Available and Emerging Biomarkers to Inform Decision-Making for Patients with Early-Stage Prostate Cancer (PC) and Use of Active Surveillance

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Disclosures

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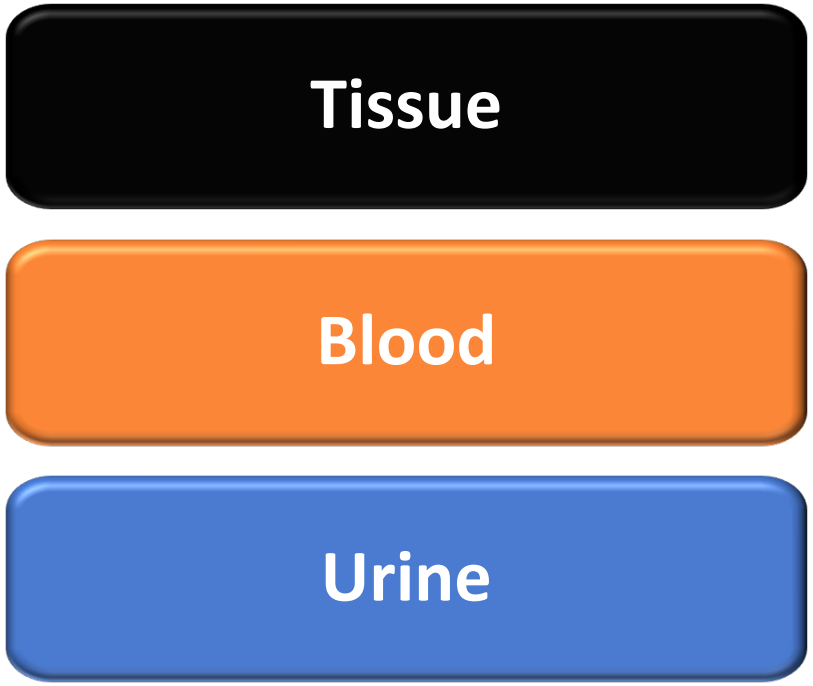
Prostate Cancer: Current Needs

- **Refine PSA**
- Increase the likelihood of an initial **positive biopsy that will identify significant prostate cancer**
- Reduce **unnecessary repeat** biopsies
- **Stratify** low risk from higher risk cancers
- Will **PCMs (Prostate Cancer Markers) improve our management?**

PCMs



What is a biomarker?

A molecule that can be found in blood, tissue or body fluids that is a sign of a normal or abnormal process

Pathological Outcomes in Men with Low Risk and Very Low Risk Prostate Cancer: Implications on the Practice of Active Surveillance

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Abbreviations and Acronyms

AS = active surveillance
BMI = body mass index
GS = Gleason score
LR = low risk
NOCC = nonorgan confined cancer
PSA = prostate specific antigen
VLR = very LR

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For another article on a related topic see page 1410.

Purpose: We assessed oncologic outcomes at surgery in men with low risk and very low risk prostate cancer who were candidates for active surveillance.

Materials and Methods: In a prospectively collected institutional database, we identified 7,486 subjects eligible for active surveillance who underwent radical retropubic prostatectomy. Candidates were designated as being at low risk (stage T1c/T2a, prostate specific antigen 10 ng/ml or less, and Gleason score 6 or less) or very low risk (stage T1c, prostate specific antigen density 0.15 or less, Gleason score 6 or less, 2 or fewer positive biopsy cores, 50% or less cancer involvement per core) based on preoperative data. Adverse findings were Gleason score upgrade (score 7 or greater) and nonorgan confined cancer on surgical pathology. The relative risk of adverse findings in men at low risk with very low risk disease was evaluated in a multivariate model using Poisson regression.

Results: A total of 7,333 subjects met the criteria for low risk disease and 153 had very low risk disease. The proportion of subjects at low risk found to have Gleason score upgrade or nonorgan confined cancer on final pathology was 21.8% and 23.1%, respectively. Corresponding values in those at very low risk were 13.1% and 8.5%, respectively. After adjusting for age, race, year of surgery, body mass index, and prostate specific antigen at diagnosis, the relative risk of Gleason score upgrade in men with low risk vs very low risk disease was 1.89 (95% CI 1.21—2.95). The relative risk of nonorgan confined cancer was 2.06 (95% CI 1.19—3.57).

Conclusions: Men with very low risk prostate cancer were at significantly lower risk for adverse findings at surgery compared to those with low risk disease. These data support the stratification of low risk cancer when selecting and counseling men who may be appropriate for active surveillance.

