Disclosures

Bayer pharma, J & J, *Study Advisory Committee*

AUA and NCCN Prostate Cancer Early Detection Guidelines Panel member

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Learning Objectives

- Discuss how biomarker testing and imaging can *guide management decision* in prostate cancer
- Review relevant guideline recommendations.

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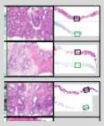
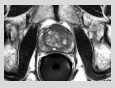
What is a Biomarker?

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





Imaging as a biomarker



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Part I. Prostate Cancer Diagnosis

- Biomarkers
- MRI

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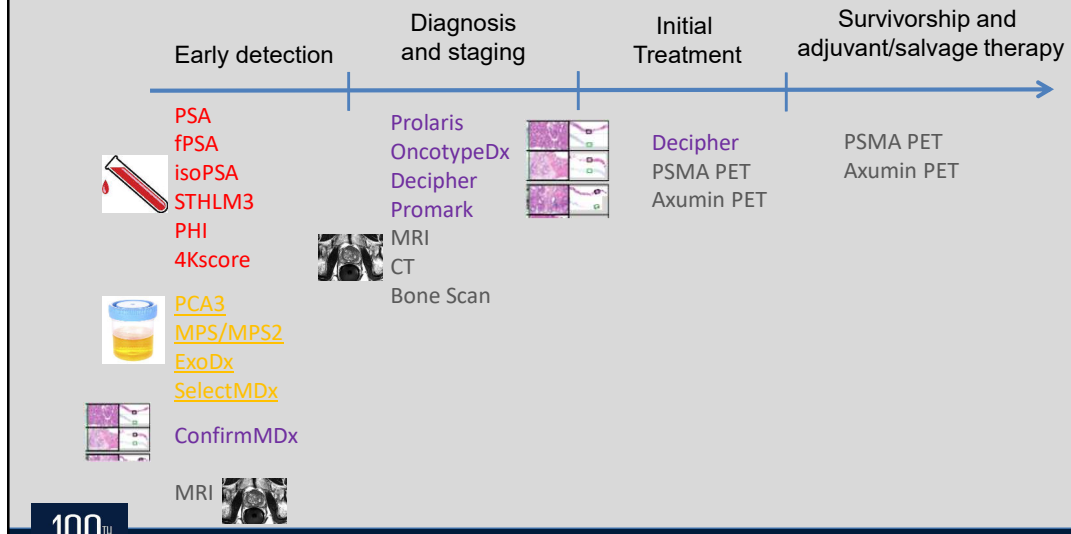
Biomarkers in Localized Prostate Cancer Continuum of Care



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Biomarkers for Early Detection of Prostate Cancer

SERUM	URINE	TISSUE
PSA	ExoDx**	ConfirmMDx
isoPSA	Select MDx	
phi	MPS/MPS2**	
4K Score	miR Sentinel**	
Proclarix		
STHML-3		

** DRE not needed

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Biomarkers for Early Detection of Prostate Cancer

Table 2. Summary of early detection biomarkers usage, performance, and guideline inclusion.

Test	Source	Insurance coverage	Clinical use	AUC initial Bx csPCa	AUC repeat Bx csPCa	Similar performance in racially diverse population	MRI + biomarker integration strategy evaluated	EAU	NCCN
4k Score	Blood	Widespread	Initial or Repeat Biopsy	0.82	0.87	Y	Y	Y	Y
phi	Blood	Widespread	Initial or Repeat Biopsy	0.82	0.88 (+ clinical variables)	N			
SelectMDx	Post-DRE Urine	Medicare	Initial Biopsy	0.82 (+ clinical variables)	-	Un Inc St			
ExoDx	Urine	Widespread	Initial or Repeat Biopsy	0.74 (alone) 0.73-0.77 (+ clinical variables)	0.66	Un Inc St			
MPS	Post-DRE Urine	Not Covered (Pending)	Initial or Repeat Biopsy	0.77	No Published Data	Y			
PCA3	Post-DRE Urine	Widespread (Prior negative)	Repeat Biopsy	0.78 (+ clinical variables)	0.79 (+ clinical variables)	Un Incompletely Studied			
ConfirmMDx	Tissue Based	Medicare	Repeat Biopsy	-	0.76	Y	N	Y	Y

AUC, area under the curve; EAU, European Association of Urology; MPS, MyProstateScore; MRI, multiparametric; NCCN, National Comprehensive Cancer Network; PCA, prostate cancer antigen.

- Decrease need for biopsy:
  → 20 – 30% less biopsies.
- Minimize detection of GG1 PCa.
- Misses < 5% GG2+.

Farha M, Salami SS, Ther Adv Urol 2022

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Lack/Limited Biomarker Validation Studies in Blacks

Table 2. Summary of early detection biomarkers usage, performance, and guideline inclusion.

Test	Source	Insurance coverage	Clinical use	AUC initial Bx csPCa	AUC repeat Bx csPCa	Similar performance in racially diverse population	MRI + biomarker integration strategy evaluated	EAU	NCCN
4k Score	Blood	Widespread	Initial or Repeat Biopsy	0.82	0.87	Y	Y	Y	Y
phi	Blood	Widespread	Initial or Repeat Biopsy	0.82	0.88 (+ clinical variables)	N	Y	Y	Y
SelectMDx	Post-DRE Urine	Medicare	Initial Biopsy	0.82 (+ clinical variables)	-	Unstudied/ Incompletely Studied	Y	Y	Y
ExoDx	Urine	Widespread	Initial or Repeat Biopsy	0.74 (alone) 0.73-0.77 (+ clinical variables)	0.66	Unstudied/ Incompletely Studied	Y	N	Y
MPS	Post-DRE Urine	Not Covered (Pending)	Initial or Repeat Biopsy	0.77	No Published Data	Y	N	N	Y
PCA3	Post-DRE Urine	Widespread (Prior negative)	Repeat Biopsy	0.78 (+ clinical variables)	0.79 (+ clinical variables)	Unstudied/ Incompletely Studied	N	Y	Y
ConfirmMDx	Tissue Based	Medicare	Repeat Biopsy	-	0.76	Y	N	Y	Y

AUC, area under the curve; EAU, European Association of Urology; MPS, MyProstateScore; MRI, multiparametric; NCCN, National Comprehensive Cancer Network; PCA, prostate cancer antigen.

Black patients are known to have lower ERG expression

Farha M, Salami SS, Ther Adv Urol 2022

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Use of Serum and Urine Biomarkers as Adjunct to PSA

AUA — **OPTIONAL**

NCCN — **OPTIONAL**

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer — **OPTIONAL**

Not for Screening
Do not order reflexively
Only if it might CHANGE management

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Important Considerations…

- Why are you getting the test?
- Patients and providers want a test that “tells them” the “right answer”.
  - Unfortunately, the tests generally just give percentage risk or score.
- Know the data, use tests that works for you and your patients.
- Have an action plan that the patient agrees to before ordering the test.
- Don’t order too many tests or order tests reflexively!
- Was the biomarker validated in the patient population of interest?

