EARLY STAGE PROSTATE CANCER PROGNOSIS
Biopsy Gleason Scores 3+3 and 3+4

Confidence for better treatment decisions

INTRODUCING

ProMark™

PROTEOMIC PROGNOSTIC TEST

for PROSTATE CANCER

Metamark™

Make treatment decisions with Confidence

ProMark: A first-of-its-kind protein-based prognostic test for prostate cancer.

Predict cancer aggressiveness* in patients with biopsy Gleason Scores of 3+3 and 3+4.

- ☑ Developed **specifically for use on prostate biopsy tissue.**
- ☑ Independent, **standalone** test for prostate cancer.
- ☑ Provides a **personalized prediction** that the cancer can be managed without aggressive treatment, or an indication that aggressive therapy may be appropriate.
- ☑ Outperforms and **requires substantially less tissue** than conventional gene-expression-based prostate cancer prognostic tests.
- ☑ Advanced **automated** image recognition technology provides **objective** identification of tumor cells and quantitative measurement of predictive protein biomarker expression levels.
- ☑ Generates an **individual risk score** delivered within an **intuitive report** allowing for productive discussion with your patient.

* Adverse prostate pathology: Gleason ≥4+3 and/or non-organ-confined disease (T3a, T3b, N1, or M1)

We're here to help

We are committed to helping your patient through the ProMark billing process, and will work with his insurance plan to get the proper level of coverage for ProMark. The ProMark billing process also provides the opportunity, upon request, for your patient to determine his potential out-of-pocket costs before we run the test.

The **ProMark Patient Assistance Program** can help your patient manage any out-of-pocket costs not covered by his insurance plan.

About ProMark

Utilizing an automated image analysis technology that identifies tumor and benign tissue, ProMark measures the quantitative expression levels of eight protein biomarkers that individually correlate with tumor aggressiveness and together predict your individual patient's risk of aggressive disease.[6]

This unique approach allows ProMark to outperform conventional gene expression-based diagnostic assays.[7-9]

- A ProMark risk score provides a personalized prediction independent of clinical and pathological characteristics.[1,2,4,6]
- In addition, when combined with existing risk stratification methods, ProMark provides information above and beyond to support additional confidence for clinical decision-making.[7]

Unlike genomic based tests that require pathologists to indicate the areas of tumors, ProMark technology allows for analysis of proteins, a more direct reflection of biologic activity, directly from the cancerous regions of interest.

ProMark was developed with eight carefully selected biomarkers which are resistant to sampling variability and exhibit univariate performance for both disease aggressiveness and lethal outcome.

