Putting the PSA in Perspective

AND - New Biomarkers to Support Personalized Decision-making Along the Continuum of Care

History of the PSA

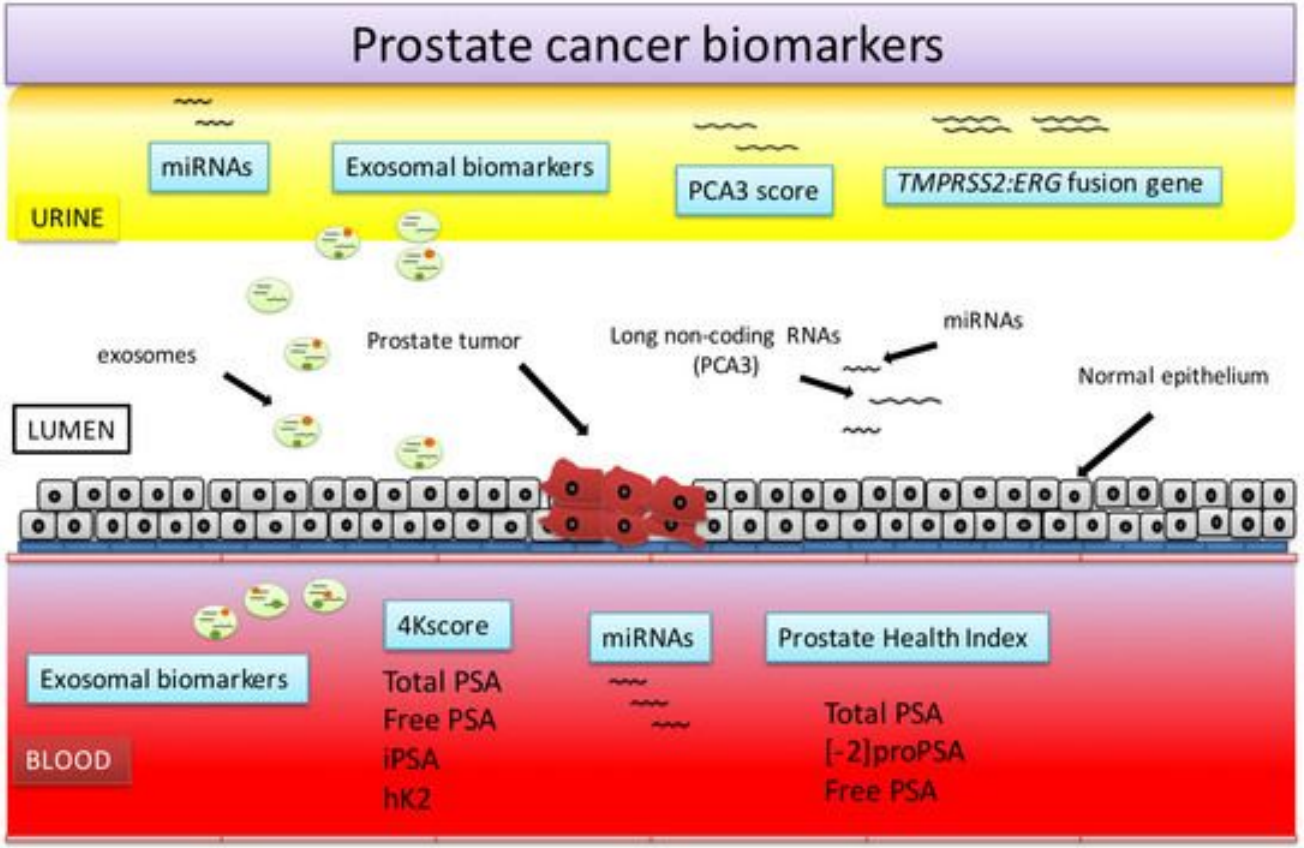
- Approved by the FDA in 1986 to monitor disease progression for men already diagnosed
- Approved in 1994 to screen for the possible presence of prostate cancer
- Sensitive, not specific...
- Since its introduction as a screening tool, each year:
  - about 2,500 lives are spared due to early detection.
  - About 100,000 men are subjected to aggressive treatment with no lifesaving benefit, and sometimes serious quality of life consequences.
- How to best administer the PSA is an evolving science.
- PSA is a gateway screening tool to newer and much more advanced biomarkers that help personalize care and reduce unnecessary pain and suffering.

Current Recommendations

- USPSTF: Doctors should discuss prostate screening with male patients.

- National Comprehensive Cancer Network (NCCN) A man having a baseline PSA of more than 1.0 ng/mL in his 40s is at the greatest risk of the future development of advanced prostate cancer.