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The Case for Prostate mpMRI Prior to Biopsy

- To direct biopsies at regions suspicious for cancer.

↑ Sensitivity: find more cancer.

- MAYBE to avoid systematic 12-core biopsies.
- MAYBE to avoid biopsy in patients with negative MRI.

↑ Specificity: do fewer biopsies.

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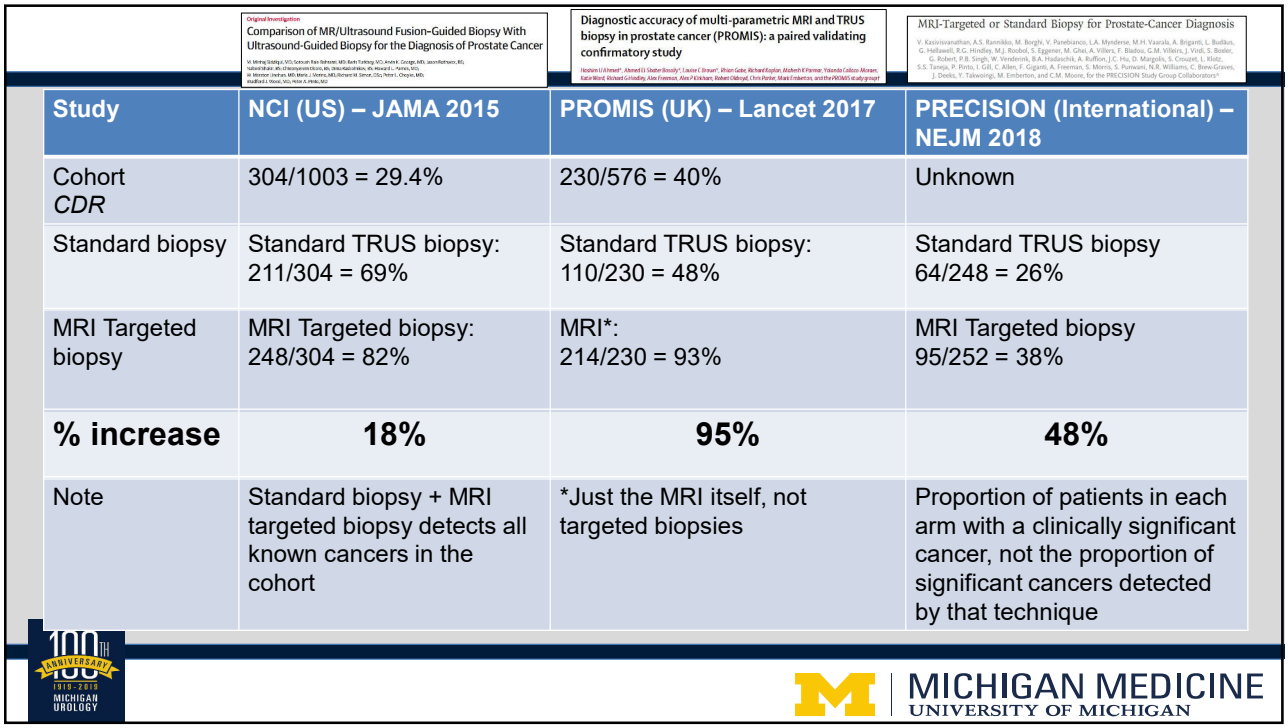

Study	NCI (US) – JAMA 2015	PROMIS (UK) – Lancet 2017	PRECISION (International) – NEJM 2018
Cohort *CDR*	304/1003 = 29.4%	230/576 = 40%	Unknown
Standard biopsy	Standard TRUS biopsy: 211/304 = 69%	Standard TRUS biopsy: 110/230 = 48%	Standard TRUS biopsy 64/248 = 26%
MRI Targeted biopsy	MRI Targeted biopsy: 248/304 = 82%	MRI*: 214/230 = 93%	MRI Targeted biopsy 95/252 = 38%
% increase	**18%**	**95%**	**48%**
Note	Standard biopsy + MRI targeted biopsy detects all known cancers in the cohort	*Just the MRI itself, not targeted biopsies	Proportion of patients in each arm with a clinically significant cancer, not the proportion of significant cancers detected by that technique

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Summary of AUA Recommendations for Use of MRI in EDPC

		Initial Biopsy	Repeat Biopsy
MRI		**Optional**	**Required** (if not done)
MRI positive (PIRADS 3 – 5)	**Targeted***	**Required**	**Required**
	Systematic	**Optional**	**Optional**
MRI negative (PIRADS 1 & 2)	**Targeted**	**N/A**	**N/A**
	Systematic	**Required***	**Optional**

Targeted Biopsy:

- 2 or more biopsies per target.
- Computer/software registration or cognitive registration.

AUA Guideline 2023

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Part II. Prostate Cancer Staging and Risk Stratification

- Biomarkers
- MRI
- PSMA PET scan

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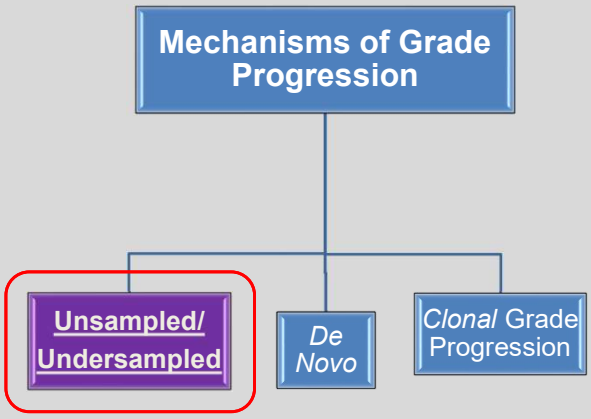
Tools to Detect Progression on Active Surveillance



- PSA/PSAD (> 0.15 ng/dL/cc).
- Biopsies.
- Biomarkers.
- MRI.
- Evolving tools: Micro Ultrasound, PSMA PET/CT, Nomograms, Artificial intelligence.

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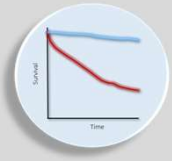
Genomic Biomarkers Facilitate Personalization of Therapy



- **Prognostic** biomarkers provide information on outcomes of the disease *independent of the treatment received.*
  - *Prolaris (CCP), Decipher (GC), Oncotype (GPS), Promark.*

- **Predictive** biomarkers identifies response or resistance to a specific therapy – but *not all treatments*.
  - *Decipher (GC): adjuvant XRT, ADT in high risk.*
  - *AR-V7.*
  - *ArteraAI®*
- **Both** can be used to personalize therapy.

