Leonard S. Marks, Yves Fradet, Ina Lim Deras, Amy Blase, Jeannette Mathis, Sheila M. J. Aubin, Anthony T. Cancio, Marie Desaulniers, William J. Ellis, Harry Rittenhouse, and Jack Groskopf

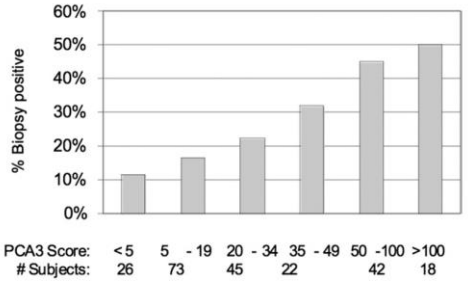


Figure 2. Probabilities of positive biopsy findings at different PCA3 score ranges. Number of subjects in each range shown at bottom.

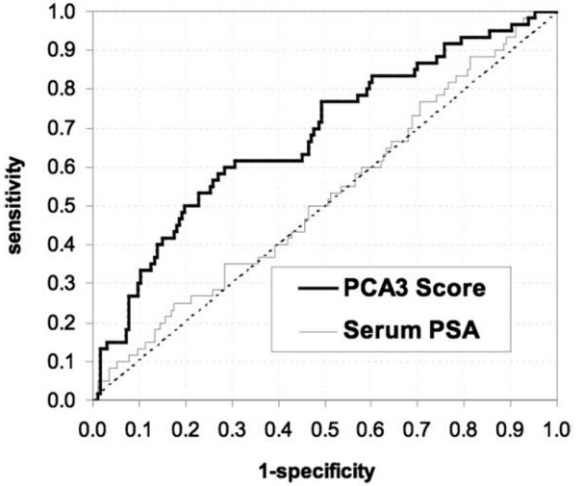


Figure 1. ROC analysis using PCA3 score or serum PSA level as diagnostic indicator and prostate biopsy as reference method.

Table 1. Sensitivity and specificity of PCA3 assay

PCA3 Score Cutoff	Sensitivity (%)	Specificity (%)	Odds Ratio
10	87	28	2.5
35	58	72	3.6
50	47	81	3.7

PCA3 Score

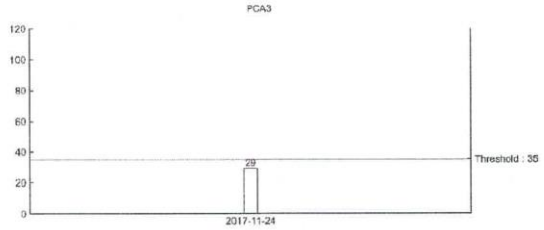
Dynacare

SCC Accredited LAB
LAB Accrédité CCN

Lab ID: 2017-264140
University Urology Associates (UUA)/Princess Margaret Hospital

Prescriber		Patient	
Name :	**NATHAN PERLIS**	Name :	
Clinic:	University Urology Associates (9002)		
Address:	123 Edward Street, Suite 1401 Toronto, ON M5G 1E2	Date of birth :	Age: 77
		Sex :	
Telephone:	416.979.9000	Health Ins.	
Fax:	416.979.9002		

Analysis	Specimen	Result	Reference value	Unit	Status
PCA3 (PCA3/PSA)	Urine	*PCA3/PSA Ratio* : **29**			**LOW RISK**



Note:
PCA3 / PSA Ratio[a]:
Elevated Risk: PCA3 / PSA Ratio ≥ 35[b]
Low Risk: PCA3 / PSA Ratio < 35[b]
Indeterminate-: Insufficient quantity of PSA mRNA

Method:
[a] PCA3 mRNA copies divided by PSA mRNA copies, multiplied by 1000
[b] Fradet Y., et al (2006). Performance of the PCA3 Urine test on Subjects with Previous Negative Prostate Biopsies. European Association of Urology Annual Congress, Poster Presentation: April 5-8, Paris, France.
This test is regarded by the scientific community as a useful adjunct in the diagnosis of prostate cancer. Decisions pertaining to patient care and treatment should not be based on a single test. Rather, decisions on care and treatment should be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition, including other pathological tests.

Defining a Cohort that May Not Require Repeat Prostate Biopsy Based on PCA3 Score and Magnetic Resonance Imaging: The Dual Negative Effect

Nathan Perlis,* Thamir Al-Kasab, Ardalan Ahmad, Estee Goldberg, Kamel Fadak, Rashid Sayid, Antonio Finelli, Girish Kulkarni, Rob Hamilton, Alexandre Zlotta, Sangeet Ghai and Neil Fleshner

From the Division of Urology, Department of Surgical Oncology (NP, TA-K, AA, EG, KF, RS, AF, GK, RH, AZ, NF) and Joint Department of Medical Imaging (SG), University Health Network and Division of Urology, Department of Surgery, Mount Sinai Hospital (AZ), University of Toronto, Toronto, Ontario, Canada

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Printed in U.S.A.

	Normal MRI					
	Normal PCA3			Abnormal PCA3		
Definition of PCa	Any PCa	Epstein or worse PCa	Gleason 7 PCa or >4mm CCL	Any PCa	Epstein or worse Pca	Gleason 7 or >4mm CCL
# of Patients positive on Biopsy	2 of 26 (7.7%)	0 of 26 (0%)	0 of 26 (0%)	10 of 32 (31.2%)	3 of 32 (9.4%)	3 of 32 (9.4%)
NPV of PCA3 in each scenario (95% CI, p-value)	92.3% (82.1 - 100%) p<0.0001	100% (100-100%) p<0.0001	100% (100-100%) p<0.0002			
	Abnormal MRI					
	Normal PCA3			Abnormal PCA3		
Definition of PCa	Any PCa	Epstein or worse PCa	Gleason 7 PCa or >4mm CCL	Any PCa	Epstein or worse Pca	Gleason 7 or >4mm CCL
# of Patients positive on Biopsy	14 of 49 (28.6%)	12 of 49 (24.5%)	10 of 49 (20.4%)	31 of 47 (66.6%)	22 of 47 (46.8%)	24 of 47 (48.9%)
NPV of PCA3 in each scenario (95% CI, p-value)	71.4% (58.8%-84.1) p=0.003	75.5% (63.5-87.5%) p=0.0004	79.6% (68.3%-90.9%) p<0.0001			

Table 3. Chart identifying number of patients with prostate cancer on repeat biopsy stratified by MRI, PCA3 test and definition of prostate cancer. Abnormal MRI = PIRADs-v2 3-5, Abnormal PCA3 = 35 or greater. CCL = cancer core length, NPV = negative predictive value

In a man with a prior negative biopsy with clinical suspicion of PC (i.e. rising PSA), dual negative mpMRI and PCA3 tests is highly predictive for the absence of clinically significant prostate cancer.