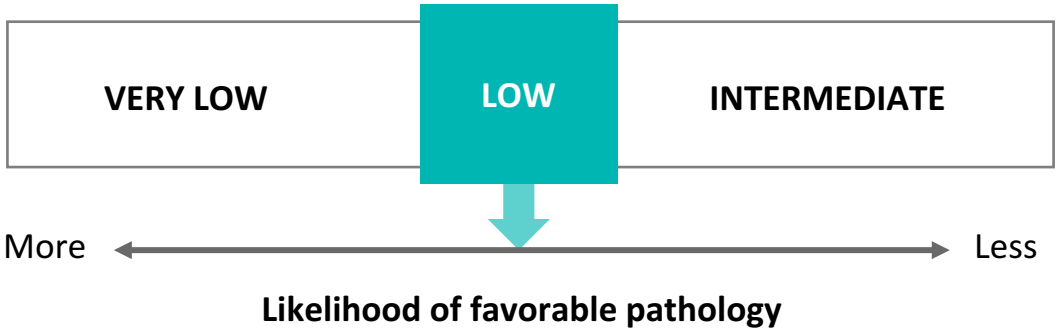
Comparison of Molecular Tests

Prostate Cancer Molecular Test Grid

Test	Description	Validated Endpoint(s)	Biomarker Selection Specific for Prostate Cancer	Specimen	Patient Access
oncotype DX Prostate Cancer Assay	**Genomic Prostate Score (GPS)** Predicts the likelihood of adverse pathology using multiple genetic pathways	**Adverse Pathology at RP** Likelihood of high-grade disease Likelihood of non-organ-confined disease **5-year BCR** NCCN Guidelines®	YES	**Positive Biopsy** NCCN Very Low, Low, Low-intermediate risk GS 3+3, 3+4	**Medicare Reimbursed for NCCN Very Low/Low** Financial Assistance Available: Patient contacted if out-of-pocket >$100
Prolaris®	**Cell Cycle Progression Score (CCP)** Reports the risk of dying from untreated disease in 10 years, using a single pathway	In a biopsy setting: **10-year Untreated Mortality** in a post-RP setting: **10-year BCR** **Metastasis** NCCN Guidelines®	NO	**Prostatectomy Positive Biopsy** AUA Low-High Risk	**Medicare Reimbursed for NCCN Very Low/Low** Financial Assistance Available: Patient contacted if out-of-pocket >$375
ProMark®	**ProMark Score** Predicts likelihood of adverse pathology using protein staining	**Adverse Pathology at RP** Likelihood of high-grade disease Likelihood of non-organ-confined disease	YES	**Positive Biopsy** GS 3+3, 3+4	Financial Assistance Available: Patient contacted if out-of-pocket >$350
ConfirmMDx®	**ConfirmMDx result** Predicts likelihood of negative repeat biopsy	**Negative Repeat Biopsy**	YES	**Negative Biopsy HGPIN Biopsy**	**Medicare Reimbursed** Financial Assistance Available: Patient contacted if out-of-pocket >$500
Decipher®	**Genomic Classifier** Predicts the probability of metastasis after surgery	**5-year Metastasis**	YES	**Prostatectomy** pT3 or pT2 w/positive margin	**Medicare Reimbursed** Financial Assistance Available: Patient contacted if out-of-pocket >$395
4Kscore®	**4Kscore** Provides probability of aggressive cancer	**Likelihood of GS 3+4 and higher at biopsy**	YES	**Blood** Biopsy-eligible patients	Financial Assistance is not reported on website