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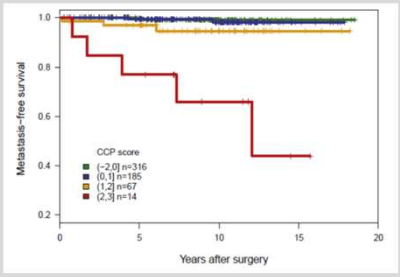
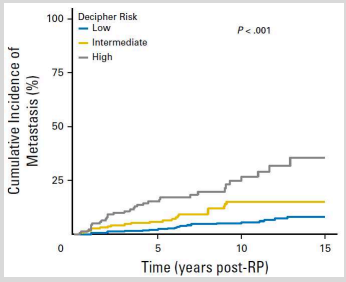
Genomic Biomarkers Provides Independent Prognostic Information

Prolaris



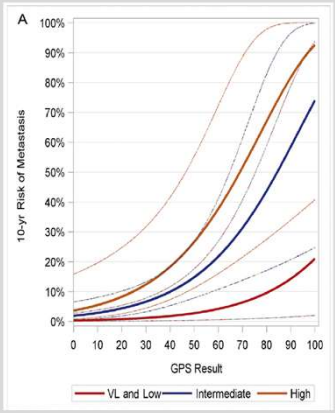
Bishoff JT, et al. *J Urol.2014;*192(2):409-414.

Decipher



Spratt et al. J Clin Oncol. 2017 Jun 20;35(18):1991-1998

Oncotype



Van Den Eeden SK, et al. *Eur Urol*. 2018;73(1):129-138.

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Tissue-Based Biomarkers in Active Surveillance

- Mixed and inconclusive data in retrospective AS cohorts.
  - Limited by tumor heterogeneity and multifocality.
- Have not been prospectively tested or shown to improve long-term outcomes in AS.

Salami et al, JCI Insight, 2018 Wei et al, Eur Uro, 2018; Kornberg et al, J Ur, 2019; Lin et al, JCO 2020; Salami et al, Eur Uro, 2021; Spratt et al, JNCI Cancer Spectr. 2023

How Guideline Statements on Molecular Biomarkers

- ASCO 2022 (*Eggener et al, JCO, 2019*):
  - "Routine ordering of molecular biomarkers is not recommended."
  - "…use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision." e.g., high volume GG1, GG1 with abnl DRE or high PSAD, low volume GG2.

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Guideline Statements on Molecular Biomarkers

- AUA 2022 (*Eastham et al, J Urol, 2022*):
  - **Statement 2:** Clinicians may selectively use tissue-based genomic biomarkers when added risk stratification may alter clinical decision making. (Expert Opinion).
  - **Statement 3:** Clinicians should not routinely use tissue-based genomic biomarkers for risk stratification or clinical decision-making. (Moderate Recommendation; Evidence Level: Grade B).

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Guideline Statements on Molecular Biomarkers

- EAU 2024
  - "…these tests should not be offered routinely but only in subsets of patients where the test result provides clinically actionable information, such as for instance in men with favourable intermediate-risk PCa who might opt for AS"
- NCCN 2024
  - "These tools are recommended to be used when they have the potential ability to change disease management. These tools should not be ordered reflexively."

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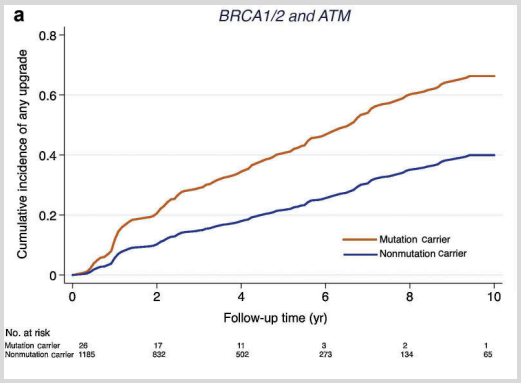
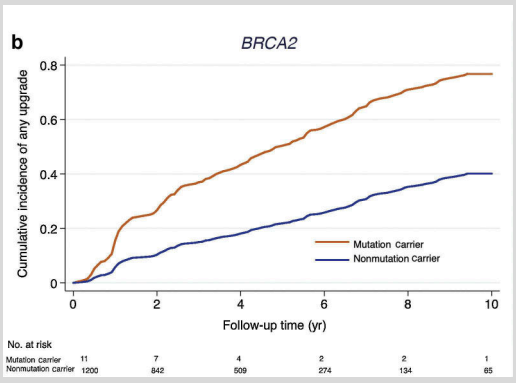
Germline Mutations in *BRCA1/2*, *ATM* are Associated with Grade Progression





Upgrading in 278/1185 (**23%)** noncarriers vs. 11/26 (**42%**) mutation carriers.

Carter B, et al. Eur Urol. 2018.

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Need Predictive Biomarkers: ArteraAI Test®

NEJM Evidence

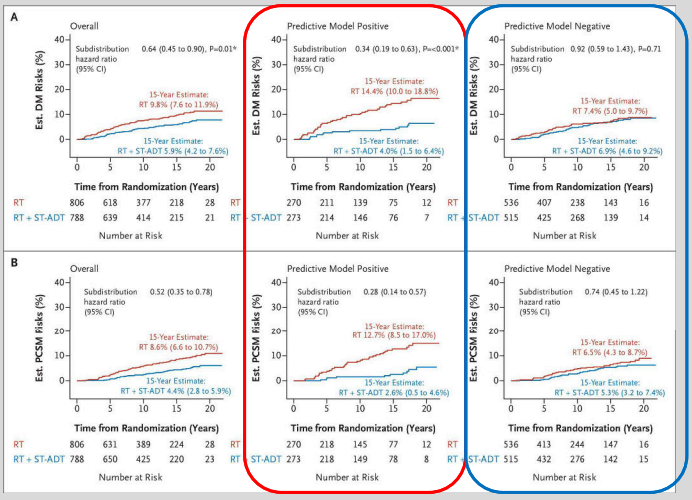
ORIGINAL ARTICLE

Artificial Intelligence Predictive Model for Hormone Therapy Use in Prostate Cancer

AI Model: Age, PSA, Gleason, T-Stage, **H/E Image**.

NRG/RTOG 9408 validation

- Model positive (n = 543): ADT significantly reduced the risk of DM.
- Model negative (n = 1051), ADT did not provide benefit.