Four Kallikrein (4K test)

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journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

A Multi-institutional Prospective Trial in the USA Confirms that the 4Kscore Accurately Identifies Men with High-grade Prostate Cancer

Dipen J. Parekh [a,], Sanoj Punnen [a], Daniel D. Sjoberg [b], Scott W. Asroff [c], James L. Bailen [d], James S. Cochran [e], Raoul Concepcion [f], Richard D. David [g], Kenneth B. Deck [h], Igor Dumbadze [i], Michael Gambla [j], Michael S. Grable [k], Ralph J. Henderson [l], Lawrence Karsh [m], Evan B. Krisch [n], Timothy D. Langford [o], Daniel W. Lin [p], Shawn M. McGee [q], John J. Munoz [r], Christopher M. Pieczonka [s], Kimberley Rieger-Christ [t], Daniel R. Saltzstein [u], John W. Scott [v], Neal D. Shore [w], Paul R. Sieber [x], Todd M. Waldmann [y], Fredrick N. Wolk [z], Stephen M. Zappala [aa]*

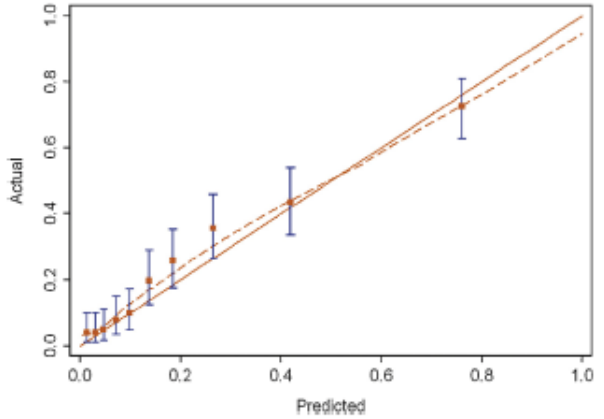
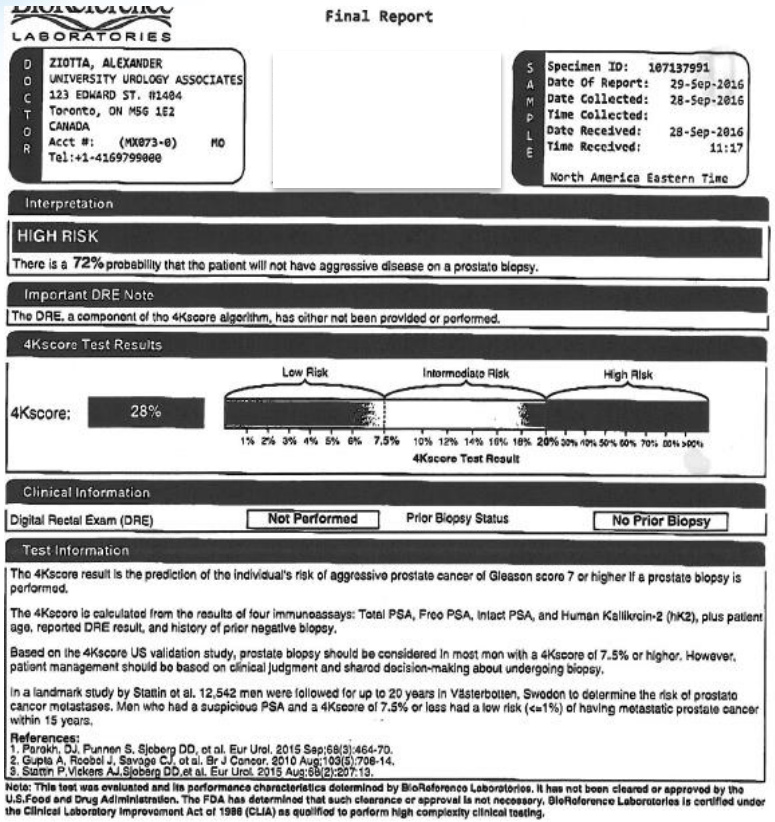


Fig. 2 – Model calibration showing predicted versus actual Gleason ≥7 cancer detected using the 4Kscore in the validation cohort.

Table 3 – Biopsies avoided and Gleason ≥7 cancers with delayed diagnosis for various 4Kscore cutoff values

4Kscore cutoff	Biopsies performed (*n*)	Biopsies avoided, *n* (%)	Gleason ≥7 cancers, *n* (%)		Gleason score for delayed diagnosis of Gleason ≥7 cancers, *n* (%)		
			Detected	Delayed diagnosis	3 + 4	4 + 3	4 + 4 or higher
0%	1012	0 (0)	231 (23)	0 (0)	0 (0)	0 (0)	0 (0)
≥6%	705	307 (30)	218 (22)	13 (1.3)	10 (1.0)	3 (0.3)	0 (0)
≥9%	578	434 (43)	207 (20)	24 (2.4)	15 (1.5)	7 (0.7)	2 (0.2)
≥12%	499	523 (51)	199 (20)	32 (3.2)	20 (2.0)	7 (0.7)	5 (0.5)
≥15%	421	591 (58)	183 (18)	48 (4.7)	33 (3.3)	9 (0.9)	6 (0.6)



LABORATORIES

Final Report

DOCTOR
ZIOTTA, ALEXANDER
UNIVERSITY UROLOGY ASSOCIATES
123 EDWARD ST. #1404
Toronto, ON M5G 1E2
CANADA
Acct #: (MX073-0) MD
Tel:+1-4169799000

SAMPLE
Specimen ID: 107137991
Date Of Report: 29-Sep-2016
Date Collected: 28-Sep-2016
Time Collected:
Date Received: 28-Sep-2016
Time Received: 11:17
North America Eastern Time

Interpretation

HIGH RISK

There is a **72%** probability that the patient will not have aggressive disease on a prostate biopsy.

Important DRE Note

The DRE, a component of the 4Kscore algorithm, has either not been provided or performed.

4Kscore Test Results

4Kscore: 28%

Low Risk | Intermediate Risk | High Risk

1% 2% 3% 4% 5% 6% 7.5% 10% 12% 14% 16% 18% 20% 30% 40% 50% 60% 70% 80% >80%

4Kscore Test Result

Clinical Information

Digital Rectal Exam (DRE): Not Performed

Prior Biopsy Status: No Prior Biopsy

Test Information

The 4Kscore result is the prediction of the individual's risk of aggressive prostate cancer of Gleason score 7 or higher if a prostate biopsy is performed.

The 4Kscore is calculated from the results of four immunoassays: Total PSA, Free PSA, Intact PSA, and Human Kallikrein-2 (hK2), plus patient age, reported DRE result, and history of prior negative biopsy.

Based on the 4Kscore US validation study, prostate biopsy should be considered in most men with a 4Kscore of 7.5% or higher. However, patient management should be based on clinical judgment and shared decision-making about undergoing biopsy.