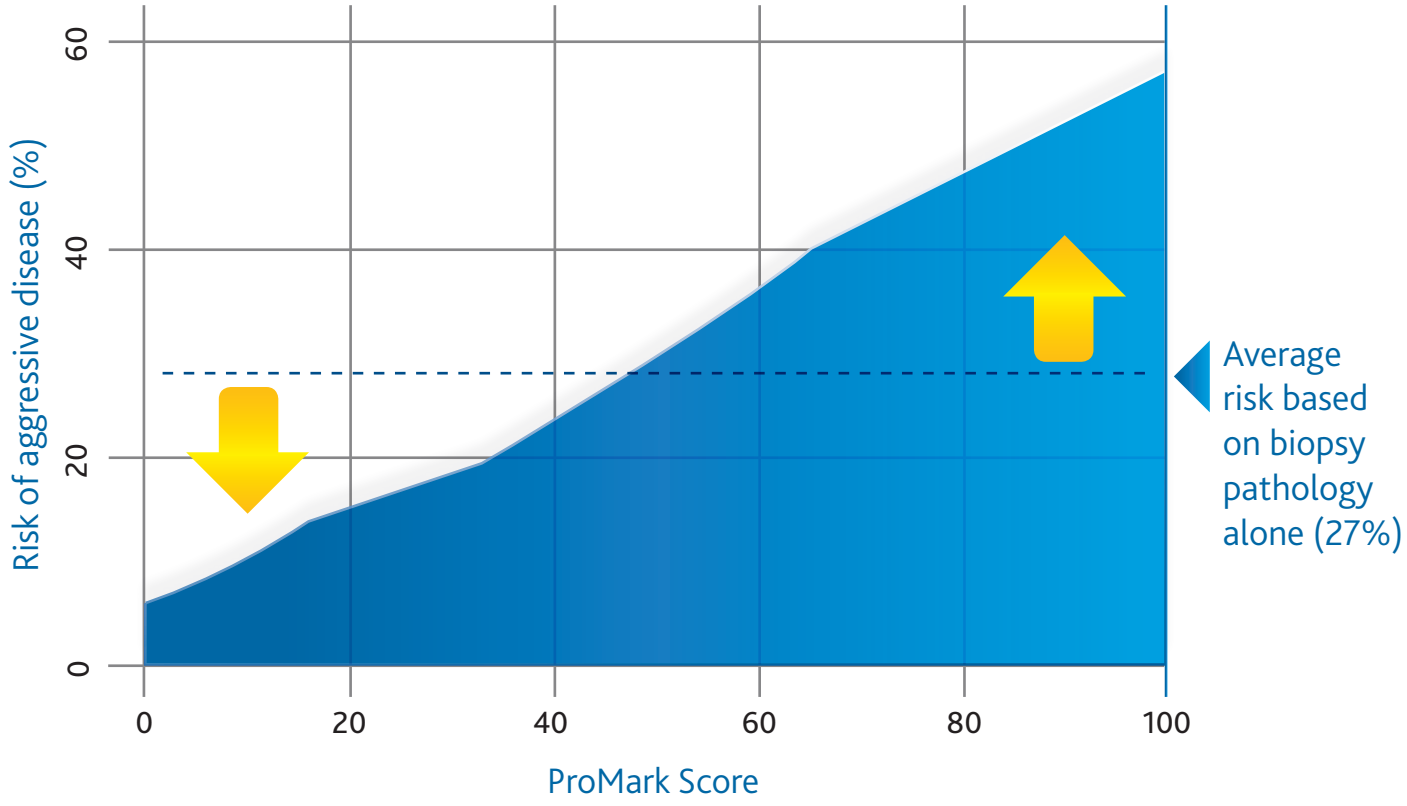
1. DERL1 (in both tumor and benign)	A protein involved in endoplasmic reticulum degradation of misfolded lumen proteins
2. CUL2 (in both tumor and benign)	A bundling protein that anchors actin to a variety of intracellular structures
3. SMAD4	A component of the transforming growth factor-β signaling pathway involved in the regulation of cell proliferation, apoptosis, and differentiation
4. PDSS2	An enzyme that synthesizes the phenyl side-chain of coenzyme Q, a key element in the respiratory chain
5. HSPA9	A member of the heat shock protein 70 family involved in cell proliferation, stress response, and the maintenance of the mitochondria
6. FUS	A component of the heterogeneous nuclear ribonucleoprotein (hnRNP) complex involved in pre-mRNA splicing and the export of fully processed RNA into the cytoplasm
7. pS6 (phosphorylated S6)	A component of the 40s ribosome subunit involved in protein synthesis; its Phosphorylation reflects the PI3K and core MAPK pathway signaling activity
8. YBOX1	A component of the transforming growth factor-β signaling pathway involved in the regulation of cell proliferation, apoptosis, and differentiation

ProMark is currently offered in our CLIA-certified, CAP-accredited laboratory in Cambridge, MA.[5]

Meaningful **clinical data**

"Development and Clinical Validation of an in situ Biopsy Based Multi-Marker Assay for Risk Stratification in Prostate Cancer"
— **Clinical Cancer Research**, March 2015

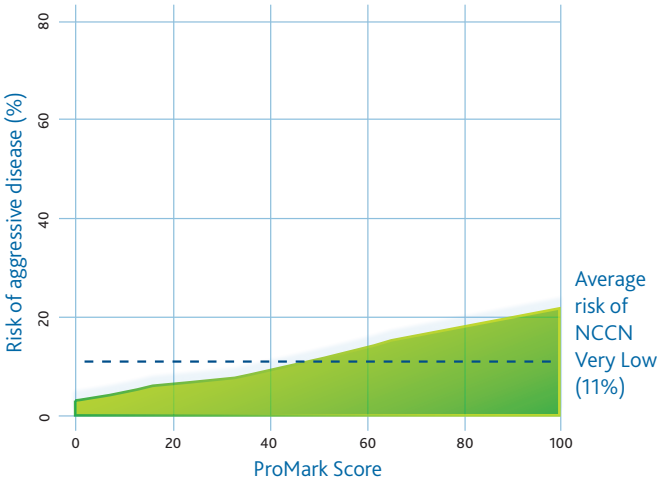
In a study consisting of more than 650 patients with biopsy Gleason Scores of 3+3 and 3+4, ProMark successfully and independently separated 'favorable' (surgical Gleason ≤3+4 and organ-confined disease) from 'non-favorable' (surgical Gleason ≥4+3 and/or non-organ-confined disease) pathology, improving the prediction of aggressive cancer in men with biopsy Gleason Scores of 3+3 and 3+4.