Spratt et al. NEJM Evid 2023 Aug;2(8):EVIDoa2300023

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NCCN Guidelines 2024

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Prostate Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF RISK STRATIFICATION

Table 2. Risk Stratification: Selected Advanced Tools for Localized Prostate Cancer

Category	Tool	Predictive	Prognostic	Prognostic Endpoint Trained For[f]	Simon Level of Evidence[1,d]	Treatment Implications
Gene Expression						
	22-gene genomic classifier (GC) (Decipher)	No	Yes	Metastasis	IB	See Table 3
	31-gene cell cycle progression (CCP) assay (Prolaris)	No	Yes	See footnote[g]	IIIC[i]	
	17-gene Genomic Prostate Score (GPS) assay	No	Yes	Adverse pathology	IIIC	
AI Pathology						
	Multimodal artificial intelligence (ArteraAI Prostate)	Yes	Yes	BCR, DM, PCSM[h]	IB Predictive IB Prognostic	See Table 3
Germline						
	HRD	No	Unclear	—	VD	
Risk Stratification: Selected Advanced Tools Post-RP						
Gene Expression						
	22-gene GC	No	Yes	Metastasis	IB	See Table 3
	31-gene CCP assay	No	Yes	See footnote[g]	IVD	
	17-gene GPS assay	No	Yes	Adverse pathology	IVD	

HRD = Homologous recombination deficiency, DM= distant metastases, PCSM = Prostate cancer-specific mortality

Schaeffer et al, 2024

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MRI Performance in Active Surveillance Cohorts

- Significant interobserver variability (*kappa,* 0.15 – 0.61).
- Performance issues:
  - No difference in upgrading by systematic (27%) vs. MRI targeted (33%).
  - No difference in upgrading if upfront MRI (23%) vs after diagnosis (19%).
  - Progression missed by MRI but detected by systematic Bx in 31 – 36%.
  - NPV: 70 – 85%.
- No more often than every **2** years.

Vargas et al, J Urol 2012; Frye et al, J Urol, 2017
Tran et al, Eur Urol, 2017; Nasseri et al, J Urol, 2017
Klotz et al, Eur Urol, 2019; Liss et al, J Urol 2020
Rajwa et al, Eur Uro, 2021; Salami et al, Eur Uro, 2021
Luiting et al, Eur Urol, 2022

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MRI for Active Surveillance: Guideline Statements

- ASCO (2016): “The AS protocol may include ancillary tests that are still under investigation. These could include mpMRI and genomic testing… mpMRI should not be used as a replacement for surveillance biopsy.” (*Chen et al, JCO, 2016*)

- AUA Guideline (2022), Statement 18: “In patients selecting active surveillance, clinicians should utilize multiparametric magnetic resonance imaging (mpMRI) to augment risk stratification, but this should not replace periodic surveillance biopsy. (*Expert Opinion; Eastham et al, J Urol, 2022*)

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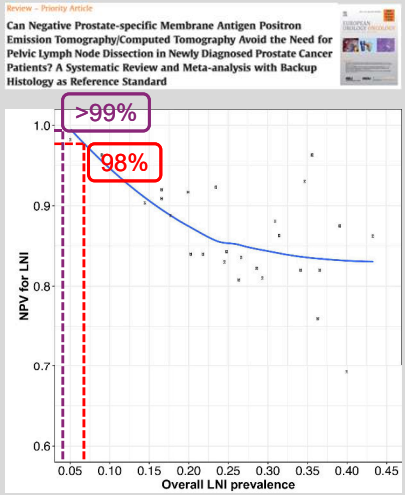
PSMA PET/CT Provides Accurate Staging for Prostate Cancer



27 2,832

- **AUC:** 0.84
- **Sensitivity:** 58%
- **Specificity:** 95%
- **NPV:** 87%

Stabile et al, Eur Urol Oncol. 2022 Feb;5(1):1-17

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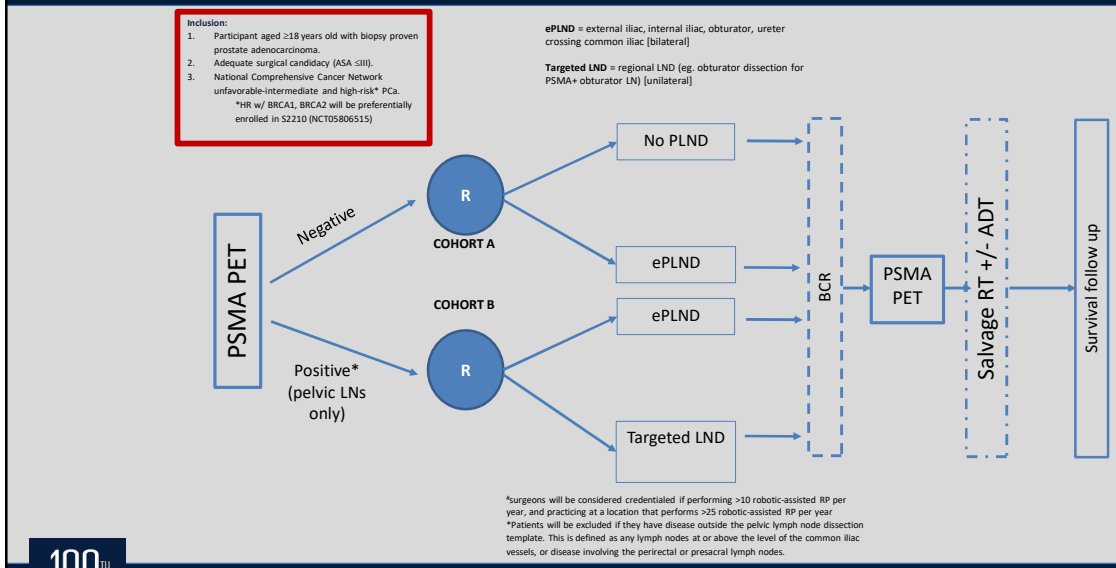
APPLY-PSMA: A Trial to Evaluate Targeted/No PLND



SWOG CANCER RESEARCH NETWORK

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Concluding Comments

- Biomarkers can improve detection of GG2 prostate cancer.
- Consider if test result will impact decision-making before ordering.
- Genomic biomarkers have limited role in active surveillance.
  - Limited by cancer heterogeneity and multifocality.
  - Use selectively.
- MRI improves detection of high-grade prostate cancer.
- PSMA PET scan facilitates staging prior to initial treatment.

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Thank YOU!

 @samsimsal

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Mack Roach III, MD
Professor Radiation Oncology & Urology, *UCSF*

Biomarker and Advanced Imaging-integrated Management of Prostate Cancer: Radiation Oncologist Perspective

AUA 2026, Washington D.C., 5/15/26

Disclosures:

- Full-time faculty at UCSF (Departments of Radiation Oncology & Urology) (> 35 yrs)
- Consulted /Advised / Lectured / Testified for most companies providing various types of hormonal therapy for prostate ca. over the past >30 yrs.
  - Most recently October 4th, 2024 – "Xtandi" (Astellas Ad Board)
- ACCURAY Advisory Board/Speaker in the past.
- Consulted with Imaging Companies related to PSMA PET
- No other relevant disclosures

UCSF University of California San Francisco

Goals of this Presentation (10 min.):

1. Issues in using PSMA PET and MRI imaging.
2. History of prostate ca. biomarkers and the lessons learned from the 1st biomarker (PSA).
3. Opportunities and limitations and associated with of biomarkers (e.g., genes, A.I., …)*
4. Examples of unanswered questions and how they impact the management of patients

UCSF University of California San Francisco

Research

JAMA Oncology | Original Investigation

Diagnostic Accuracy of 68Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection

A Multicenter Prospective Phase 3 Imaging Trial

Table 2. ^{68}Ga-PSMA-11 Test Characteristics for the Composite 3 Blinded Reads and Overall Majority Rule Read