In a landmark study by Stattin et al. 12,542 men were followed for up to 20 years in Västerbotten, Swedon to determine the risk of prostate cancer metastases. Men who had a suspicious PSA and a 4Kscore of 7.5% or less had a low risk (<=1%) of having metastatic prostate cancer within 15 years.

References:
1. Parekh, DJ, Punnen S, Sjoberg DD, et al. Eur Urol. 2015 Sep;68(3):464-70.
2. Gupta A, Roobol J, Savage CJ, et al. Br J Cancer. 2010 Aug;103(5):708-14.
3. Stattin P,Vickers AJ,Sjoberg DD,et al. Eur Urol. 2015 Aug;68(2):207-13.

In a man with clinical suspicion of PC (i.e. elevated PSA) but undecided about biopsy, 4k score can help predict the likelihood of having clinically significant cancer and may inform a decision to avoid biopsy.

Select MDX

EUROPEAN UROLOGY 70 (2016) 740–748

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Platinum Priority – Prostate Cancer

Editorial by Robert A. Gardiner, Paul Mainwaring and Martin F. Lavin on pp. 749–750 of this issue

Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker–Based Risk Score

Leander Van Neste [a,1], Rianne J. Hendriks [b,1], Siebren Dijkstra [b,1], Geert Trooskens [c], Erik B. Cornel [d], Sander A. Jannink [c], Hans de Jong [c], Daphne Hessels [c], Frank P. Smit [c], Willem J.G. Melchers [e], Gisèle H.J.M. Leyten [b,f], Theo M. de Reijke [f], Henk Vergunst [g], Paul Kil [h], Ben C. Knipscheer [i], Christina A. Hulsbergen-van de Kaa [j], Peter F.A. Mulders [b], Inge M. van Oort [b], Wim Van Criekinge [k], Jack A. Schalken [b,]*

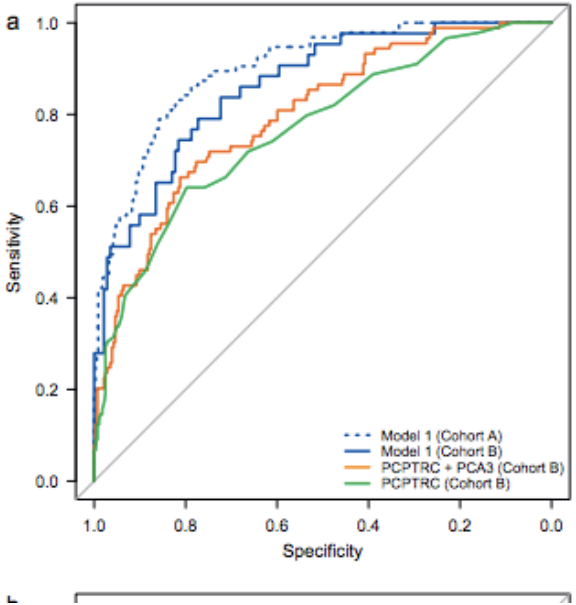


Table 3 – Odds ratios, 95% confidence intervals, and *p* values for risk factors as obtained in the training cohort during development of the risk score

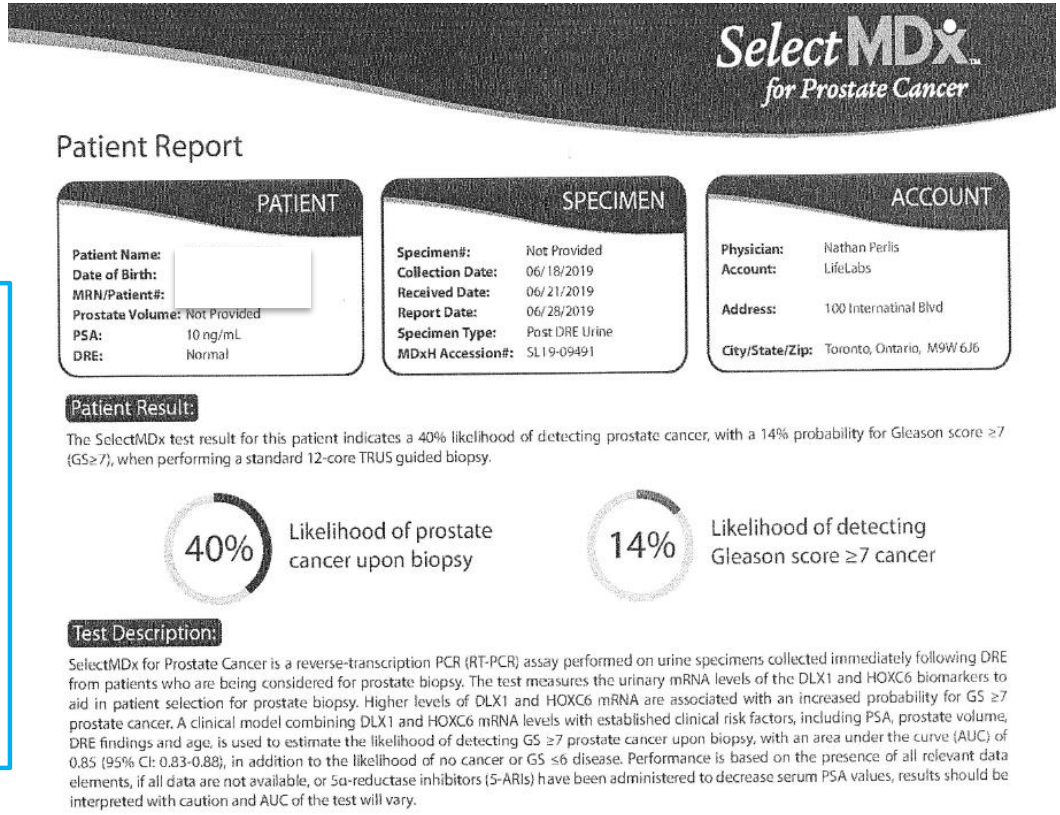
Parameter	Model 1, OR; CI (*p*)	Model 2, OR; CI (*p*)
HOXC6 and DLX1	1.68; 1.38–2.05 (0.003)	1.96; 1.40– 2.73 (<0.001)
PSAD	2.91; 1.40–6.06 (0.004)	3.78; 1.89–7.53 (<0.001)
DRE	5.53; 2.89–10.56 (<0.001)	–
Previous biopsy	0.28; 0.09–0.83 (0.02)	0.21; 0.07– 0.63 (0.005)
PSA	5.40; 0.81–35.94 (0.081)	3.42; 0.59–19.98 (0.17)
Family history	1.76; 0.81–3.80 (0.15)	1.56; 0.76–3.18 (0.2)
Age	1.01; 0.97–1.05 (0.7)	1.01; 0.97–1.06 (0.5)

CI = confidence interval; DRE = digital rectal examination; OR = odds ratio; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density.

robust predictor for the detection of high-grade PCa, as illustrated by a successful validation in this independent cohort by a direct comparison with cohort A ($p = 0.3$ for the difference between AUCs). In cohort B, model 2 reached an

Select MDX

In a man with clinical suspicion of PC (i.e. elevated PSA) but undecided about biopsy, Select MDX score can help predict the likelihood of having clinically significant cancer and may inform a decision to avoid biopsy.