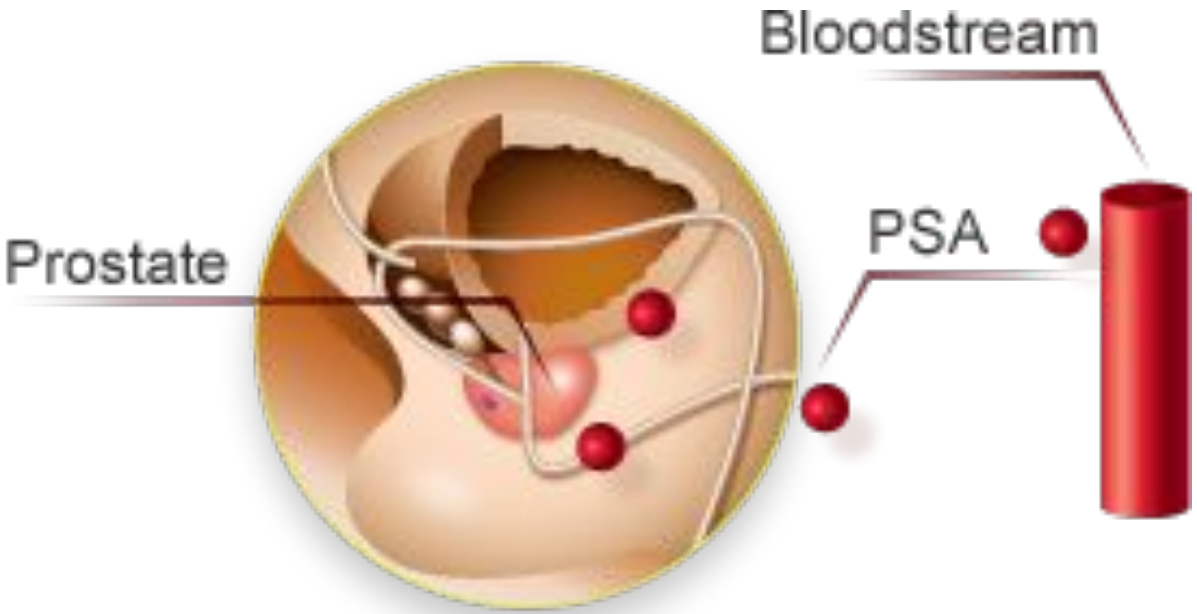
Urine and Blood Biomarkers



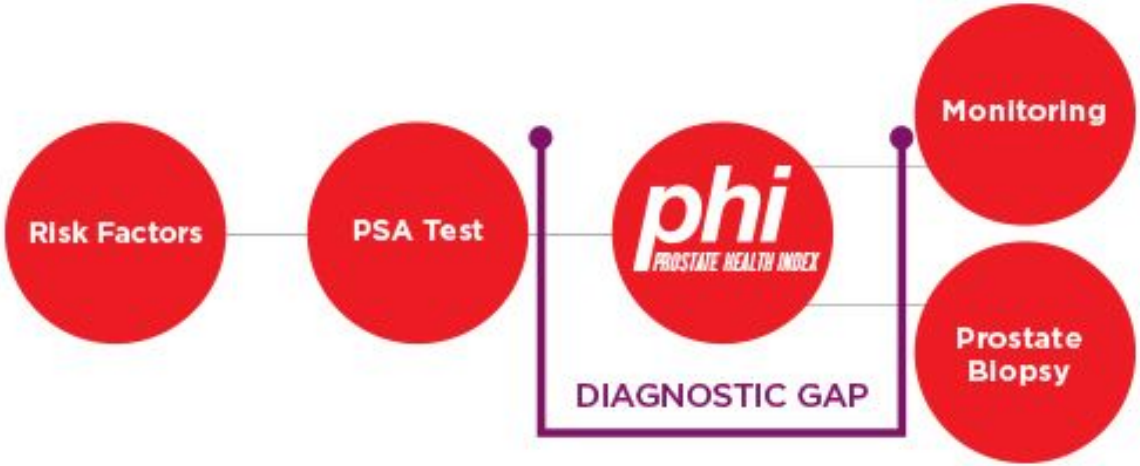
Biomarkers for Early Detection

- Prostate-specific antigen (PSA)*
- Prostate Health Index (phi)*
- PCA3
- 4Kscore
- SelectMDx
- ERG Protein Tissue Marker

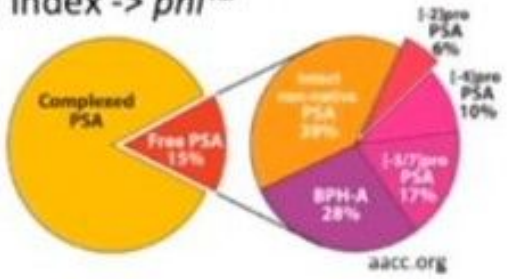
Prostate Specific Antigen (PSA)



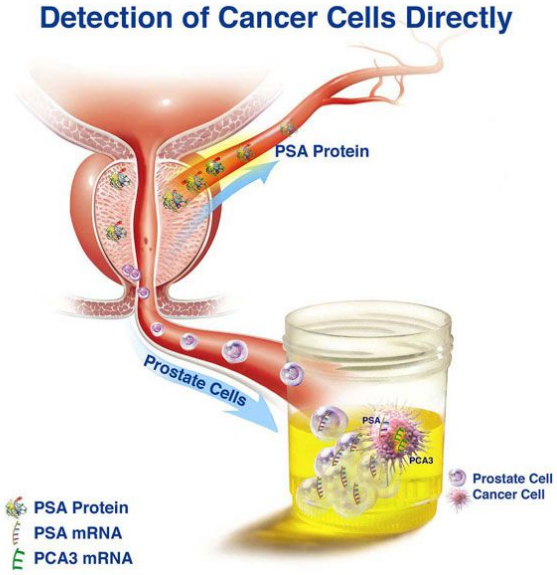
Prostate Health Index (PHI)



- Prostate Health Index -> *phi*™
  - Pro[-2]PSA
  - Free PSA
  - Total PSA



PCA3



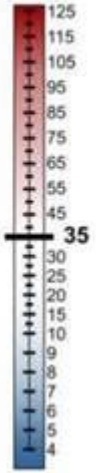
$$\text{PCA3 Score} = \frac{\text{PCA3 mRNA}}{\text{PSA mRNA}} \times 1000$$

(abnormal if >35)

Step 1: PSA & PCA3 mRNA anneals to complementary DNA primers attached to magnetic particles

Step 2: The mRNA is amplified using reverse transcription PCR

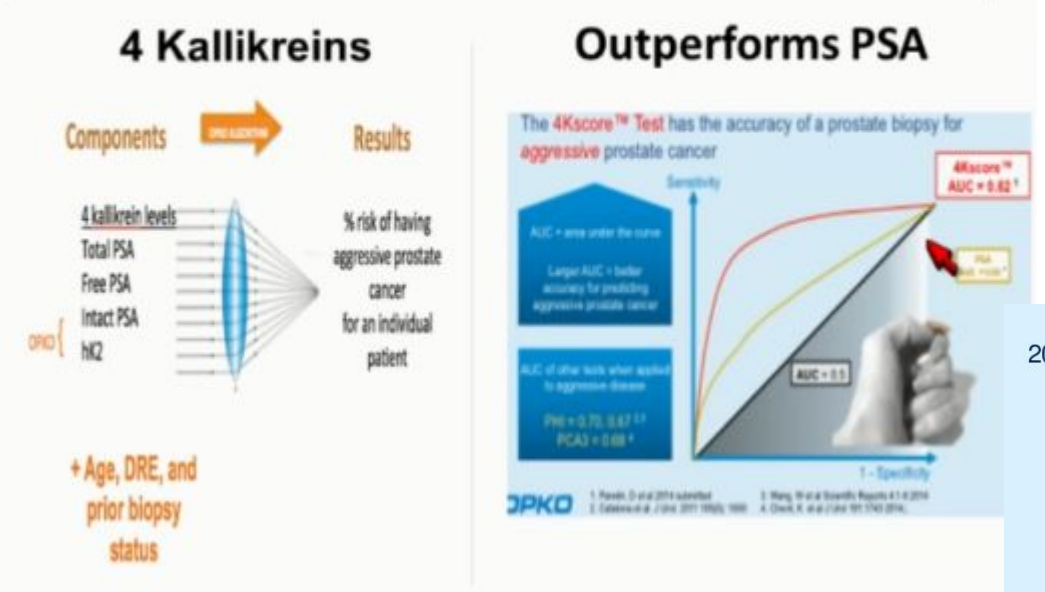
Step 3: The mRNA is detected using chemiluminescent probe