Test characteristic	Read 1	Read 2	Read 3	Majority read
True positive	30	33	29	30
False positive	13	16	15	10
True negative	189	186	187	192
False negative	45	42	46	45
Sensitivity[a]	0.40 (0.30-0.51)	0.44 (0.33-0.55)	0.39 (0.28-0.50)	0.40 (0.30-0.51)
Specificity[a]	0.94 (0.89-0.96)	0.92 (0.88-0.95)	0.93 (0.88-0.95)	0.95 (0.91-0.97)
PPV[a]	0.70 (0.55-0.81)	0.67 (0.53-0.79)	0.66 (0.51-0.78)	0.75 (0.60-0.86)
NPV[a]	0.81 (0.75-0.85)	0.82 (0.76-0.86)	0.80 (0.75-0.85)	0.81 (0.76-0.85)

Hope et al. JAMA Oncology 7; 11:1635-1642, 2021

European Association of Urology

Prostate Cancer

EUROPEAN UROLOGY 7 5 (2 019) 5 0 6 – 514

A Novel Nomogram to Identify Candidates for Extended Pelvic Lymph Node Dissection Among Patients with Clinically Localized Prostate Cancer Diagnosed with Magnetic Resonance Imaging-targeted and Systematic Biopsies. Gandaglia, Ploussard … Briganti

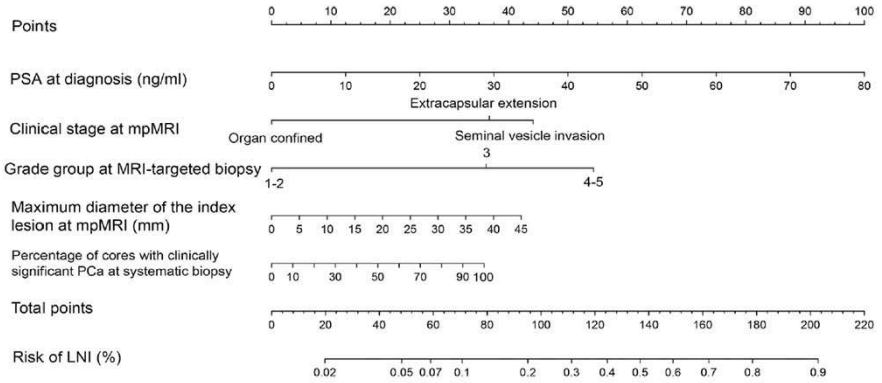


Fig. 1 –
Novel nomogram predicting the probability of lymph node invasion (LNI) for patients diagnosed via targeted biopsies and treated with radical prostatectomy and extended pelvic lymph node dissection. mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PSA = prostate-specific antigen.

European Association of Urology

Prostate Cancer

EUROPEAN UROLOGY (2025)

13% + nodes!!!

External Validation of Nomograms for the Identification of Pelvic Nodal Dissection Candidates Among Prostate Cancer Patients with Negative Preoperative Prostate-specific Membrane Antigen Positron Emission Tomography. Gandaglia … Briganti

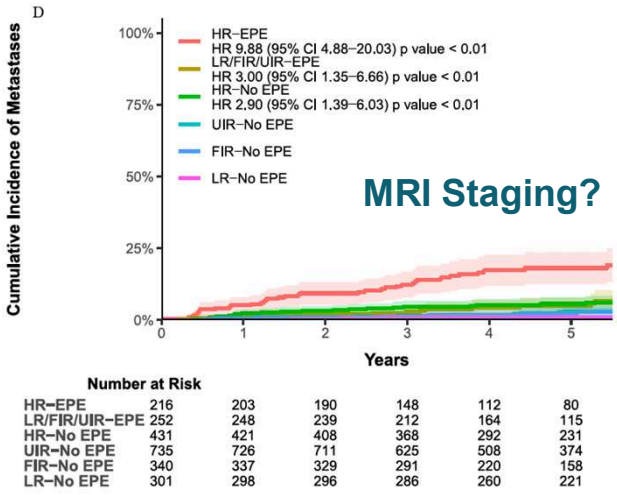
Clinical implications according to treatment option:
(MSKCC vs Briganti 2017 vs Briganti 2019 vs Amsterdam-Brisbane-Sydney vs Briganti 2023)

Treatment option	Patients in whom PLND is not recommended according to the cutoff (below cutoff)	Patients below cutoff with histological LNI	Patients in whom PLND is recommended according to the cutoff (above cutoff)	Patients above cutoff with histological LNI
MSKCC, 5% cutoff	27 (9.6)	1 (3.7)	255 (90)	35 (14)
MSKCC, 7% cutoff	39 (14)	2 (5.1)	243 (86)	34 (14)
MSKCC, 10% cutoff	53 (19)	3 (5.7)	229 (81)	33 (14)
Briganti 2017, 5% cutoff	45 (16)	1 (2.2)	237 (84)	35 (15)
Briganti 2017, 7% cutoff	52 (18)	1 (1.9)	230 (82)	35 (15)
Briganti 2017, 10% cutoff	74 (26)	2 (2.7)	208 (74)	34 (16)
Briganti 2019 [a], 5% cutoff	38 (14)	2 (5.3)	234 (86)	33 (14)
Briganti 2019 [a], 7% cutoff	51 (19)	3 (5.9)	221 (81)	32 (14)
Briganti 2019 [a], 10% cut-off	74 (27)	4 (5.4)	198 (73)	31 (16)
Amsterdam-Brisbane-Sydney, 5% cutoff	12 (4.3)	1 (8.3)	270 (96)	35 (13)
Amsterdam-Brisbane-Sydney, 7% cutoff	30 (11)	3 (10)	252 (89)	33 (13)
Amsterdam-Brisbane-Sydney, 10% cutoff	59 (21)	6 (10)	223 (79)	30 (14)
Briganti 2023, 5% cutoff	133 (47)	5 (3.8)	149 (53)	31 (21)
Briganti 2023, 7% cutoff	174 (62)	8 (4.6)	108 (38)	28 (26)
Briganti 2023, 10% cutoff	213 (76)	15 (7)	69 (24)	21 (30)

LNI = lymph node invasion; MSKCC = Memorial Sloan Kettering Cancer Center; PLND = pelvic lymph node dissection.
[a] Available for 272 patients.

UCSF University of California San Francisco

Cumulative incidence of metastases by the NCCN risk group in the presence of EPE (modified from Figure 2).



Number at Risk

HR−EPE	216	203	190	148	112	80
LR/FIR/UIR−EPE	252	248	239	212	164	115
HR−No EPE	431	421	408	368	292	231
UIR−No EPE	735	726	711	625	508	374
FIR−No EPE	340	337	329	291	220	158
LR−No EPE	301	298	296	286	260	221

Prognostic significance of magnetic resonance imaging detected extra-prostatic extension in localized prostate, Cancer. Kumar et al., Cancer, 2025

UCSF University of California San Francisco

"Biomarkers" - short for biological marker:

" … a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure."