SelectMDx for Prostate Cancer

Patient Report

PATIENT		SPECIMEN		ACCOUNT	
Patient Name:		Specimen#:	Not Provided	Physician:	Nathan Perlis
Date of Birth:		Collection Date:	06/18/2019	Account:	LifeLabs
MRN/Patient#:		Received Date:	06/21/2019	Address:	100 International Blvd
Prostate Volume:	Not Provided	Report Date:	06/28/2019	City/State/Zip:	Toronto, Ontario, M9W 6J6
PSA:	10 ng/mL	Specimen Type:	Post DRE Urine		
DRE:	Normal	MDxH Accession#:	SL19-09491		

Patient Result:

The SelectMDx test result for this patient indicates a 40% likelihood of detecting prostate cancer, with a 14% probability for Gleason score ≥7 (GS≥7), when performing a standard 12-core TRUS guided biopsy.

40% Likelihood of prostate cancer upon biopsy

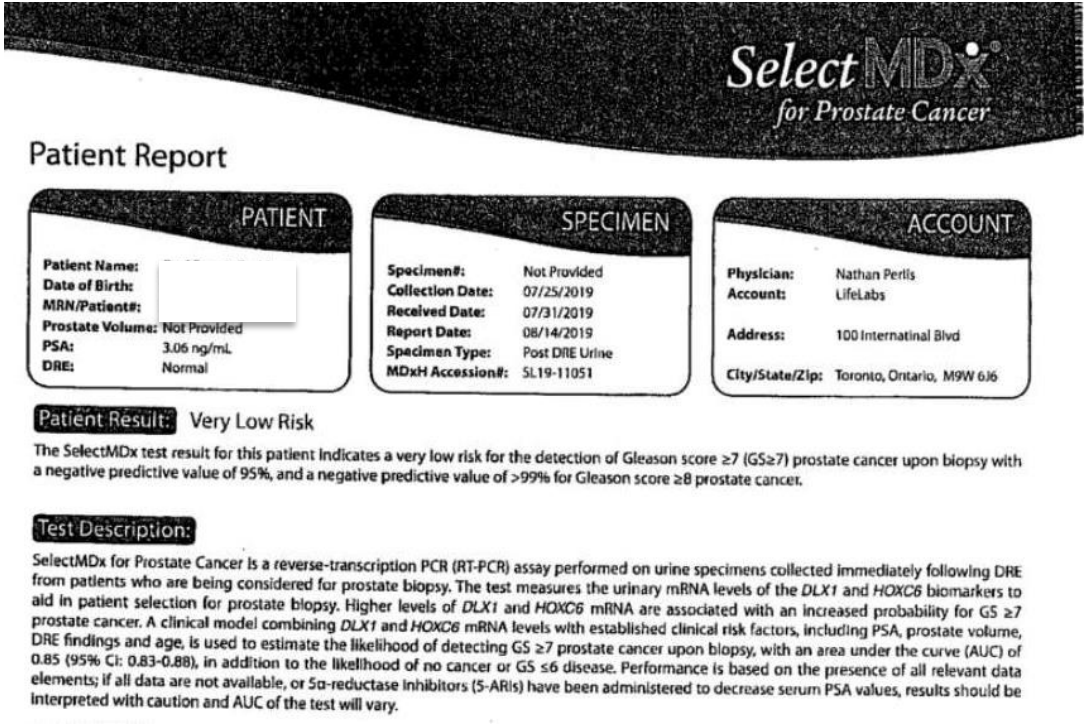
14% Likelihood of detecting Gleason score ≥7 cancer

Test Description:

SelectMDx for Prostate Cancer is a reverse-transcription PCR (RT-PCR) assay performed on urine specimens collected immediately following DRE from patients who are being considered for prostate biopsy. The test measures the urinary mRNA levels of the DLX1 and HOXC6 biomarkers to aid in patient selection for prostate biopsy. Higher levels of DLX1 and HOXC6 mRNA are associated with an increased probability for GS ≥7 prostate cancer. A clinical model combining DLX1 and HOXC6 mRNA levels with established clinical risk factors, including PSA, prostate volume, DRE findings and age, is used to estimate the likelihood of detecting GS ≥7 prostate cancer upon biopsy, with an area under the curve (AUC) of 0.85 (95% CI: 0.83-0.88), in addition to the likelihood of no cancer or GS ≤6 disease. Performance is based on the presence of all relevant data elements, if all data are not available, or 5α-reductase inhibitors (5-ARIs) have been administered to decrease serum PSA values, results should be interpreted with caution and AUC of the test will vary.

Select MDX

In a man where suspicion of GI7 PC is borderline (i.e. mildly elevated PSA) but undecided about biopsy, Select MDX score can may inform a decision to avoid or proceed with biopsy.



SelectMDx for Prostate Cancer

Patient Report

PATIENT		SPECIMEN		ACCOUNT	
Patient Name:		Specimen#:	Not Provided	Physician:	Nathan Perlis
Date of Birth:		Collection Date:	07/25/2019	Account:	LifeLabs
MRN/Patient#:		Received Date:	07/31/2019	Address:	100 International Blvd
Prostate Volume:	Not Provided	Report Date:	08/14/2019	City/State/Zip:	Toronto, Ontario, M9W 6J6
PSA:	3.06 ng/mL	Specimen Type:	Post DRE Urine		
DRE:	Normal	MDxH Accession#:	SL19-11051		

Patient Result: Very Low Risk

The SelectMDx test result for this patient indicates a very low risk for the detection of Gleason score ≥7 (GS≥7) prostate cancer upon biopsy with a negative predictive value of 95%, and a negative predictive value of >99% for Gleason score ≥8 prostate cancer.

Test Description:

SelectMDx for Prostate Cancer is a reverse-transcription PCR (RT-PCR) assay performed on urine specimens collected immediately following DRE from patients who are being considered for prostate biopsy. The test measures the urinary mRNA levels of the *DLX1* and *HOXC6* biomarkers to aid in patient selection for prostate biopsy. Higher levels of *DLX1* and *HOXC6* mRNA are associated with an increased probability for GS ≥7 prostate cancer. A clinical model combining *DLX1* and *HOXC6* mRNA levels with established clinical risk factors, including PSA, prostate volume, DRE findings and age, is used to estimate the likelihood of detecting GS ≥7 prostate cancer upon biopsy, with an area under the curve (AUC) of 0.85 (95% CI: 0.83-0.88), in addition to the likelihood of no cancer or GS ≤6 disease. Performance is based on the presence of all relevant data elements; if all data are not available, or 5α-reductase inhibitors (5-ARIs) have been administered to decrease serum PSA values, results should be interpreted with caution and AUC of the test will vary.