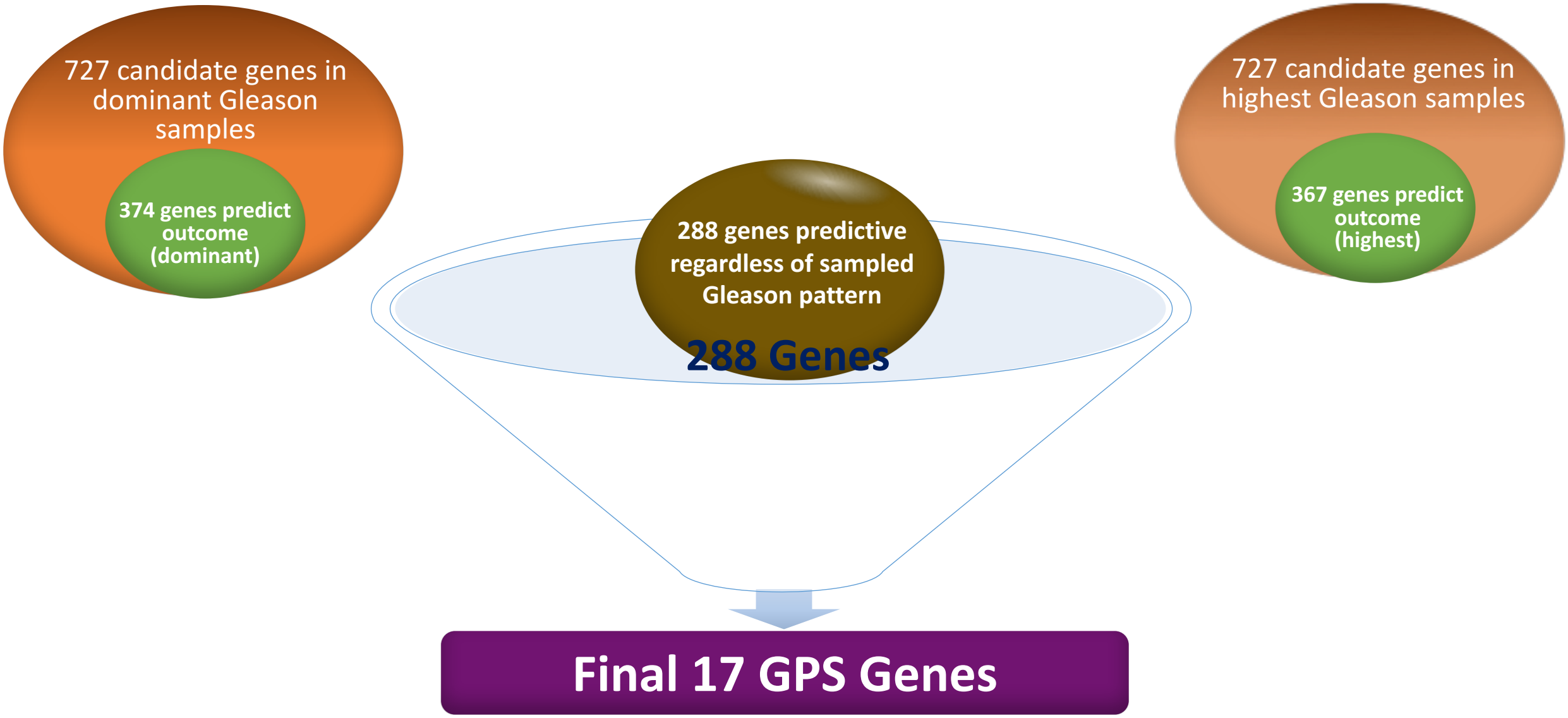
Oncotype DX

- Biopsy-based, 12 prostate cancer-specific genes test that has been clinically validated to predict the likelihood of adverse pathology using multiple genomic pathways, allows better personalized risk stratification to determine who is best suited for active treatment vs active surveillance
- Using the original needle positive biopsy
- Test independently predicts:
  - Likelihood of high-grade disease
  - Likelihood of non-organ-confined disease
  - Biochemical recurrence after RP
- Genomic Prostate Score from 0 to 100
- Covered by Medicare for qualified patients



Klein, et al. Eur Urol. 2014.
Cullen, et al. Eur Urol. 2014.

Gene Selection for the Oncotype DX® GPS Assay



GPS Incorporates Multiple Biologic Pathways Predictive of Prostate Cancer Aggressiveness