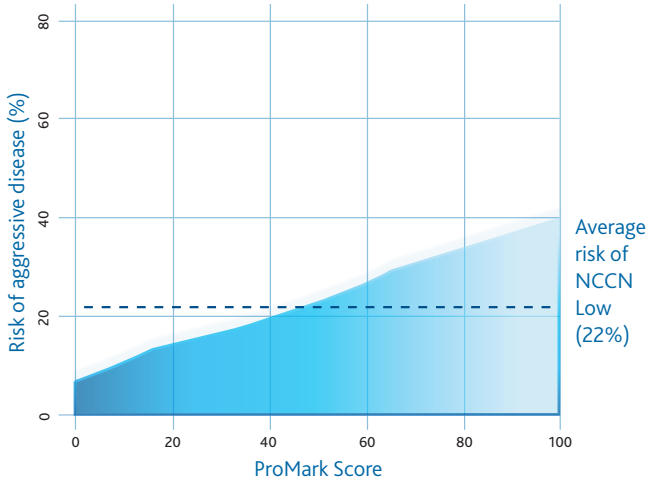
A ProMark Score transitions your patient from being a member of a population, to being an individual who has personalized information about his specific risk.

ProMark also provides **INDIVIDUALIZED PROGNOSTIC INFORMATION THAT ADDS TO CURRENT RISK STRATIFICATION SYSTEMS**, as exhibited using the NCCN classifications below:

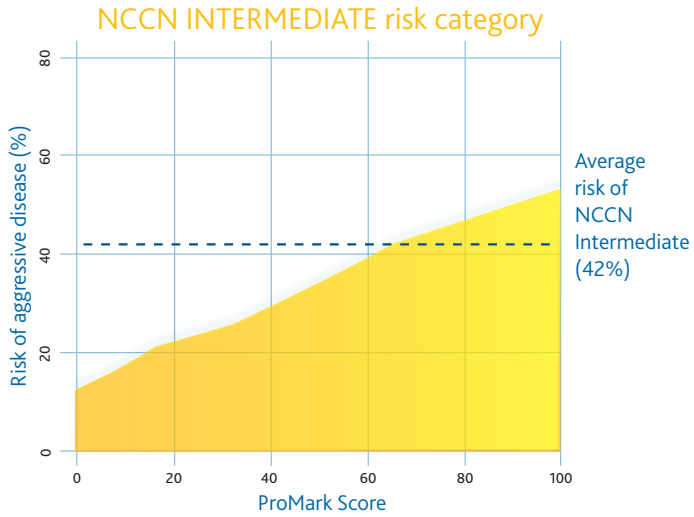
NCCN VERY LOW risk category



NCCN LOW risk category



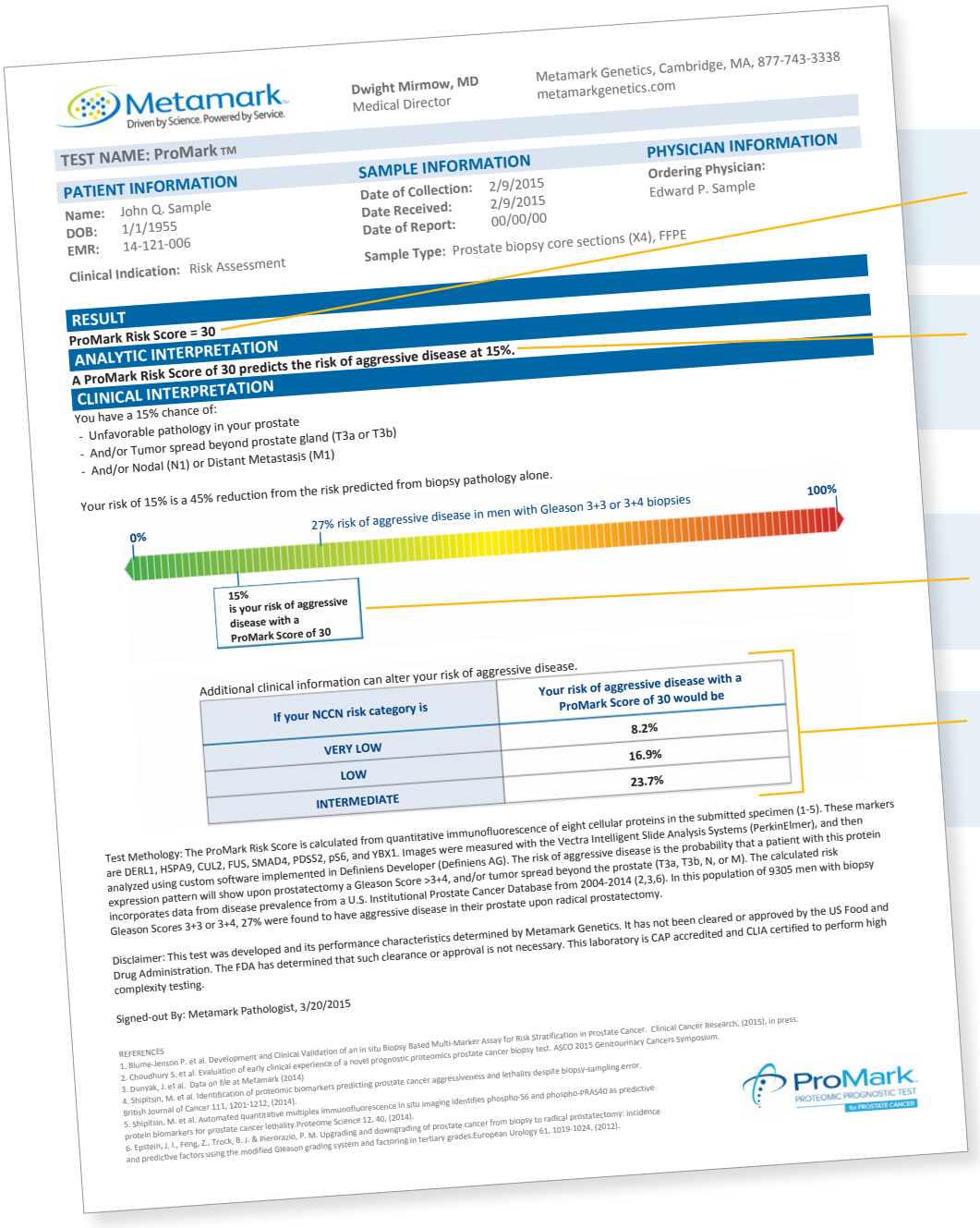
NCCN INTERMEDIATE risk category



Use proven data to **MAKE THE RIGHT TREATMENT DECISIONS** for your patient.

Personalized results

The ProMark report provides personalized information that is **EASY TO INTERPRET AND DISCUSS WITH YOUR PATIENT.**



Metamark
Driven by Science. Powered by Service.

Dwight Mirmow, MD
Medical Director

Metamark Genetics, Cambridge, MA, 877-743-3338
metamarkgenetics.com

TEST NAME: ProMark ™

PATIENT INFORMATION
Name: John Q. Sample
DOB: 1/1/1955
EMR: 14-121-006
Clinical Indication: Risk Assessment

SAMPLE INFORMATION
Date of Collection: 2/9/2015
Date Received: 2/9/2015
Date of Report: 00/00/00
Sample Type: Prostate biopsy core sections (X4), FFPE

PHYSICIAN INFORMATION
Ordering Physician:
Edward P. Sample

RESULT
ProMark Risk Score = 30

ANALYTIC INTERPRETATION
A ProMark Risk Score of 30 predicts the risk of aggressive disease at 15%.

CLINICAL INTERPRETATION
You have a 15% chance of:
- Unfavorable pathology in your prostate
- And/or Tumor spread beyond prostate gland (T3a or T3b)
- And/or Nodal (N1) or Distant Metastasis (M1)

Your risk of 15% is a 45% reduction from the risk predicted from biopsy pathology alone.

0%
27% risk of aggressive disease in men with Gleason 3+3 or 3+4 biopsies
100%
15% is your risk of aggressive disease with a ProMark Score of 30

Additional clinical information can alter your risk of aggressive disease.