Tissue based tests

Decipher, Prolaris, Oncotype DX

- Uses biopsy or RP specimen tissue
- Predictive tests
  - Genomic classifiers
- Typically used to consider whether or not to treat
  - Primary or adjuvant

Decipher

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

Daniel E. Spratt, Kasra Yousefi, Samineh Deheshi, Ashley E. Ross, Robert B. Den, Edward M. Schaeffer, Bruce J. Trock, Jingbin Zhang, Andrew G. Glass, Adam P. Dicker, Firas Abdollah, Shuang G. Zhao, Lucia L.C. Lam, Marguerite du Plessis, Voleak Choeurng, Zaid Haddad, Christine Buerki, Elai Davicioni, Sheila Weinmann, Stephen J. Freedland, Eric A. Klein, R. Jeffrey Karnes, and Felix Y. Feng

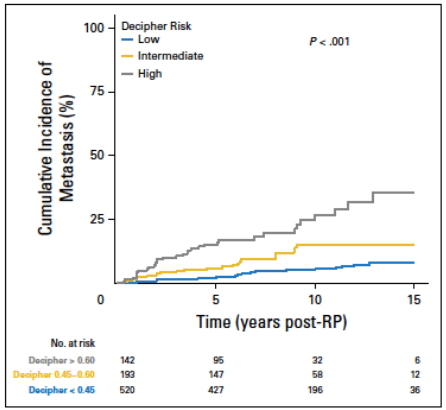


Fig 3. Individual patient-level analysis for the cumulative incidence of metastasis over time stratified by genomic-risk groups (also referred to as the Decipher risk categories): low, intermediate, and high. RP, radical prostatectomy.

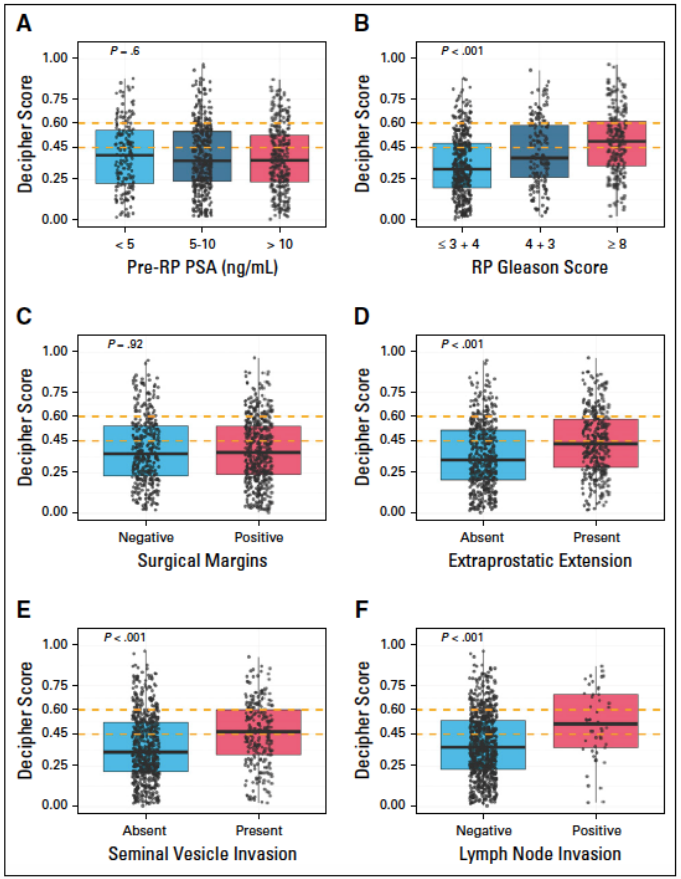
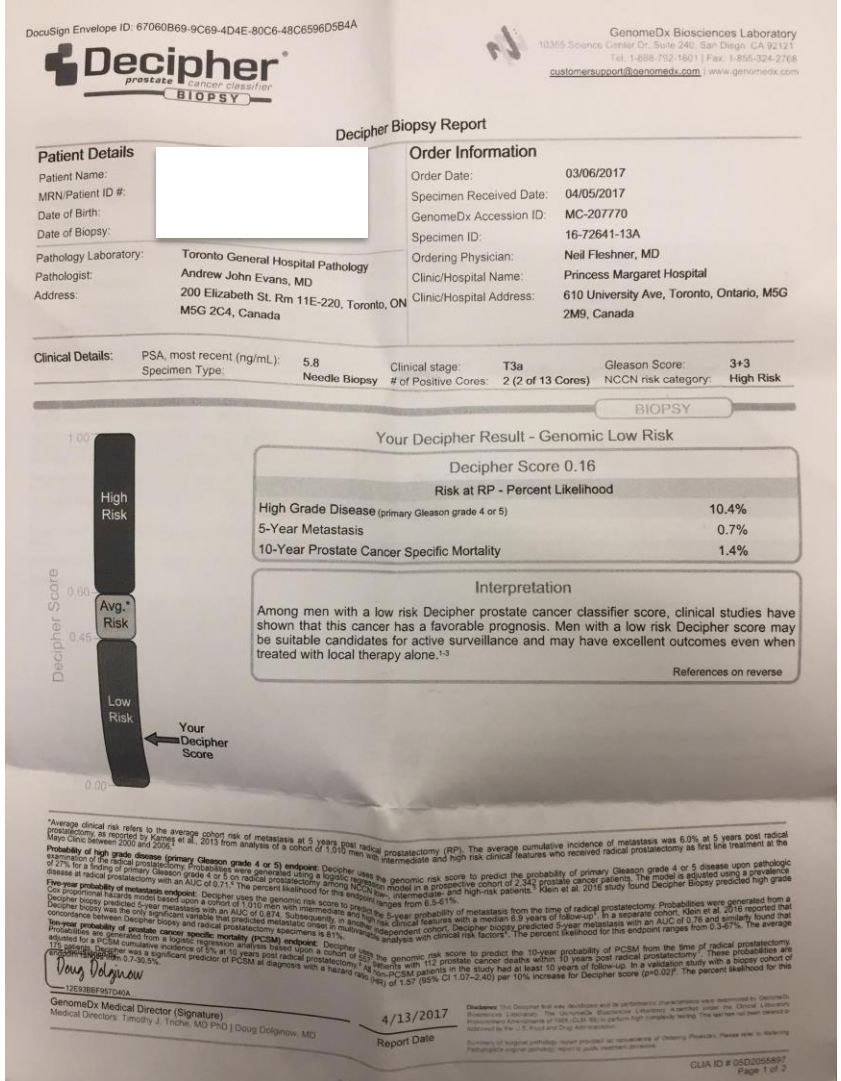


Fig 2. Correlation of the genomic-risk score (Decipher Score) to the following clinicopathologic variables: (A) preoperative prostate-specific antigen (PSA), (B) radical prostatectomy (RP) Gleason score, (C) surgical margins, (D) extracapsular extension, (E) seminal vesicle invasion, and (F) lymph node invasion.