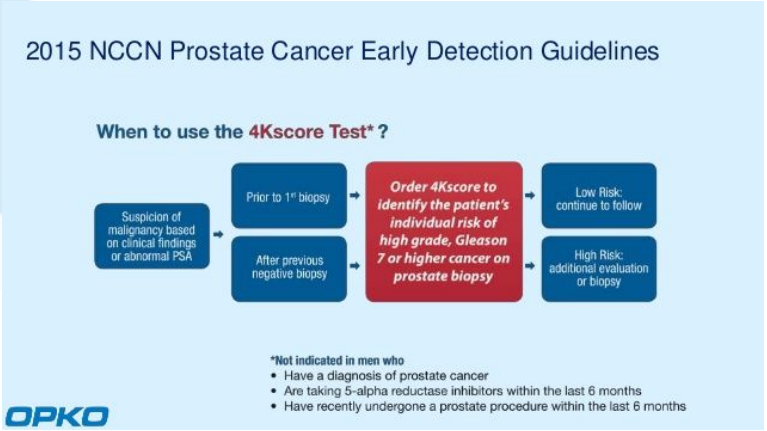
Increased Probability of Positive Biopsy

Decreased Probability of Positive Biopsy

4K Score


4 Kallikreins
Components
Results
4 kallikrein levels
Total PSA
Free PSA
Intact PSA
hK2
OPKO
% risk of having aggressive prostate cancer for an individual patient
+ Age, DRE, and prior biopsy status

Outperforms PSA
The 4Kscore™ Test has the accuracy of a prostate biopsy for aggressive prostate cancer
Sensitivity
4Kscore™ AUC = 0.82
AUC = 0.5
1 - Specificity
OPKO


2015 NCCN Prostate Cancer Early Detection Guidelines
When to use the 4Kscore Test* ?
Suspicion of malignancy based on clinical findings or abnormal PSA
Prior to 1st biopsy
After previous negative biopsy
Order 4Kscore to identify the patient's individual risk of high grade, Gleason 7 or higher cancer on prostate biopsy
Low Risk: continue to follow
High Risk: additional evaluation or biopsy
*Not indicated in men who
• Have a diagnosis of prostate cancer
• Are taking 5-alpha reductase inhibitors within the last 6 months
• Have recently undergone a prostate procedure within the last 6 months
OPKO

SelectMDx

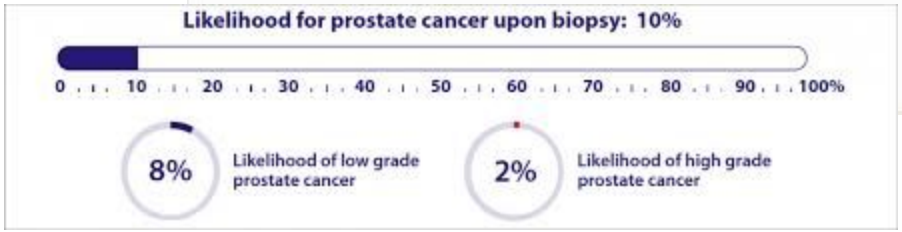
SelectMDx helps identify men at increased risk for aggressive cancer

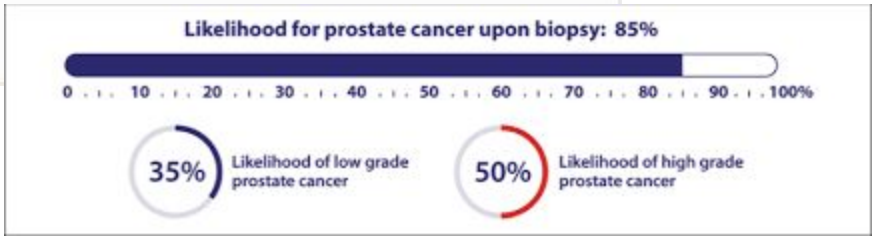
Improves patient risk stratification for prostate biopsy