Genes Associated with Worse Outcome

Stromal Response
BGN
COL1A1
SFRP4

Proliferation
TPX2

Genes Associated with Better Outcome

Androgen Signaling
AZGP1
FAM13C
KLK2
SRD5A2

Cellular Organization
FLNC
GSN
GSTM2
TPM2

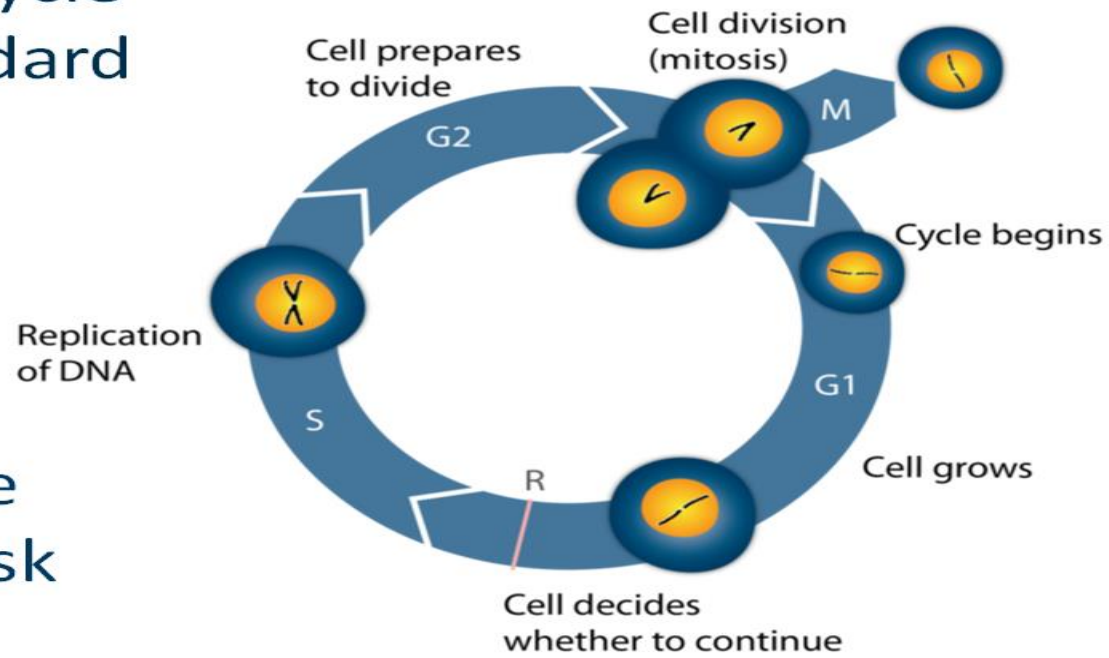
Reference Genes

ARF1
ATP5E
CLTC
GPS1
PGK1

The combination of multiple pathways is more predictive than any single pathway

THE PROLARIS® TEST

- Combines RNA expression of cell cycle progression (CCP) genes with standard clinicopathologic parameters
  - 31 genes across multiple cell cycle progression pathways
  - 15 housekeeper genes
- Each 1 unit change in Prolaris score equals a doubling (or halving) of risk
- Validated on multiple tissue types
  - Biopsy tissue
  - Radical prostatectomy tissue
- Provides personalized risk assessment
  - Prognostic for BCR, metastasis, and PCa mortality



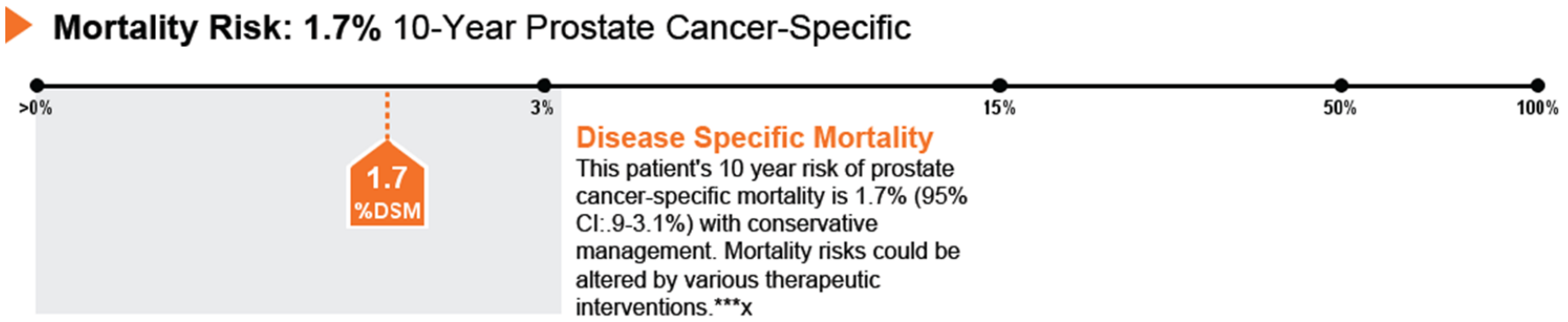
Prolaris®

CCP Score Adds Significant Prognostic Information

Study	Endpoint	Multivariate model*			
		Hazard ratio (95% CI)	CCP score p-value	PSA p-value	Gleason Score p-value
TURP conservatively managed	CaP death	**2.6 (1.9, 3.4)**	$<10^{-10}$	$<10^{-7}$	0.028
Needle Biopsy conservatively managed	CaP death	**1.7 (1.3, 2.1)**	$<10^{-4}$	0.017	0.0022
Rad Prostatectomy 1	BCR	**1.7 (1.4, 2.2)**	$<10^{-5}$	$<10^{-8}$	0.015
Rad Prostatectomy 2	BCR	**2.0 (1.4, 2.8)**	$<10^{-4}$	0.12	0.17
External Beam XRT	BCR	**2.1 (1.0, 4.2)**	0.035	0.054	0.20