In a man with localized prostate cancer Decipher can be used to

Predict metastasis
Better risk stratify patients
Triage adjuvant or salvage therapy (NCCN guideline)



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Decipher prostate cancer classifier BIOPSY

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customersupport@genomedx.com | www.genomedx.com

Decipher Biopsy Report

Patient Details
Patient Name:
MRN/Patient ID #:
Date of Birth:
Date of Biopsy:
Pathology Laboratory: Toronto General Hospital Pathology
Pathologist: Andrew John Evans, MD
Address: 200 Elizabeth St. Rm 11E-220, Toronto, ON M5G 2C4, Canada

Order Information
Order Date: 03/06/2017
Specimen Received Date: 04/05/2017
GenomeDx Accession ID: MC-207770
Specimen ID: 16-72641-13A
Ordering Physician: Neil Fleshner, MD
Clinic/Hospital Name: Princess Margaret Hospital
Clinic/Hospital Address: 610 University Ave, Toronto, Ontario, M5G 2M9, Canada

Clinical Details: PSA, most recent (ng/mL): 5.8 | Clinical stage: T3a | Gleason Score: 3+3
Specimen Type: Needle Biopsy | # of Positive Cores: 2 (2 of 13 Cores) | NCCN risk category: High Risk

BIOPSY

Your Decipher Result - Genomic Low Risk

Decipher Score 0.16	
Risk at RP - Percent Likelihood	
High Grade Disease (primary Gleason grade 4 or 5)	10.4%
5-Year Metastasis	0.7%
10-Year Prostate Cancer Specific Mortality	1.4%

Interpretation
Among men with a low risk Decipher prostate cancer classifier score, clinical studies have shown that this cancer has a favorable prognosis. Men with a low risk Decipher score may be suitable candidates for active surveillance and may have excellent outcomes even when treated with local therapy alone.[1-3]

References on reverse

*Average clinical risk refers to the average cohort risk of metastasis at 5 years post radical prostatectomy (RP). The average cumulative incidence of metastasis was 6.0% at 5 years post radical prostatectomy, as reported by Kames et al., 2013 from analysis of a cohort of 1,010 men with intermediate and high risk clinical features who received radical prostatectomy as first line treatment at the Mayo Clinic between 2000 and 2006.

Probability of high grade disease (primary Gleason grade 4 or 5) endpoint: Decipher uses the genomic risk score to predict the probability of primary Gleason grade 4 or 5 disease upon pathologic examination of the radical prostatectomy. Probabilities were generated using a logistic regression model in a prospective cohort of 2,342 prostate cancer patients. The model is adjusted using a prevalence of 27% for a finding of primary Gleason grade 4 or 5 on radical prostatectomy among NCCN intermediate- and high-risk patients.[1] Klein et al. 2016 study found Decipher Biopsy predicted high grade disease at radical prostatectomy with an AUC of 0.71.[4] The percent likelihood for this endpoint ranges from 6.5-61%.

Five-year probability of metastasis endpoint: Decipher uses the genomic risk score to predict the 5-year probability of metastasis from the time of radical prostatectomy. Probabilities were generated from a Cox proportional hazards model based upon a cohort of 1,010 men with intermediate and high risk clinical features with a median 6.8 years of follow-up[1]. In a separate cohort, Klein et al. 2016 reported that Decipher biopsy predicted 5-year metastasis with an AUC of 0.874. Subsequently, in another high risk clinical features with an AUC of 0.76 and similarly found that Decipher biopsy was the only significant variable that predicted metastatic onset in multivariate analysis with clinical risk factors[4]. The percent likelihood for this endpoint ranges from 0.3-67%. The average concordance between Decipher biopsy and radical prostatectomy specimen is 81%.

Ten-year probability of prostate cancer specific mortality (PCSM) endpoint: Decipher uses the genomic risk score to predict the 10-year probability of PCSM from the time of radical prostatectomy. Probabilities are generated from a logistic regression analysis based upon a cohort of 525 patients with 112 prostate cancer deaths within 10 years post radical prostatectomy[1]. These probabilities are adjusted for a PCSM cumulative incidence of 5% at 10 years post radical prostatectomy. At diagnosis, 71% of non-PCSM patients in the study had at least 10 years of follow-up. In a validation study with a biopsy cohort of 676 patients, Decipher was a significant predictor of PCSM at diagnosis with a hazard ratio (HR) of 1.57 (95% CI 1.07–2.40) per 10% increase for Decipher score (p=0.02)[5]. The percent likelihood for this endpoint ranges from 0.7-30.5%.

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GenomeDx Medical Director (Signature)
Medical Directors: Timothy J. Triche, MD PhD | Doug Dolginow, MD
4/13/2017
Report Date

Disclaimer: This Decipher test was developed and its performance characteristics were determined by GenomeDx Biosciences Laboratory. The GenomeDx Biosciences Laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) to perform high complexity testing. The test has not been cleared or approved by the U.S. Food and Drug Administration.

Summary of surgical pathology report provided as reference for Ordering Physician. Please refer to Ordering Pathologist's original pathology report to guide treatment decisions.

CLIA ID # 05D2055897
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Decipher Test Impacts Decision Making Among Patients Considering Adjuvant and Salvage Treatment After Radical Prostatectomy: Interim Results From the Multicenter Prospective PRO-IMPACT Study