Oxford Languages

PSA, the 1st "modern" biomarker: "Localized Prostate Cancer"

- First showed, pretreatment PSA (>20 ng/ml), predicted OS UCSF & U of M (*Roach et al*., 2003).
- Showed "ultra-high) preTx PSA (>50 ng/ml) is "overrated" (*Rodrigues, Bae, Roach* et al., (2010)
- First showed the importance of PSA nadir after EBRT & ADT in a RCT (Cury, Roach et al. 2013)
- PSA failure as a surrogate endpoint for OS based on data from RTOG 9202 (Dignam et al. 2018)
- PSA a biomarker in the salvage setting (RTOG 9601 Dess (2020) & POSEIDON Kishan (2026)

SERUM PROSTATE-SPECIFIC ANTIGEN AND SURVIVAL AFTER EXTERNAL BEAM RADIOTHERAPY FOR CARCINOMA OF THE PROSTATE

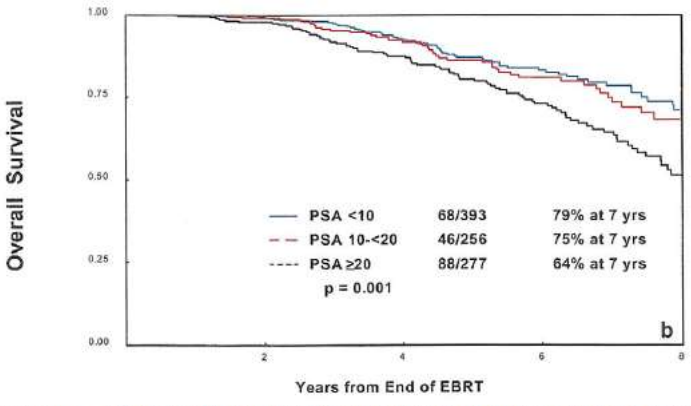


FIGURE 2. *(a) PFS and (b) OS for patients treated with RT alone by pPSA level.*

Urology 61: 730-735, 2003

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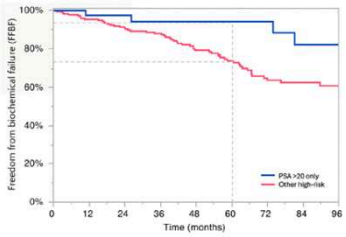
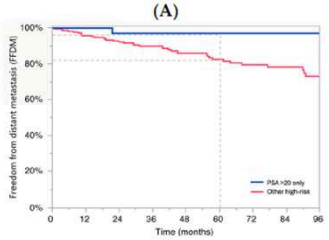
High-Risk Prostate Cancer Treated with Radiation Therapy: Favorable Outcomes in Men with PSA > 20 as the Sole High-Risk Factor. Shimomura et al. J of Clinical Medicine 2026



(A)



(B)

Figure 2. (A) Freedom from biochemical failure (n = 282). Kaplan-Meier curve (Y-axis, % FFBF; X-axis, time in months) showing FFBF from radiation treatment completion for HR prostate cancer patients by HR factor (PSA > 20 as the only HR factor, blue, n = 49; all other HR prostate cancer patients, red, n = 233). Dashed-line represents 5-year FFBF for each subgroup. Log-rank test, p = 0.05.

(B) Freedom from distant metastasis (n = 282). Kaplan-Meier curve (Y-axis, % FFDM; X-axis, time in months) showing FFDM from radiation treatment initiation for HR prostate cancer patients by HR factor (PSA > 20 as the only HR factor, blue, n = 49; all other HR prostate cancer patients, red, n = 233). Dashed-line represents 5-year FFDM for each subgroup. Log-rank test, p = 0.05.

Kattan Nomograms PSA Failure vs Metastatic

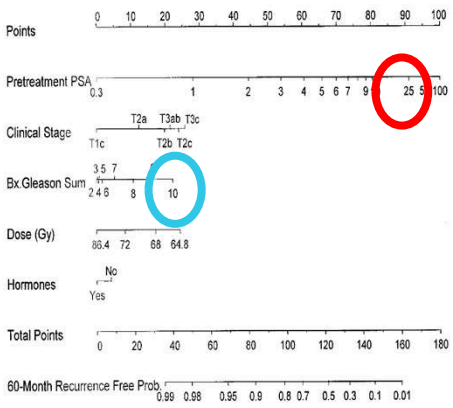


Fig 2. Radiotherapy nomogram based on 1,042 patients treated at MSKCC for predicting PSA recurrence after radiation therapy.

Pretreatment Nomogram for Predicting the Outcome of Three-Dimensional Conformal Radiotherapy in Prostate Cancer. JCO 18:3352-3359, 2000

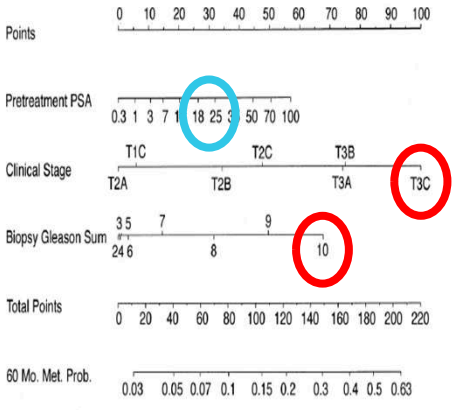


Fig 2. Nomogram for 60-month probability of metastasis (60 Mo. Met. Prob.) .... PSA, prostate-specific antigen.

Pretreatment Nomogram That Predicts 5-Year Probability of Metastasis Following Three-Dimensional Conformal Radiation Therapy for Localized Prostate Cancer. JCO 21:4568-4571, 2003