Prolaris

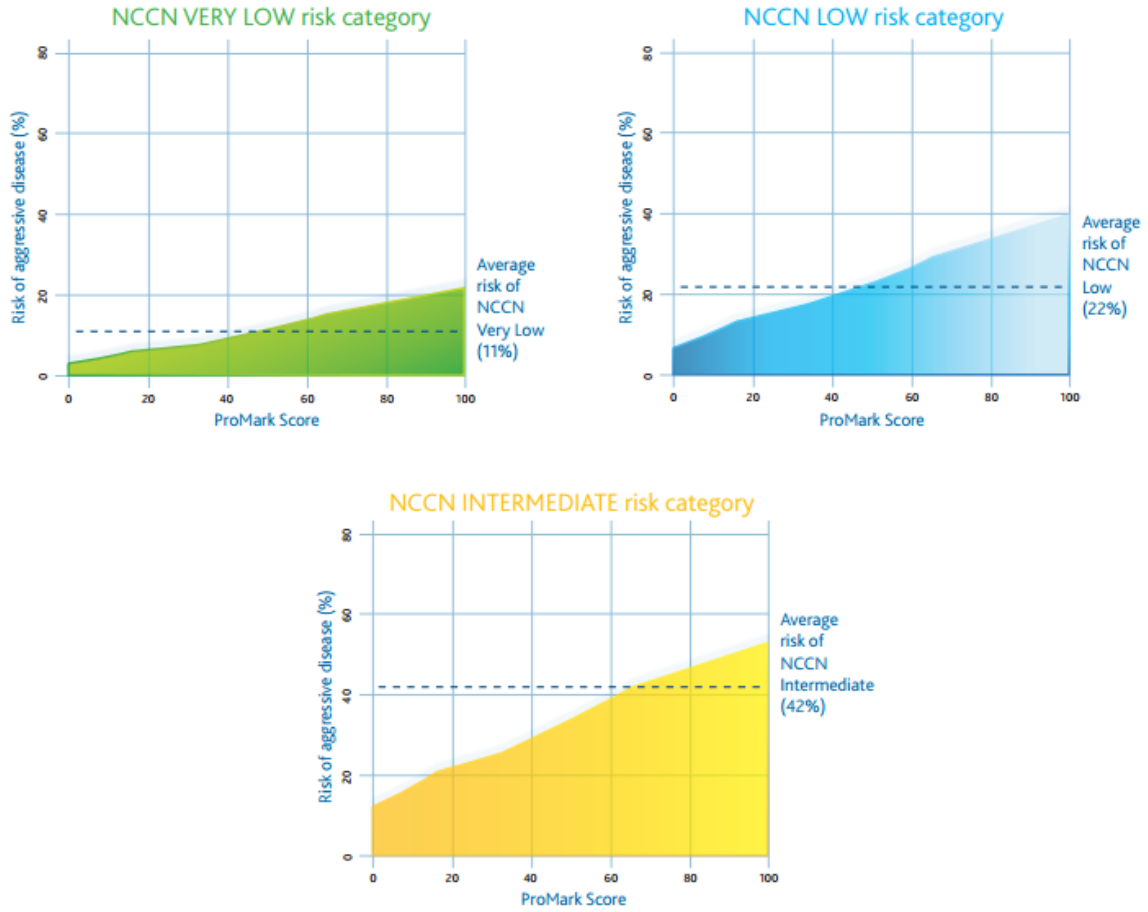
- Uses 31 cell cycle-related genes
- Predicts disease-specific mortality and disease aggressiveness in prostate cancer patients following needle biopsy
- Post-prostatectomy patients to better estimate the risk of biochemical recurrence
- Prolaris score is combined with patient's clinical-pathologic values to estimate a 10-year prostate cancer-specific mortality risk
- Endpoints of aggressiveness, mortality risk and US distribution percentile
  - Validated in relevant endpoints: BCR, metastasis, DSM
- Scores from 0 to 10
  - AS zone for helping with AS decision in untreated patients
- Prolaris Biopsy covered by Medicare for qualified patients



Koch MO, et al. Cancer Biomark. 2016;17(1):83-88.