For patients being considered for initial prostate biopsy

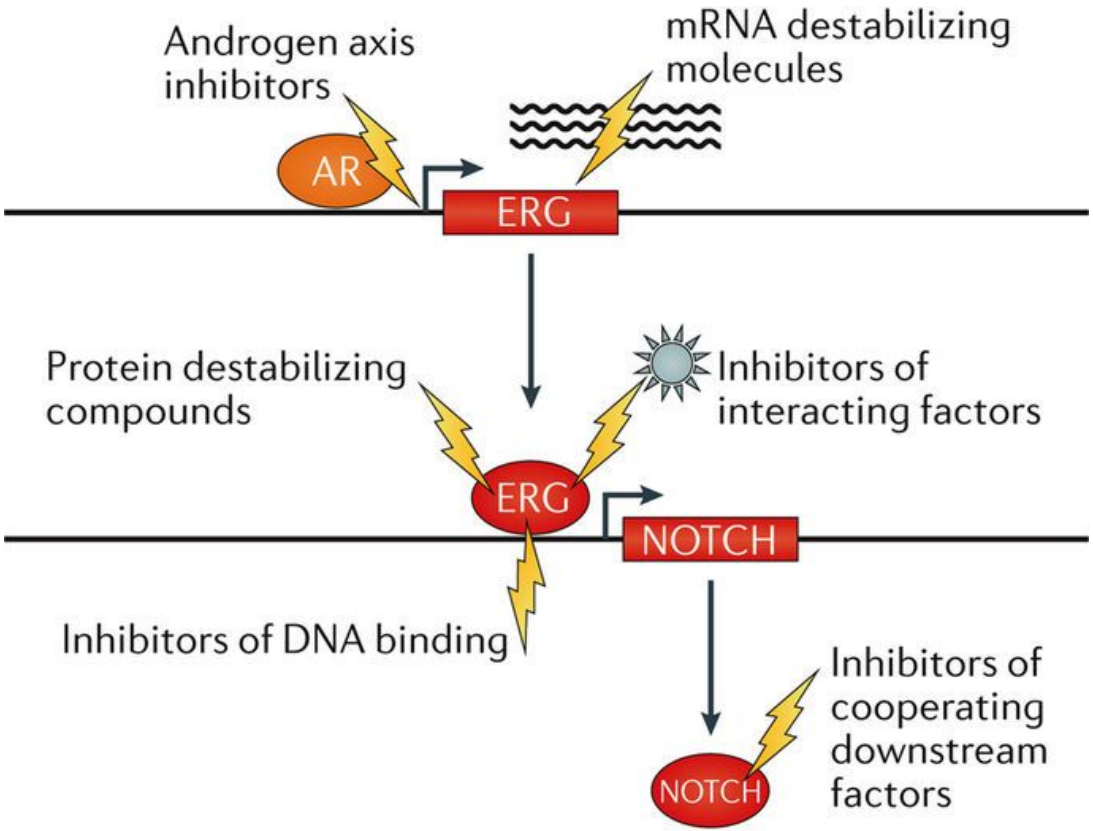
- Identify men at high risk for aggressive cancer
- Assay performed on non-invasive, urine sample

Very Low Risk
99.6% NPV for GS ≥8
98% NPV for GS ≥7





ERG Protein Tissue Marker



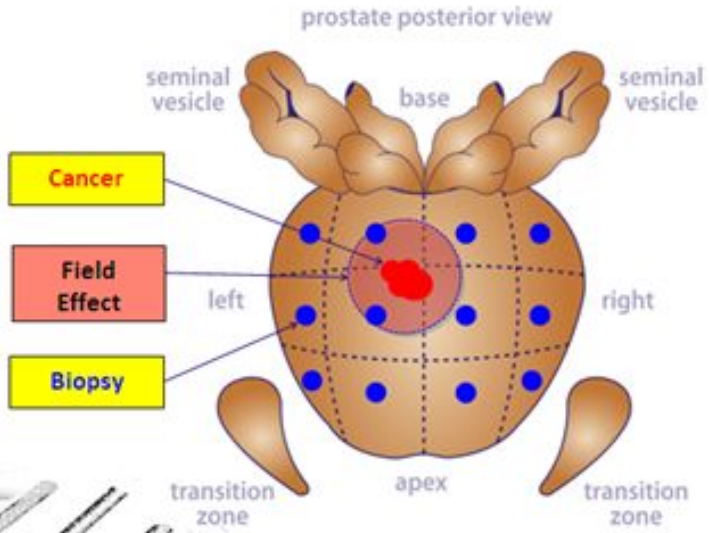
Biomarkers for Confirming Need for Repeat Biopsy

- PCA3*
- 4Kscore
- ConfirmMDx
- Know Error®

Confirm MDx

Epigenetic Changes Influence Gene Expression Without Changing the Genome

- *Confirm*MDx™ for Prostate Cancer detects an epigenetic field effect with the "cancerization" process at the DNA level
- This field effect around the cancer lesion can be present despite the normal appearance of cells
- Detection of field effects extends the coverage of the biopsy helping to rule in, or rule out, occult cancers



Know Error

A New Study by the INSTITUTE of MEDICINE Reveals...

...more than **5%** of diagnoses are in error, translating to...

5%
IOM ambulatory error rate

20
Average number of patient visits per physician per day

34%
Percentage of visits involving a diagnostic question

62
Average number of diagnostic errors per physician per year

184
Average number of days worked per year per physician

3,680
Patient visits per year per physician

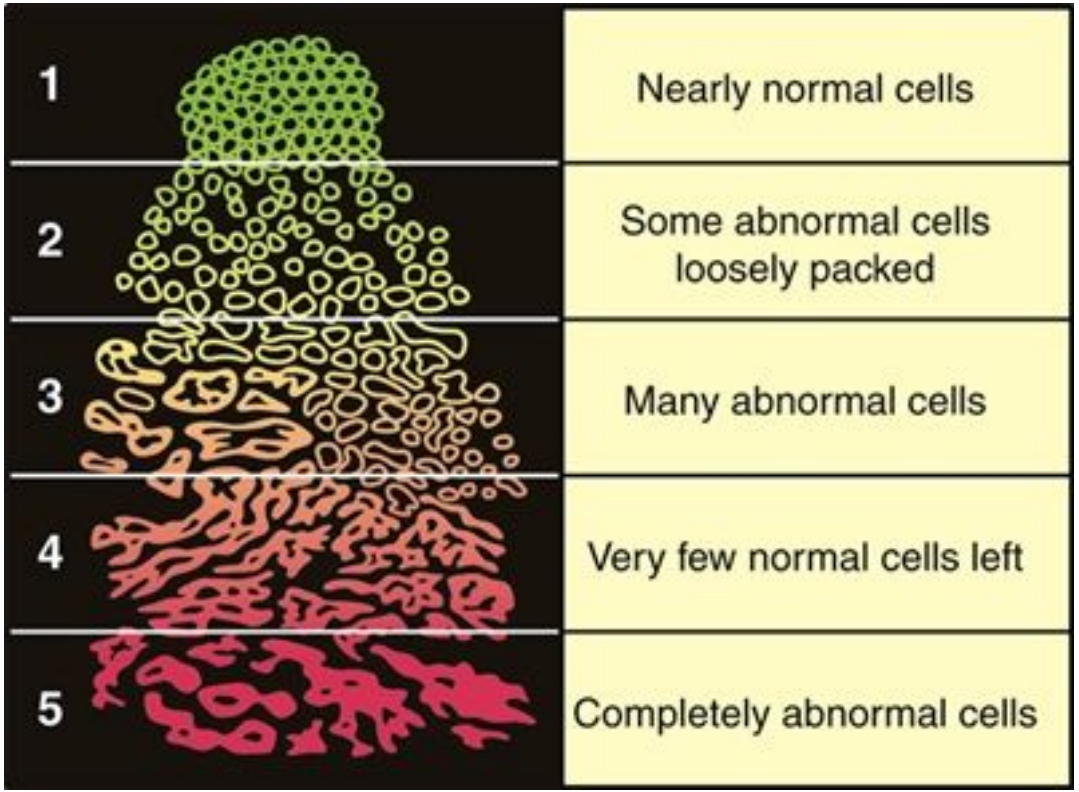
295,000
Number of primary care physicians, NPs and PAs in the United States