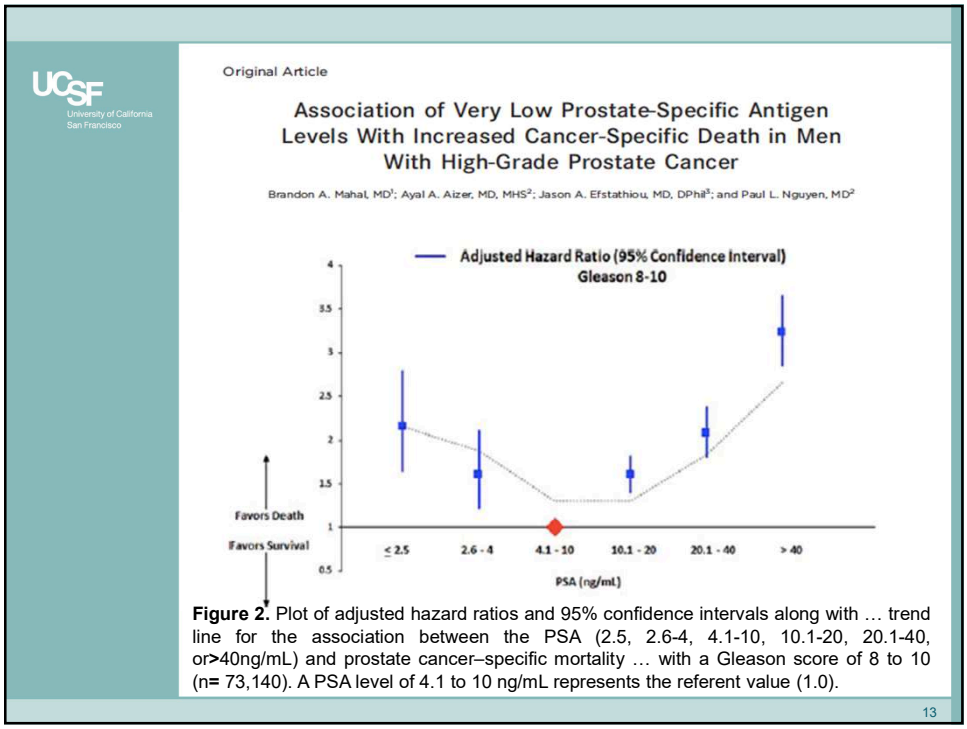
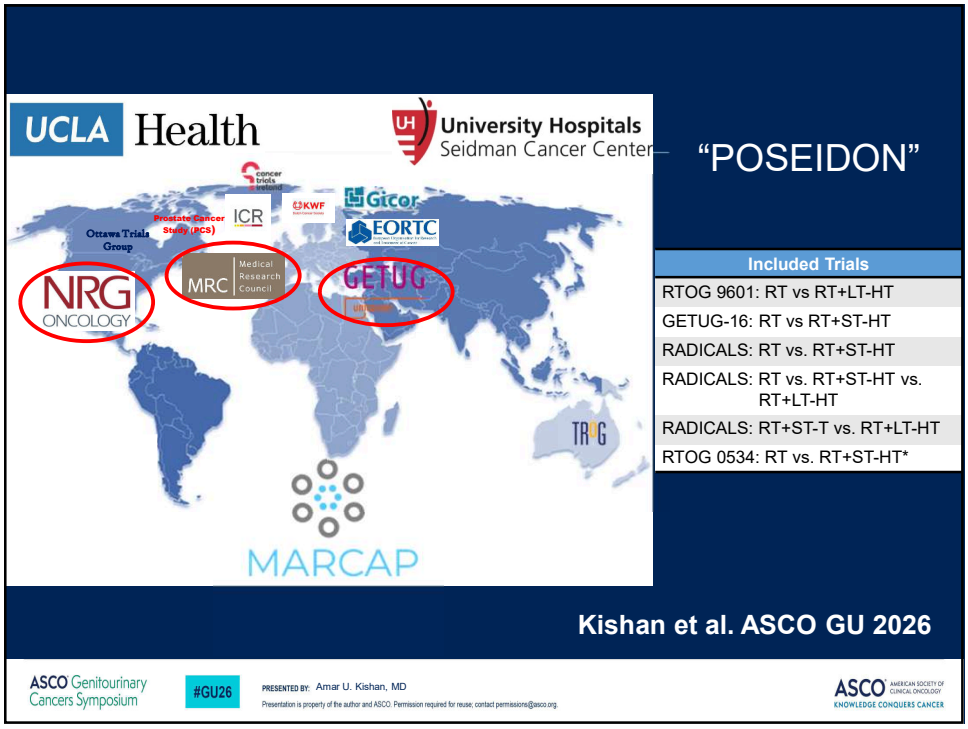
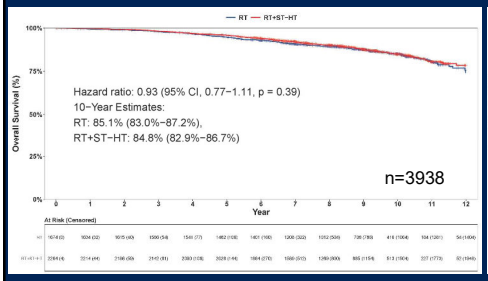


Figure 2. Plot of adjusted hazard ratios and 95% confidence intervals along with … trend line for the association between the PSA (2.5, 2.6-4, 4.1-10, 10.1-20, 20.1-40, or>40ng/mL) and prostate cancer–specific mortality … with a Gleason score of 8 to 10 (n= 73,140). A PSA level of 4.1 to 10 ng/mL represents the referent value (1.0).

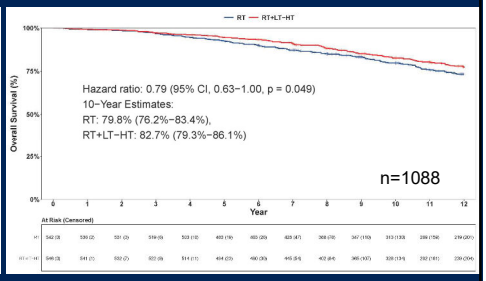


Survival Results: HT-Duration

"POSEIDON"



median PSA 0.3



median PSA 0.5

Kishan et al. ASCO GU 2026

"POSEIDON"

Limitations (per Kishan)

- Patients treated over 17-year period (1998-2015)
- 70% of patients in RT±LT-HT cohort on RTOG 9601, using bicalutamide monotherapy (not ADT)
- Improvement in earlier endpoints (e.g., EFS) by HT may be of value to patients, even if the OS benefit is not robust
- Enrollment predated use of prognostic biomarkers (e.g., Decipher) and advanced molecular imaging (e.g., PSMA PET)
  - Data from biomarker-driven trials such as NRG GU-006 will be highly informative

Limitations (per Roach)

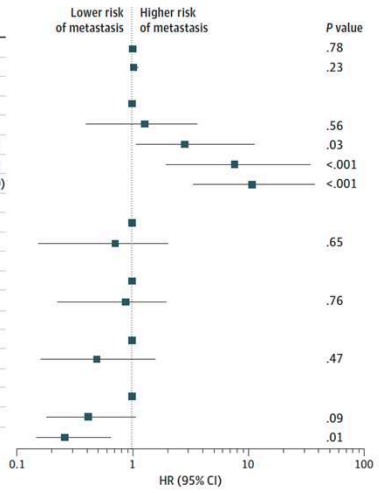
- Follow-up too short ("80% of deaths rule")
- Heterogeneity of patients included ("too much noise") targeting, dose, volume, follow-up, eligibility …
- Favorable nature of post operative patients (1998-2015)
- Data from biomarker-driven trials such as NRG GU-006 are highly informative

Kishan et al. ASCO GU 2026

Active Monitoring, Surgery, and Radiotherapy for Cribriform-Positive and Cribriform-Negative Prostate Cancer A Secondary Analysis of the PROTECT Randomized Clinical Trial. Sushentsev et al. JAMA Oncology 2025