ProMark

- Proteomic assay utilizing automated image analysis technology that identifies tumor and benign tissues
- Measures the quantitative expression levels of eight protein biomarkers
  - DERL1, CUL2, SMAD4, PDSS2, HSPA9, FUS, pS6, YBOX1
- Patients with biopsy Gleason Scores 3+3 and 3+4
- Identify tumor aggressiveness
- Scores from 0 to 100
- Covered by Medicare for qualified patients



Decipher

- Localized prostate cancer
  - Uses a biopsy to calculate the prognosis to determine if active surveillance, local therapy or multi-modal therapy is needed
  - Based on the patient's personal tumor-based genomics
- Post radical prostatectomy
  - Uses the expression of biomarkers to calculate the probability of clinical metastasis within 5 years of radical prostatectomy surgery
  - Analyzes a small tissue sample that was removed during surgery
  - Predicts probability of metastasis after surgery and provides independent assessment of tumor aggression
  - Measures the expression levels of 22 RNA biomarkers involved in multiple biological pathways across the genome that are associated with aggressive prostate cancer
- Endpoints of probability of high grade disease, 5-year probability of metastasis and 10-year probability of prostate cancer specific mortality
- Decipher Score
  - 0 – 0.45 = Low Risk
  - 0.45 – 0.6 = Average Risk
  - 0.6 -1 = High Risk
- Covered by Medicare for qualified patients post-RP

Karnes RJ, et al. J Urol. 2013. 190(6):2047-2053.

What is Decipher Biopsy?

Classifies men into Decipher High or Low genomic risk for:

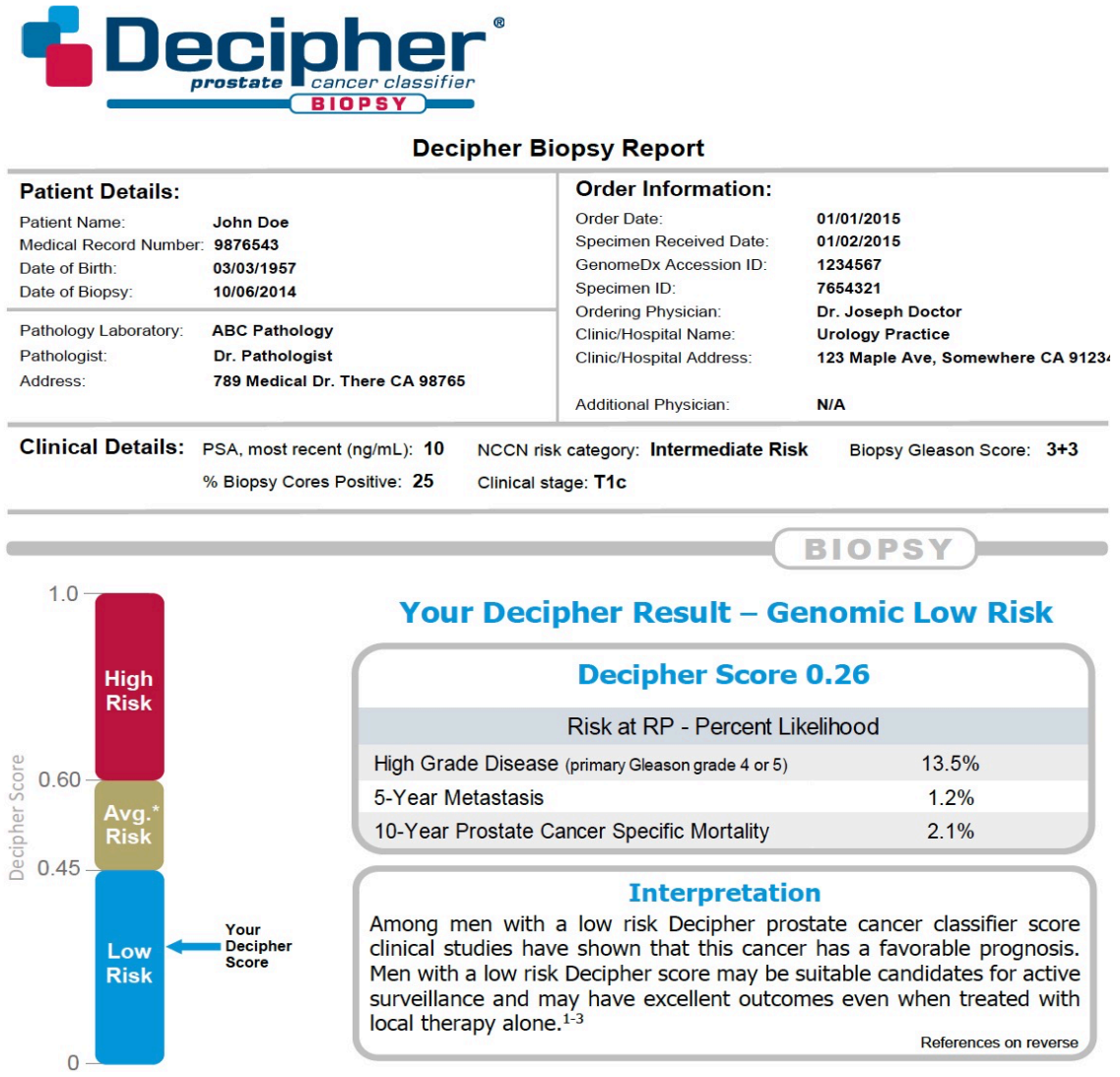
1. % likelihood High Grade Disease (Gleason 4 or 5)