18,437,000
Estimated number of primary care diagnostic errors per year in the United States

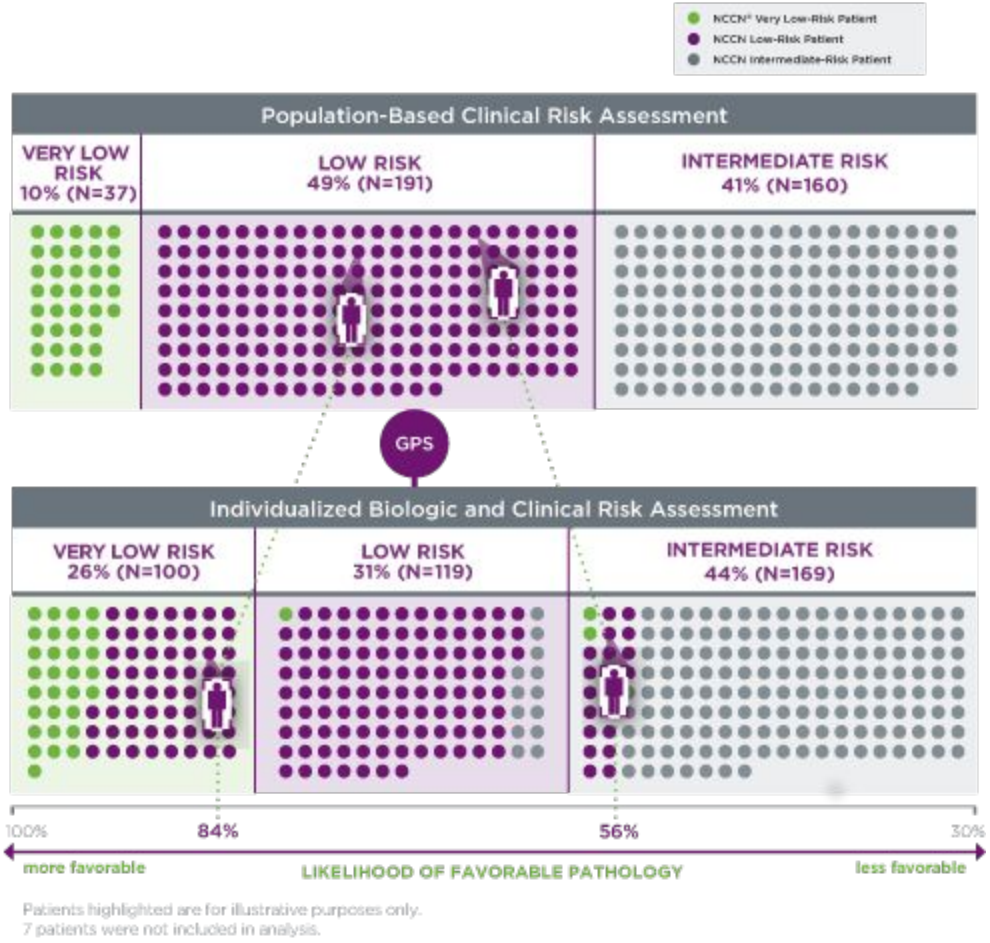
Biomarkers for Treatment Decision Support