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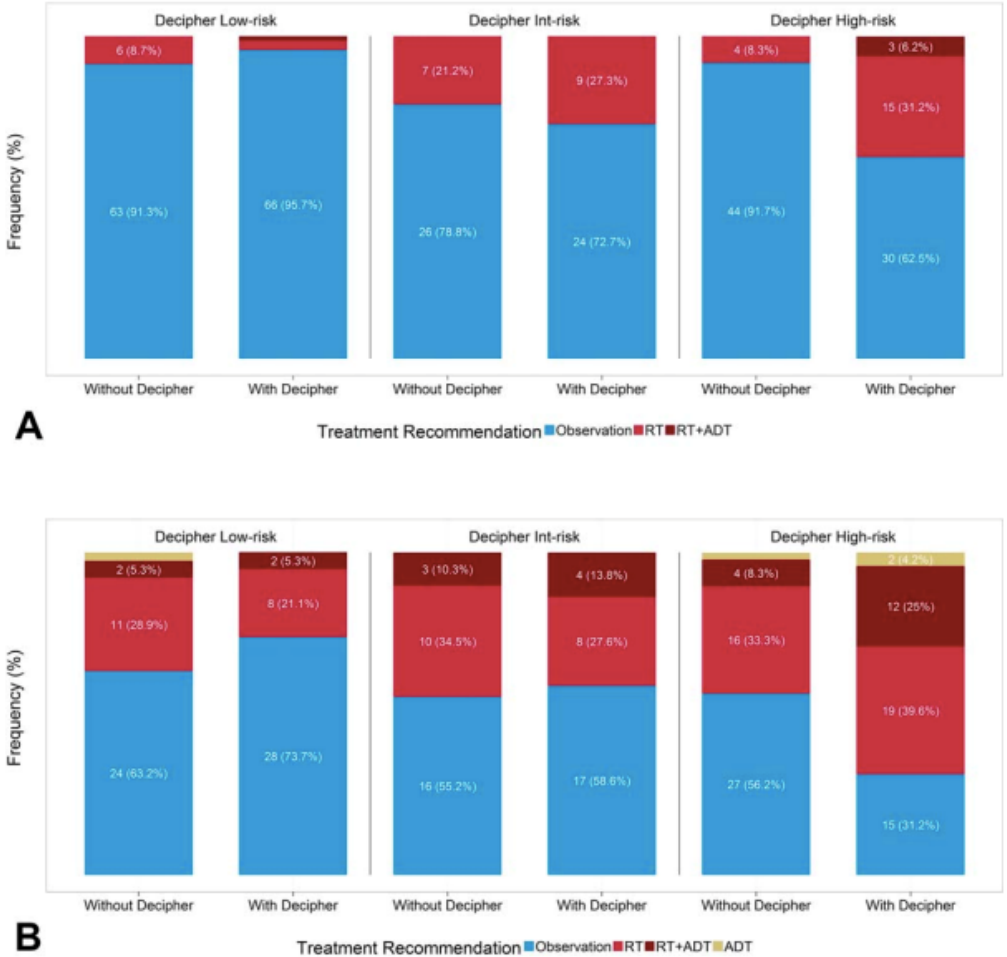
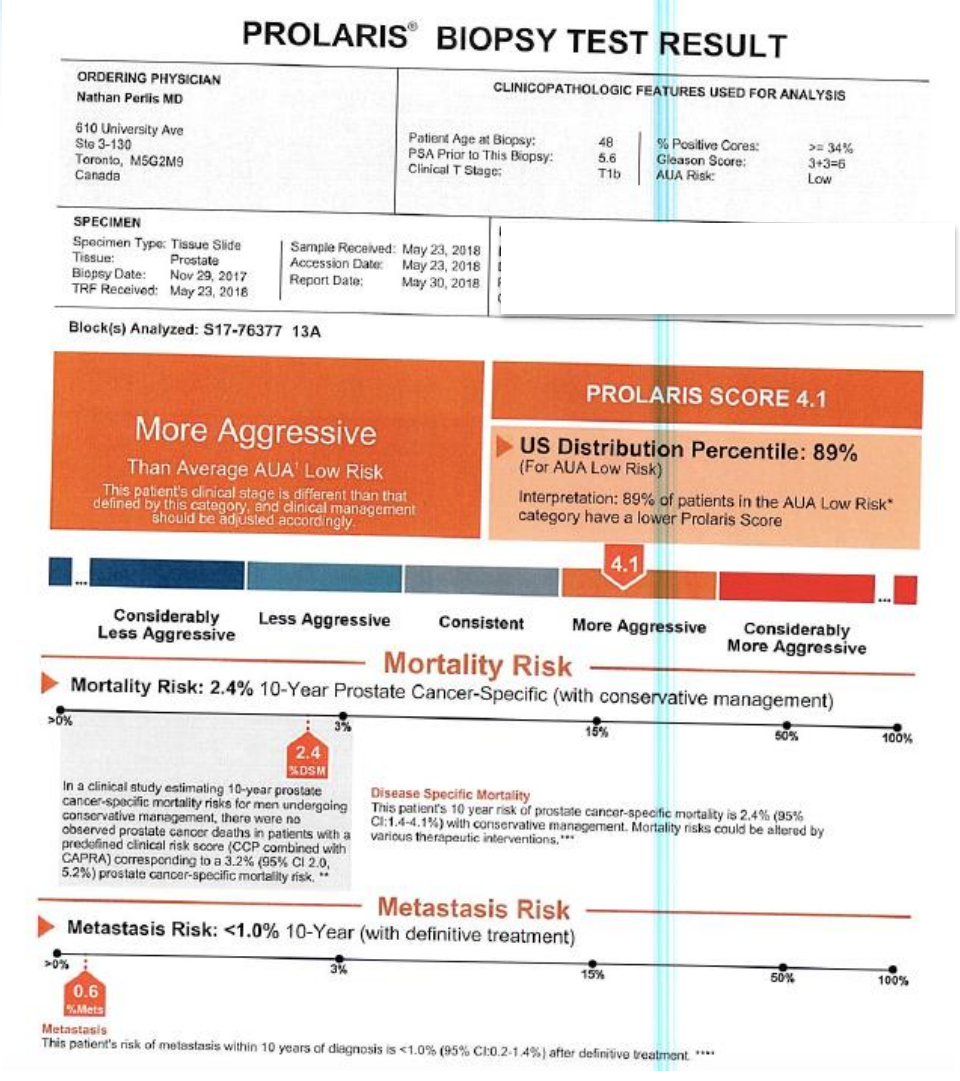


Figure 2. (A) Changes in treatment recommendation by Decipher risk category in the adjuvant radiotherapy arm. (B) Chang treatment recommendation by Decipher risk category in the salvage radiotherapy arm. ADT indicates androgen deprivation apy; Int, intermediate; RT, radiotherapy.

Prolaris



PROLARIS® BIOPSY TEST RESULT

ORDERING PHYSICIAN
Nathan Perlis MD
610 University Ave
Ste 3-130
Toronto, M5G2M9
Canada

CLINICOPATHOLOGIC FEATURES USED FOR ANALYSIS

Patient Age at Biopsy:	48	% Positive Cores:	>= 34%
PSA Prior to This Biopsy:	5.6	Gleason Score:	3+3=6
Clinical T Stage:	T1b	AUA Risk:	Low

SPECIMEN

Specimen Type:	Tissue Slide	Sample Received:	May 23, 2018
Tissue:	Prostate	Accession Date:	May 23, 2018
Biopsy Date:	Nov 29, 2017	Report Date:	May 30, 2018
TRF Received:	May 23, 2018		

Block(s) Analyzed: S17-76377 13A

More Aggressive
Than Average AUA[1] Low Risk
This patient's clinical stage is different than that defined by this category, and clinical management should be adjusted accordingly.