If your NCCN risk category is	Your risk of aggressive disease with a ProMark Score of 30 would be
VERY LOW	8.2%
LOW	16.9%
INTERMEDIATE	23.7%

Test Methology: The ProMark Risk Score is calculated from quantitative immunofluorescence of eight cellular proteins in the submitted specimen (1-5). These markers are DERL1, HSPA9, CUL2, FUS, SMAD4, PDSS2, pS6, and YBX1. Images were measured with the Vectra Intelligent Slide Analysis Systems (PerkinElmer), and then analyzed using custom software implemented in Definiens Developer (Definiens AG). The risk of aggressive disease is the probability that a patient with this protein expression pattern will show upon prostatectomy a Gleason Score >3+4, and/or tumor spread beyond the prostate (T3a, T3b, N, or M). The calculated risk incorporates data from disease prevalence from a U.S. Institutional Prostate Cancer Database from 2004-2014 (2,3,6). In this population of 9305 men with biopsy Gleason Scores 3+3 or 3+4, 27% were found to have aggressive disease in their prostate upon radical prostatectomy.

Disclaimer: This test was developed and its performance characteristics determined by Metamark Genetics. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This laboratory is CAP accredited and CLIA certified to perform high complexity testing.

Signed-out By: Metamark Pathologist, 3/20/2015

REFERENCES
1. Blume-Jensen P. et al. Development and Clinical Validation of an in situ Biopsy Based Multi-Marker Assay for Risk Stratification in Prostate Cancer. Clinical Cancer Research, (2015), in press.
2. Choudhury S. et al. Evaluation of early clinical experience of a novel prognostic proteomics prostate cancer biopsy test. ASCO 2015 Genitourinary Cancers Symposium.
3. Dunyak, J. et al. Data on file at Metamark (2014)
4. Shipitsin, M. et al. Identification of proteomic biomarkers predicting prostate cancer aggressiveness and lethality despite biopsy-sampling error. British Journal of Cancer 111, 1201-1212, (2014).
5. Shipitsin, M. et al. Automated quantitative multiplex immunofluorescence in situ imaging identifies phospho-S6 and phospho-PRAS40 as predictive protein biomarkers for prostate cancer lethality.Proteome Science 12, 40, (2014).
6. Epstein, J. I., Feng, Z., Trock, B. J. & Pierorazio, P. M. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades.European Urology 61, 1019-1024, (2012).

ProMark
PROTEOMIC PROGNOSTIC TEST
for PROSTATE CANCER

Individualized ProMark Score for your patient between 0 and 100

Personalized risk of aggressive disease based on your patient's ProMark Score

Relative risk of aggressive disease compared to the average risk from biopsy pathology alone

Additional information: Personalized risk of aggressive disease if combined with your patient's NCCN risk category

Distinct information for you and your patient to develop an appropriate plan of treatment.

ProMark™
PROTEOMIC PROGNOSTIC TEST
for PROSTATE CANCER

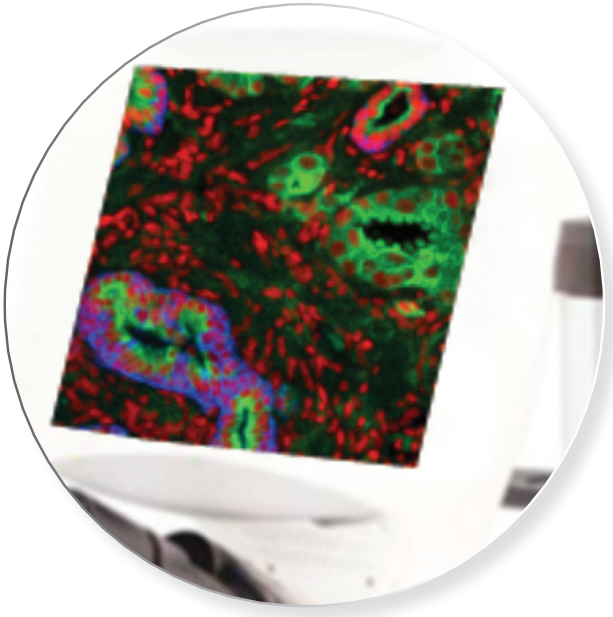
Independent, standalone information

As **the only standalone prognostic test for prostate cancer**, ProMark provides clinical value by itself without needing to be combined with other clinical or diagnostic data (NCCN, CAPRA, D'Amico) to provide a useful result.