- Gleason Score*
- Know Error®
- Oncotype DX
- Prolaris
- PTEN
- ProMarkTM

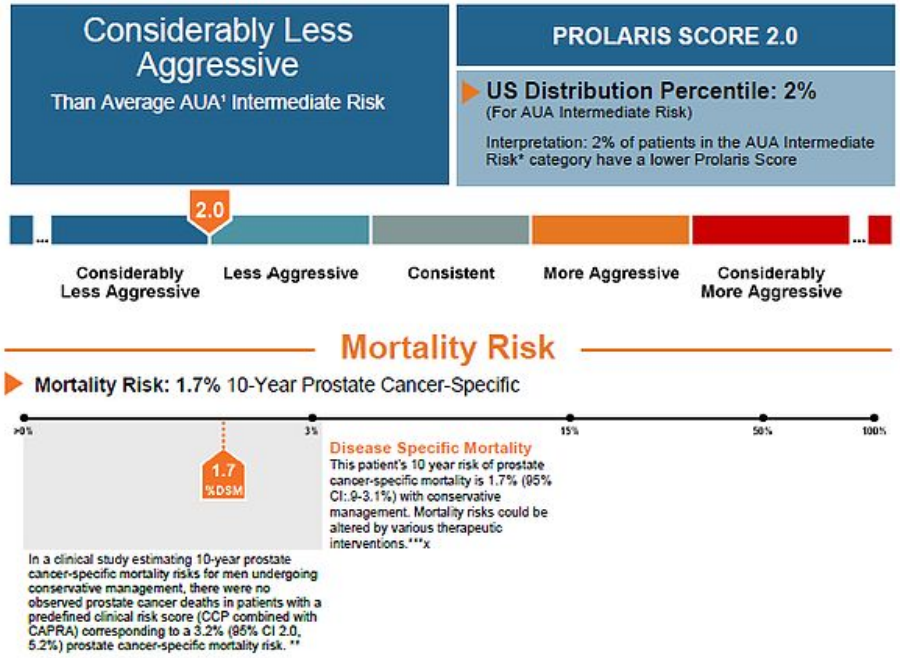
Gleason Score

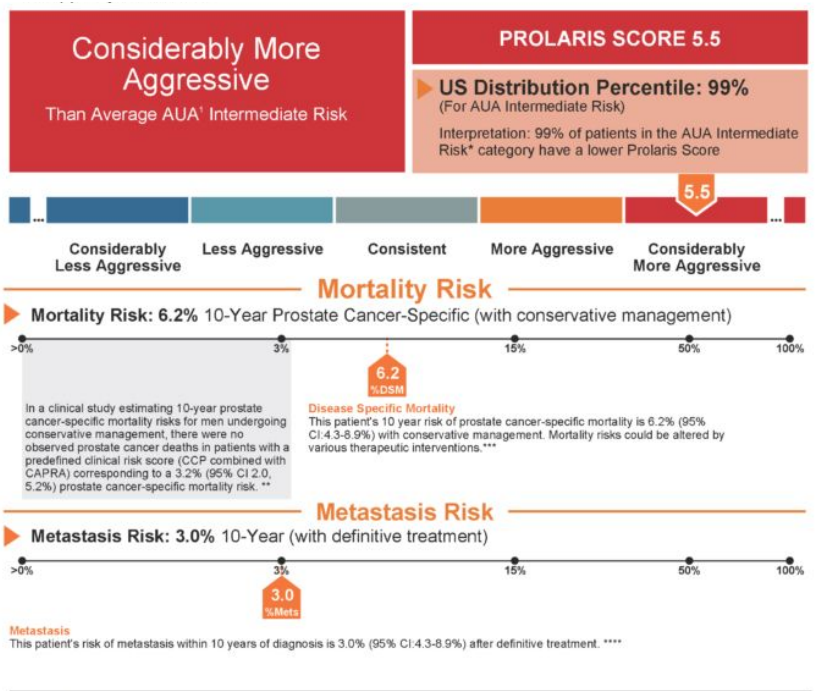


Oncotype DX

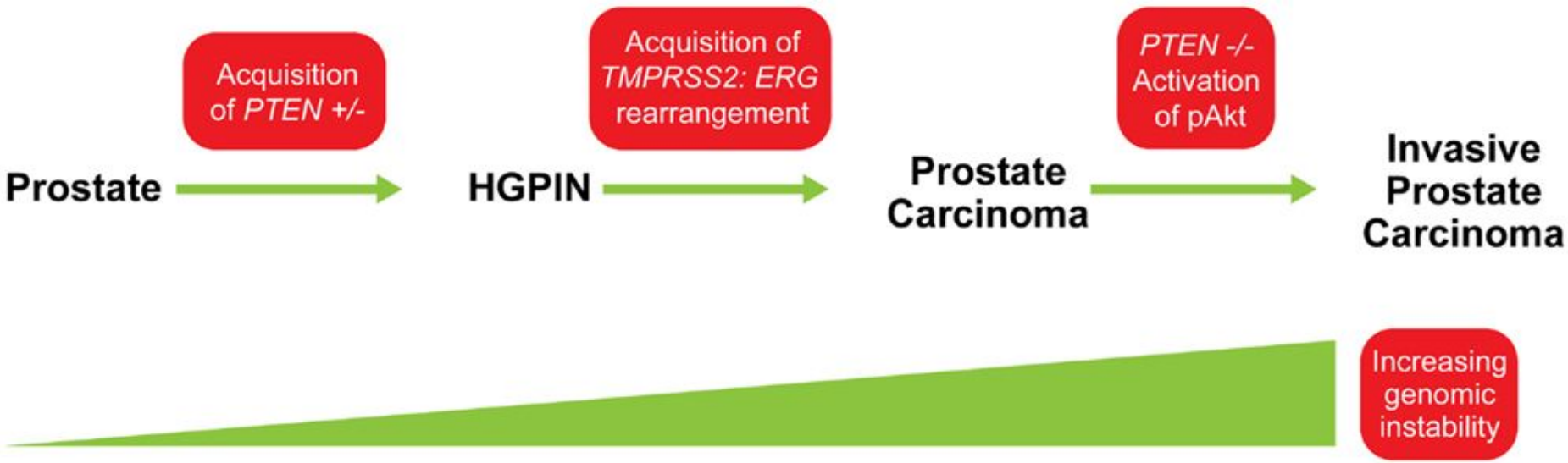

NCCN® Very Low-Risk Patient
NCCN Low-Risk Patient
NCCN Intermediate-Risk Patient
Population-Based Clinical Risk Assessment
VERY LOW RISK 10% (N=37)
LOW RISK 49% (N=191)
INTERMEDIATE RISK 41% (N=160)
GPS
Individualized Biologic and Clinical Risk Assessment
VERY LOW RISK 26% (N=100)
LOW RISK 31% (N=119)
INTERMEDIATE RISK 44% (N=169)
100%
84%
56%
30%
more favorable
LIKELIHOOD OF FAVORABLE PATHOLOGY
less favorable
Patients highlighted are for illustrative purposes only.
7 patients were not included in analysis.