PROLARIS SCORE 4.1

US Distribution Percentile: 89%
(For AUA Low Risk)
Interpretation: 89% of patients in the AUA Low Risk* category have a lower Prolaris Score

4.1

Considerably Less Aggressive | Less Aggressive | Consistent | More Aggressive | Considerably More Aggressive

Mortality Risk

Mortality Risk: 2.4% 10-Year Prostate Cancer-Specific (with conservative management)

>0% | 3% | 15% | 50% | 100%

2.4 %DSM

In a clinical study estimating 10-year prostate cancer-specific mortality risks for men undergoing conservative management, there were no observed prostate cancer deaths in patients with a predefined clinical risk score (CCP combined with CAPRA) corresponding to a 3.2% (95% CI 2.0, 5.2%) prostate cancer-specific mortality risk. **

Disease Specific Mortality
This patient's 10 year risk of prostate cancer-specific mortality is 2.4% (95% CI:1.4-4.1%) with conservative management. Mortality risks could be altered by various therapeutic interventions.***

Metastasis Risk

Metastasis Risk: <1.0% 10-Year (with definitive treatment)

>0% | 3% | 15% | 50% | 100%

0.6 %Mets

Metastasis
This patient's risk of metastasis within 10 years of diagnosis is <1.0% (95% CI:0.2-1.4%) after definitive treatment. ****

Oncotype DX

Genomic Prostate Score® (GPS™) Report

oncotype DX® Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **18-Jan-1961** Gender: **Male** Report Number: **OR000123456-01** Report Date: **20-May-2019**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

GPS + NCCN®[1] : Low Risk

Clinical Interpretation	Clinical Endpoints	Individualized Risk (95% Confidence Interval [CI])
The combination of GPS and clinical features predicts that this patient's risk is consistent with **NCCN Low Risk** disease.[‡] In a clinical validation study including patients with NCCN Very Low, Low, and Intermediate Risk, **no patient with a GPS result <20 had metastasis or died** from prostate cancer within 10 years.[‡]	**Prostate Cancer Death Within 10 Years**[†]	<1% (95% CI: <1% - 1%)
	Metastasis Within 10 Years[†§]	4% (95% CI: 1% - 9%)
	Adverse Pathology[†] (Gleason ≥ 4+3 and/or pT3+)	31% (95% CI: 23% - 41%)

NCCN Risk Group[‖] **: Intermediate**

Physician-Provided Information[¶] **:**

Gleason Score: **3+3**	Prostate Volume (cc): **39**
PSA (ng/mL): **12.0**	PSA Density (ng/mL/cc): **0.31**
Clinical Stage: **T1c**	Number of cores positive: **2**
Max. % of tumor involvement in any core: **≤ 50%**	Number of cores collected: **14**

* The NCCN Guidelines identify a subset of Favorable Intermediate Risk patients: predominant Gleason grade 3 (Gleason score 3+4=7), percentage of positive biopsy cores <50%, and no more than one NCCN Intermediate Risk factor.

Genomic Prostate Score® (GPS™) Report

oncotype DX® Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **18-Jan-1961** Gender: **Male** Report Number: **OR000123456-01** Report Date: **20-May-2019**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

Medical Record/Patient #: **1234567-01** Specimen Source/ID: **Prostate/SP-16_0123456**

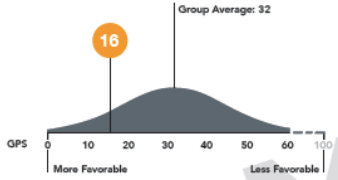
Date of Collection: **06-May-2019**

Specimen Received: **08-May-2019**

Additional Recipient: **Dr. First-Name I. Recipient-Physician-Last-Name**

Pathologist: **Dr. First-Name I. Pathologist-Last-Name**

GPS Distribution in NCCN® Intermediate Risk[2,3,5]



This patient has a GPS result that is **lower than the average GPS result** for NCCN Intermediate Risk.

Pathology Endpoints**	Individualized Risk (95% Confidence Interval [CI])
High-Grade Disease (Gleason ≥4+3)	15% (95% CI: 10% - 24%)
Non-Organ-Confined Disease (pT3+)	16% (95% CI: 11% - 25%)

The Oncotype DX Genomic Prostate Score (GPS) test is a continuous scale (0-100) that quantifies expression of 17 genes in tumor tissue as assessed by RT-PCR. The GPS test has been validated in three prospectively designed studies (N=1056) of biopsy tissue from patients with localized prostate cancer.[2,3,5]

Adverse pathology refers to the finding of an aggressive tumor (high grade) or cancer spread outside of the prostate (non-organ confined). Tumors with a low risk of adverse pathology are less likely to be aggressive and spread.

** In the clinical validation study, all patients received radical prostatectomy. The risk estimates provided are based on the patient's GPS result and NCCN risk group.

References: 1. National Comprehensive Cancer Network® NCCN Clinical Practice Guidelines in Oncology®: Prostate cancer. Version 1.2017. 2. Klein E, et al. *Eur Urol.* 2014. 3. Cullen J, et al. *Eur Urol.* 2015. 4. Brand T, et al. *Urology.* 2016. 5. Van Den Eeden SK, et al. AUA 2017. Abstract #17-6551.

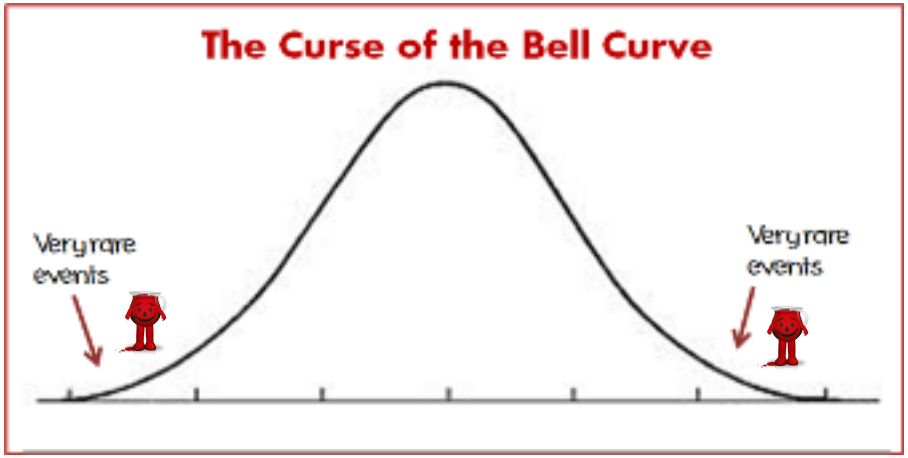
Laboratory Director(s): Patrick Joseph, MD

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the FDA, nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Summary

- “Biomarkers” are tests with fancy names
  - If no marginal benefit over standard nomogram - don’t use
- Serum and urine tests can help decide on whether or not to biopsy (4K, PCA3, Select MDX)
- Tissue tests (Decipher, OncotypeDX, Prolaris) can predict survival and adverse findings on RP and used to decide on adjuvant radiotherapy
- Expensive
- No trials yet to prospectively test whether altering treatment based on genomic classifier improves outcome

Will you drink the Kool-Aid?



Update on Biomarkers for Prostate Cancer: Should I Drink the Kool-Aid?

Nathan Perlis, MD MSc

PMH Dialogues 2019 NOTL