2. % likelihood of Metastasis 5 years post prostatectomy

3. % likelihood Prostate Cancer Specific Mortality (PCSM) 10 years

Patient Inclusion Criteria:

- NCCN Very Low Risk
- NCCN Low Risk
- NCCN Intermediate Risk
- NCCN High Risk



Decipher prostate cancer classifier BIOPSY

Decipher Biopsy Report

Patient Details:

Patient Name:	John Doe
Medical Record Number:	9876543
Date of Birth:	03/03/1957
Date of Biopsy:	10/06/2014
Pathology Laboratory:	ABC Pathology
Pathologist:	Dr. Pathologist
Address:	789 Medical Dr. There CA 98765

Order Information:

Order Date:	01/01/2015
Specimen Received Date:	01/02/2015
GenomeDx Accession ID:	1234567
Specimen ID:	7654321
Ordering Physician:	Dr. Joseph Doctor
Clinic/Hospital Name:	Urology Practice
Clinic/Hospital Address:	123 Maple Ave, Somewhere CA 9123
Additional Physician:	N/A

Clinical Details: PSA, most recent (ng/mL): 10 | NCCN risk category: Intermediate Risk | Biopsy Gleason Score: 3+3 | % Biopsy Cores Positive: 25 | Clinical stage: T1c

BIOPSY

Your Decipher Result – Genomic Low Risk

Decipher Score 0.26

Risk at RP - Percent Likelihood	
High Grade Disease (primary Gleason grade 4 or 5)	13.5%
5-Year Metastasis	1.2%
10-Year Prostate Cancer Specific Mortality	2.1%

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

Decipher Biopsy has predictive value for various endpoints (Feb 2016 - May 2017)

Publication	Institution	Patients (n)	Primary Objective/Key Results
Klein et al., Urology 2016	Cleveland Clinic	57 patients	Decipher was shown to predict risk of metastasis 10 years post RP using needle biopsy tissue. Decipher had the highest AUC (0.80; 95% CI, 0.58-0.95) compared to NCCN (0.75; 95% CI, 0.64-0.87) at predicting 10 years post-RP metastasis. The AUC was 0.88 when Decipher was combined with the NCCN model. Pre-operatively, 40% and 47% of patients were NCCN low and intermediate risk, respectively. Decipher categorized 67%, 25% and 9% of patients as low (<0.45), intermediate (0.45-0.60) and high, respectively. Furthermore, Decipher reclassified 48% of NCCN intermediate risk men as low.
Lee et al., Urology Research & Reports 2016	UCSD	22 patients	Decipher was shown to predict the presence of lymph node involvement (LNI) upon radical prostatectomy. Decipher had an AUC of 0.78 for predicting LNI, significantly higher than Gleason score, pathological stage and preoperative PSA (all AUC<0.7). On MVA, for every 10% increase in Decipher score, the odds of having LNI on RP increased by 43%. The concordance between the biopsy Decipher and RP Decipher risk groups was 86%.
Nguyen et al., PCPD 2016	DanaFarber/ Harvard	100 patients	Study suggests that patients with the highest GC risk (GC>0.6) had high rates of metastasis despite multi-modal therapy and could be considered for longer duration ADT and/or clinical trials. The Decipher genomic classifier's (GC) ability to predict distant metastases after radiation and short-course androgen deprivation therapy (ADT) using needle biopsy tissue was explored. 100 patients (NCCN intermediate and high risk) received RT + [median] 6mo ADT. GC significantly and independently predicted metastasis (HR. 1.41 on MVA) and performed with a c-index of 0.77.
Nguyen et al., European Urology, 2017	Multiple (UCSF, Cleveland Clinic, JHU + more)	235 patients	Biopsy Decipher was a significant predictor of PCSM with a 5-year PCSM rate as well as 5-year metastasis. Patients with biopsy Decipher low-, intermediate- and high-risk had a metastasis rate of 4.1%, 7.8% and 21% by 5 years post-biopsy. The risk of 5 year PCSM was 0%, 0%, and 9.4% for Decipher low, intermediate, and high, respectively (HR 1.57 56 per 10% increase in score, 57 95% CI 1.03-2.48, P=0.037).