Prolaris

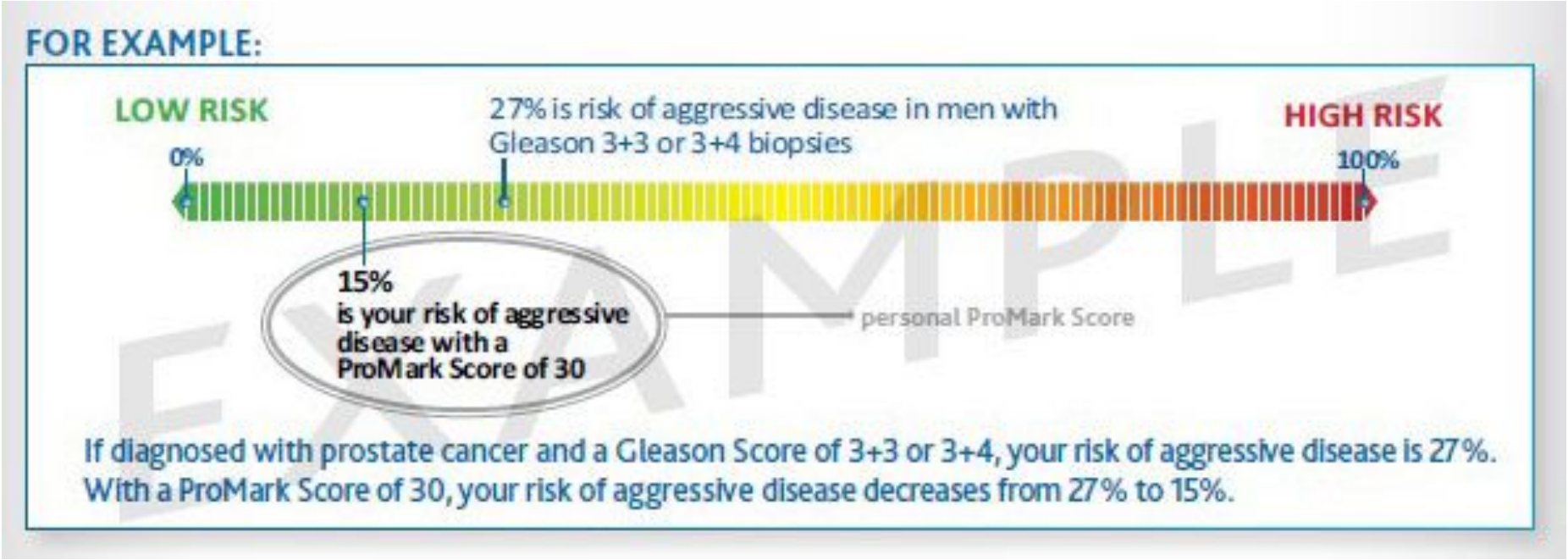

Considerably Less Aggressive
Than Average AUA¹ Intermediate Risk
PROLARIS SCORE 2.0
US Distribution Percentile: 2%
(For AUA Intermediate Risk)
Interpretation: 2% of patients in the AUA Intermediate Risk* category have a lower Prolaris Score
2.0
Considerably Less Aggressive
Less Aggressive
Consistent
More Aggressive
Considerably More Aggressive
Mortality Risk
Mortality Risk: 1.7% 10-Year Prostate Cancer-Specific
>0%
3%
15%
50%
100%
1.7 %DSM
Disease Specific Mortality
This patient's 10 year risk of prostate cancer-specific mortality is 1.7% (95% CI:.9-3.1%) with conservative management. Mortality risks could be altered by various therapeutic interventions.***x
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. **


Considerably More Aggressive
Than Average AUA¹ Intermediate Risk
PROLARIS SCORE 5.5
US Distribution Percentile: 99%
(For AUA Intermediate Risk)
Interpretation: 99% of patients in the AUA Intermediate Risk* category have a lower Prolaris Score
5.5
Considerably Less Aggressive
Less Aggressive
Consistent
More Aggressive
Considerably More Aggressive
Mortality Risk
Mortality Risk: 6.2% 10-Year Prostate Cancer-Specific (with conservative management)
>0%
3%
15%
50%
100%
6.2 %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 6.2% (95% CI:4.3-8.9%) with conservative management. Mortality risks could be altered by various therapeutic interventions.***
Metastasis Risk
Metastasis Risk: 3.0% 10-Year (with definitive treatment)
>0%
3%
15%
50%
100%
3.0 %Mets
Metastasis
This patient's risk of metastasis within 10 years of diagnosis is 3.0% (95% CI:4.3-8.9%) after definitive treatment. ****

PTEN


Acquisition of *PTEN* +/-
Acquisition of *TMPRSS2: ERG* rearrangement
PTEN -/- Activation of pAkt
Prostate
HGPIN
Prostate Carcinoma
Invasive Prostate Carcinoma
Increasing genomic instability

ProMarkTM


FOR EXAMPLE:
LOW RISK
0%
27% is risk of aggressive disease in men with Gleason 3+3 or 3+4 biopsies
HIGH RISK
100%
15%
is your risk of aggressive disease with a ProMark Score of 30
personal ProMark Score
If diagnosed with prostate cancer and a Gleason Score of 3+3 or 3+4, your risk of aggressive disease is 27%.
With a ProMark Score of 30, your risk of aggressive disease decreases from 27% to 15%.

Biomarkers for Considering the Need for Additional Treatment

- Decipher
- Prolaris

Decipher

Decipher prostate cancer classifier

GenomeDx Biosciences Laboratory
3550 Dunhill St., San Diego, CA 92121
Tel: 1-888-972-1601 | Fax: 1-855-324-2768
client.service@genomedx.com | www.genomedx.com

Patient Details
Patient Name: John13 Doe
Medical Record Number: 123456789
Date of Birth: 01/01/1940
Date of Prostatectomy: 09/01/2014

Order Information
Order Date: 09/15/2014
Specimen Received Date: 09/30/2014
GenomeDx Accession ID: DEC14068
Specimen ID: Lab9093783

Ordering Physician: x
Clinic/Hospital: y

Clinical Details

Pathology Report Date: 01/28/2013
Referring Pathologist/Laboratory: x

Pre-operative PSA (ng/mL): n/a
Gleason Score (Surgical Pathology): 4+5
☑ EPE ☐ SVI ☑ SM+ ☐ LNI ☐ BCR

Decipher Result: Genomic low risk

Summary of Decipher genomic risk results

Decipher 5 year risk of metastasis: 2.9%

Genomic risk of developing metastasis within five years of radical prostatectomy is **0.5x** the average clinical risk for a patient with adverse pathology.

Comments: Decipher indicates a patient's probability of developing metastasis within 5 years of a radical prostatectomy. The average risk* for metastasis by 5 years after surgery for clinically high-risk men is 6.0%. The Decipher risk reported here has a 95% confidence interval of 1.6% to 4.2%, which is significantly lower than average clinical risk and therefore the patient is considered to have a lower than average risk of clinical recurrence within 5 years.

*Average clinical risk refers to the average cohort risk of clinically high-risk men post surgery, established in a cohort of 1,010 clinically high-risk patients that received radical prostatectomy as first line treatment at the Mayo Clinic between 2000 and 2006. The average incidence of metastasis was 6.0% at 5 years post radical prostatectomy.

5-year Predicted Probability of Clinical Metastasis: a genomic risk score is derived by measuring the RNA-expression of 22 biomarkers in a primary prostate adenocarcinoma specimen (Erho et al., 2013). Decipher uses the genomic risk score to predict the 5 year probability for developing clinical metastasis; using a cox-proportional hazards survival model based upon a cohort of 1,010 clinically high-risk patients with 6.9 median years of Follow-up (Karnes et al., 2013). Decipher probabilities range between 0% and 100%. Decipher risk categories are determined from an optimized statistical model, representing significantly distinct metastatic risk (hazard ratios) between the risk categories. Relative risk is calculated as a ratio of the patient's Decipher probability as compared to the 6.0% average risk of clinical metastasis observed in this population of clinically high-risk men.