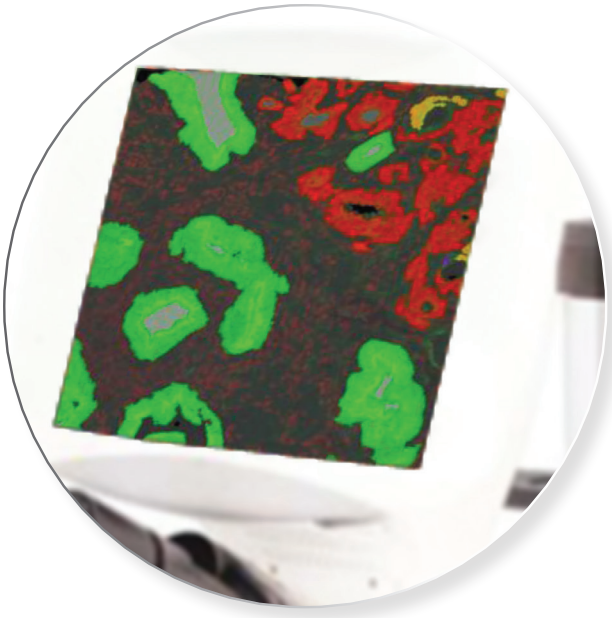
ProMark results can also be combined with additional clinical or diagnostic data to provide **even greater confidence** to guide appropriate clinical decision-making.

Cutting-edge imaging technology

ProMark, a first-of-its-kind protein-based prognostic test for prostate cancer progression, uses highly-intelligent and automated imaging technology that no other prognostic test is using today. This advanced technology allows ProMark to deliver focused and precise image analysis, and deliver a rapid and completely objective result to inform your decision-making process.



RAW IMAGE



Automated classification and measurement in BENIGN/MALIGNANT

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PROTEOMIC PROGNOSTIC TEST
for PROSTATE CANCER

A major breakthrough in prognostic testing for prostate cancer.

Information to make the right treatment decision for your patient.

Learn more.

To learn more about ProMark or to order the ProMark test for your patient:

- Talk to your regional Metamark representative
- Visit www.Metamark.us
- Call us at +1-877-743-3338

Metamark™

At Metamark, we are pioneers in science with a mission to provide breakthrough diagnostic and prognostic solutions for urological cancer care, backed by the highest level of customer support.

1 Blume-Jensen, P. et al. Development and Clinical Validation of an in situ Biopsy Based Multi-Marker Assay for Risk Stratification in Prostate Cancer. Clinical Cancer Research, doi:10.1158/1078-0432.ccr-14-2603 (2015).

2 Shipitsin, M. et al. Identification of proteomic biomarkers predicting prostate cancer aggressiveness and lethality despite biopsy-sampling error. British journal of cancer 111, 1201-1212, doi:10.1038/bjc.2014.396 (2014).

3 Shipitsin, M. et al. Automated quantitative multiplex immunofluorescence in situ imaging identifies phospho-S6 and phospho-PRAS40 as predictive protein biomarkers for prostate cancer lethality. Proteome science 12, 40, doi:10.1186/1477-5956-12-40 (2014).

4 Choudhury, S. et al. Evaluation of early clinical experience of a novel prognostic proteomics prostate cancer biopsy test. ASCO 2015 Genitourinary Cancers Symposium. (2015).

5 CLIA 22D2048749; CAP accreditation 8675321.

6 ProMark uses an automated, quantitative multiplex immunofluorescence method to measure the protein levels of 8 biomarkers (DERL1, HSPA9, CUL2, FUS, SMAD4, PDSS2, pS6, and YBX1) directly on sections of prostate biopsy tissue. The biomarkers individually and together predict the probability a cancer has not extended beyond the prostate, or has histological features of aggressive tumors.

7 The results of a ProMark assay provides, independent from clinical and pathological findings, a man's probability of non-aggressive disease. ProMark provides prognostic value above and beyond conventional clinical and pathological findings.

8 The ProMark test is intended for use on tissue from prostate biopsies with Gleason Grades 3+3 or 3+4. The ProMark test requires only 4 sections of prostate biopsy tissue, each 5 um thick, with a minimum of ~1mm2 of tumor and benign tissue.

9 >95% technical success rate; >80% overall success rate.