and recommendations for active surveillance as the only option for men with low-risk prostate cancer and life expectancy less than 10 years or very-low-risk prostate cancer and life expectancy less than 20 years. Although risk groups, life expectancy estimates, and nomograms help inform decisions, uncertainty about the risk of disease progression persists. American men continue to under-select active surveillance and their physicians may under-recommend it, likely as a result of this uncertainty.[55] In 2013, <20% of men with low-risk prostate cancer were managed with active surveillance.[56] However, active surveillance has become more common in some areas, such as Michigan, where its frequency has been measured and educational efforts have begun.[57,58]

Several tissue-based molecular assays have been developed in an effort to improve decision-making in newly diagnosed men considering active surveillance and in treated men considering adjuvant therapy or treatment for recurrence. Uncertainty about the risk of disease progression can be reduced if such molecular assays can provide accurate and reproducible prognostic or predictive information beyond NCCN risk group assignment and currently available life expectancy tables and nomograms. Retrospective case cohort studies have shown

Table 1 lists these tests in alphabetical order and provides an overview of each test, populations where each test independently predicts outcome, and supporting references. These molecular biomarker tests listed have been developed with extensive industry support, guidance, and involvement, and have been marketed under the less rigorous FDA regulatory pathway for biomarkers. Although full assessment of their clinical utility requires prospective randomized clinical trials, which are unlikely to be done, the panel believes that men with clinically localized disease may consider the use of tumor-based molecular assays at this time. Future comparative effectiveness research may allow these tests and others like them to gain additional evidence regarding their utility for better risk stratification of men with prostate cancer.

Family History and DNA Repair Mutations

Recent data indicate that of men with prostate cancer may have germline mutations in one of 16 DNA repair genes: *BRCA2* (5%), *ATM* (2%), *CHEK2* (2%), *BRCA1* (1%), *RAD51D* (0.4%), *PALB2* (0.4%), *ATR* (0.3%), and *NBN*, *PMS2*, *GEN1*, *MSH2*, *MSH6*, *RAD51C*, *MRE11A*, *BRIP1*, or *FAM175A*.[66] The overall prevalence of DNA repair gene

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA) / American Society for Radiation Oncology (ASTRO) / Society of Urologic Oncology (SUO)

CLINICALLY LOCALIZED PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE

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Purpose

CARE OPTIONS BY CANCER SEVERITY/RISK GROUP

Very Low-/Low-Risk Disease

6. Clinicians should not perform abdomino-pelvic CT or routine bone scans in the staging of asymptomatic very low- or low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade C)
7. Clinicians should recommend active surveillance as the best available care option for very low-risk localized prostate cancer patients. (Strong Recommendation; Evidence Level: Grade A)
8. Clinicians should recommend active surveillance as the preferable care option for most low-risk localized prostate cancer patients. (Moderate Recommendation; Evidence Level: Grade B)
9. Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select low-risk localized prostate cancer patients who may have a high probability of progression on active surveillance. (Conditional Recommendation; Evidence Level: Grade B)
10. Clinicians should not add ADT along with radiotherapy for low-risk localized prostate cancer with the exception of reducing the size of the prostate for brachytherapy. (Strong Recommendation; Evidence Level: Grade B)
11. Clinicians should inform low-risk prostate cancer patients considering whole gland cryosurgery that consequent side effects are considerable and survival benefit has not been shown in comparison to active surveillance. (Conditional Recommendation; Evidence Level: Grade C)
12. Clinicians should inform low-risk prostate cancer patients who are considering focal therapy or high intensity focused ultrasound (HIFU) that these interventions are not standard care options because comparative outcome evidence is lacking. (Expert Opinion)
13. Clinicians should recommend observation or watchful waiting for men with a life expectancy ≤5 years with low-risk localized prostate cancer. (Strong Recommendation; Evidence Level: Grade B)
14. Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)