GenomeDx Medical Director (Name & Signature) _____ Date _____
Medical Directors: Timothy J. Triche, MD PhD | Doug Dolginow, MD

Disclaimer The 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. This test has not been cleared or approved by the U.S. Food and Drug Administration. Summary of surgical pathology report provided for convenience of Ordering Physician. Please refer to Referring Pathologist's original pathology report to guide treatment decisions.

CLIA ID # 05D2055897
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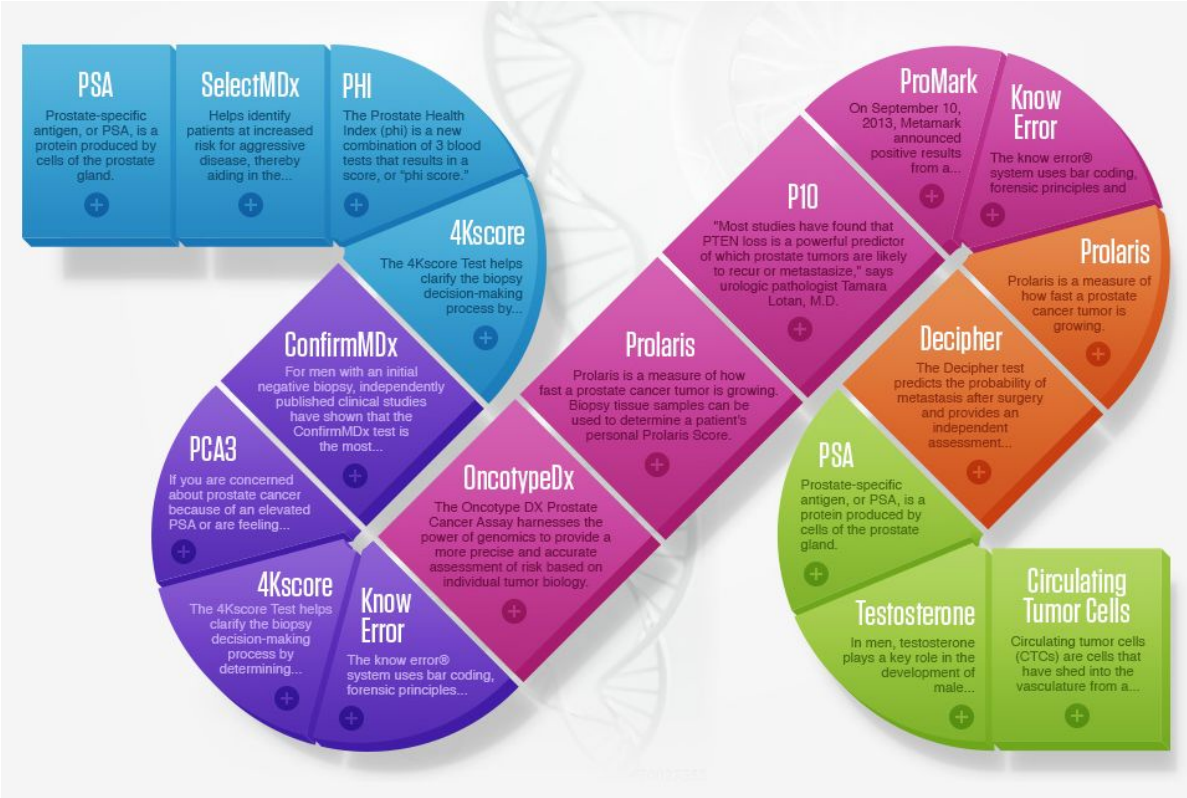
Summary


PSA
Prostate-specific antigen, or PSA, is a protein produced by cells of the prostate gland.
SelectMDx
Helps identify patients at increased risk for aggressive disease, thereby aiding in the...
PHI
The Prostate Health Index (phi) is a new combination of 3 blood tests that results in a score, or "phi score."
4Kscore
The 4Kscore Test helps clarify the biopsy decision-making process by...
ConfirmMDx
For men with an initial negative biopsy, independently published clinical studies have shown that the ConfirmMDx test is the most...
PCA3
If you are concerned about prostate cancer because of an elevated PSA or are feeling...
4Kscore
The 4Kscore Test helps clarify the biopsy decision-making process by determining...
Know Error
The know error® system uses bar coding, forensic principles...
OncotypeDx
The Oncotype DX Prostate Cancer Assay harnesses the power of genomics to provide a more precise and accurate assessment of risk based on individual tumor biology.
Prolaris
Prolaris is a measure of how fast a prostate cancer tumor is growing. Biopsy tissue samples can be used to determine a patient's personal Prolaris Score.
P10
"Most studies have found that PTEN loss is a powerful predictor of which prostate tumors are likely to recur or metastasize," says urologic pathologist Tamara Lotan, M.D.
ProMark
On September 10, 2013, Metamark announced positive results from a...
Know Error
The know error® system uses bar coding, forensic principles and
Prolaris
Prolaris is a measure of how fast a prostate cancer tumor is growing.
Decipher
The Decipher test predicts the probability of metastasis after surgery and provides an independent assessment...
PSA
Prostate-specific antigen, or PSA, is a protein produced by cells of the prostate gland.
Testosterone
In men, testosterone plays a key role in the development of male...
Circulating Tumor Cells
Circulating tumor cells (CTCs) are cells that have shed into the vasculature from a...

Test	Approximate Cost and/or Contact
PHI	$150
PCA3 (early detection)	~ $385
4K Score	$400 (call 855-452-4554)
Select MDx	$500 (60% discount for uninsured)
ERG Protein Tissue Marker	? (call 800-428-5074)
Confirm MDx	$3,300 (60% discount for uninsured)
Know Error	$295 cap on out of pocket (subject to change)
Oncotype DX	$4520 (financial assistance TBD)
Prolaris	$375 (assistance programs on website)
PTEN	$249
ProMark TM	~$350 (call 877-743-3338)
Decipher	$699

Take Home Message

- The science of early detection and decision support is rapidly evolving.

- Discussions should occur on an individual and personalized basis.

- Men need to know what tests to ask about - ***and <u>when</u>***.