Figure 3. Subgroup Intention-to-Treat Analysis

Metastatic disease:intention to treat Characteristic	No. of patients	HR (95% CI)	P value
Age, y	712	1.01 (0.95-1.07)	.78
PSA, ng/mL	712	1.04 (0.97-1.11)	.23
Histologic category			
Gleason score 6	410	1 [Reference]	
Gleason score 3 + 4 = 7 (cribriform-negative)	186	1.42 (0.42-4.79)	.56
Gleason score 3 + 4 = 7 (cribriform-positive)	50	3.75 (1.18-11.89)	.03
Gleason score ≥4 + 3 = 7 (cribriform-negative)	23	7.69 (2.43-24.32)	<.001
Gleason score ≥4 + 3 = 7 (cribriform-positive)	43	10.63 (4.16-27.20)	<.001
Gleason pattern 4, %			
≤10	577	1 [Reference]	
>10	134	0.74 (0.21-2.62)	.65
Aggregate tumor length, mm			
<4	307	1 [Reference]	
≥4	405	0.85 (0.29-2.45)	.76
Maximum tumor length, mm			
<2	246	1 [Reference]	
≥2	466	0.68 (0.24-1.94)	.47
Treatment assigned			
Active monitoring	248	1 [Reference]	
Surgery	227	0.53 (0.26-1.10)	.09
Radiotherapy with ADT	237	0.34 (0.16-0.75)	.01



Secondary multivariable Cox proportional hazards regression analysis of the intention-to-treat cohort. Prostate-specific antigen (PSA) values were log-transformed. To convert PSA to µg/L, multiply by 1.0. HR indicates hazard ratio.

UCSF University of California San Francisco

Biomarkers … and Radiotherapy

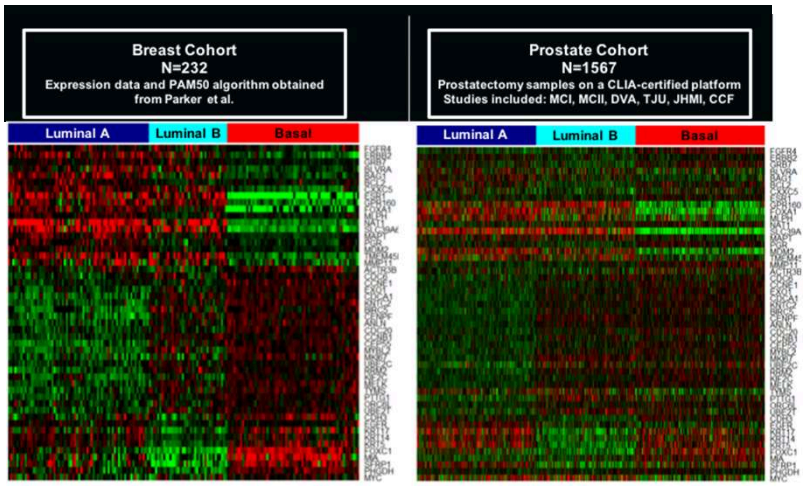
Personalized approaches are being introduced in the management of localized prostate cancer and being incorporated in NRG/RTOG Prostate Cancer Trials.

I will focus on markers I most commonly use:

1. **"Genomic Classifiers" (Decipher …)**
   a) **GS score (prognostic +/- predictive)**
   b) **Luminal and Basal subtyping**
2. **Multi-Modal Artificial Intelligence (M.M.A.I.)**
3. **ProsTox (microRNAs)**

PAM50 Clustering Readily Identifies Luminal (A and B) and Basal Subtypes in Prostate Cancer

Now validated in >20,000 prostate cancer samples



Zhao et al, JAMA Oncology 2017

NRG ONCOLOGY

Advancing Research. Improving Lives.

A Double-Blinded Placebo-Controlled Biomarker Stratified Randomized Trial of Apalutamide (APA) and Radiotherapy for Recurrent Prostate Cancer (NRG GU006, BALANCE)

Daniel E Spratt, MD, Theodore Karrison, PhD, Howard M Sandler, MD, Edwin M Posadas, MD, Ronald Chen, MD, MPH, Robert E Wallace, PhD, James I Monroe, PhD , Leonard Gomella, MD, Robert T Dess, MD, Andrew Vassil, MD, Annie Ebacher, MD, Tyler Gunter, MD, R Jeffrey Lee MD, Jessie DiNome, MD, Scott E Delacroix, Jr, MD, Jeff Michalski, MD, Xinglei Shen, MD, Trevor Johnson, MS, Paul Nguyen, MD, Felix Feng, MD

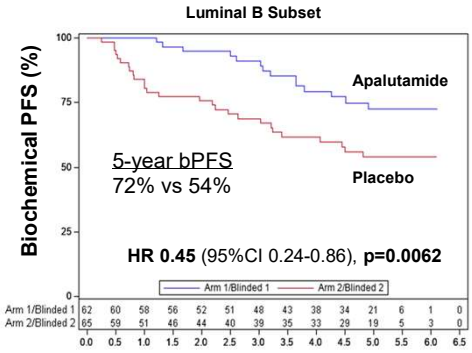
ASTRO 67th Annual Meeting
September 28, 2025
Moscone Center San Francisco

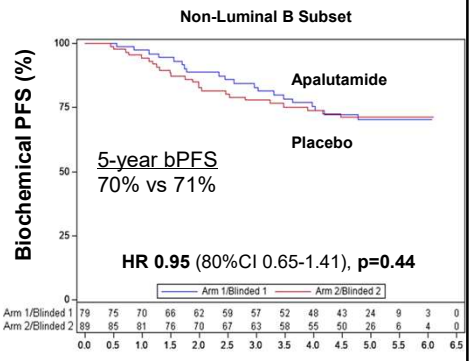
University Hospitals Seidman Cancer Center
Case Western Reserve University
Radiation Oncology Reimagined

@DrSpratticus
@RadoncUH

NCI National Clinical Trials Network
NCI Community Oncology Research Program

Primary Endpoint Results





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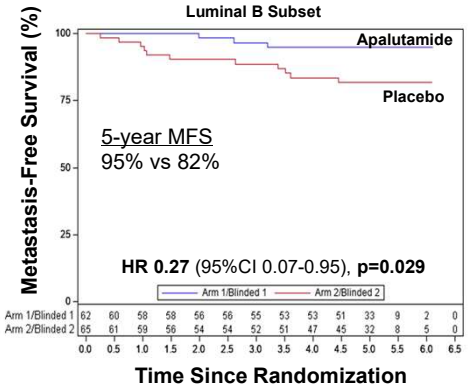
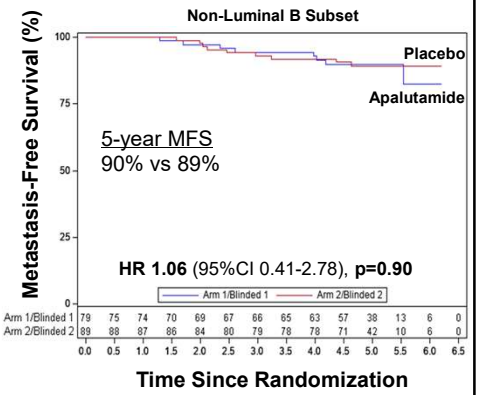
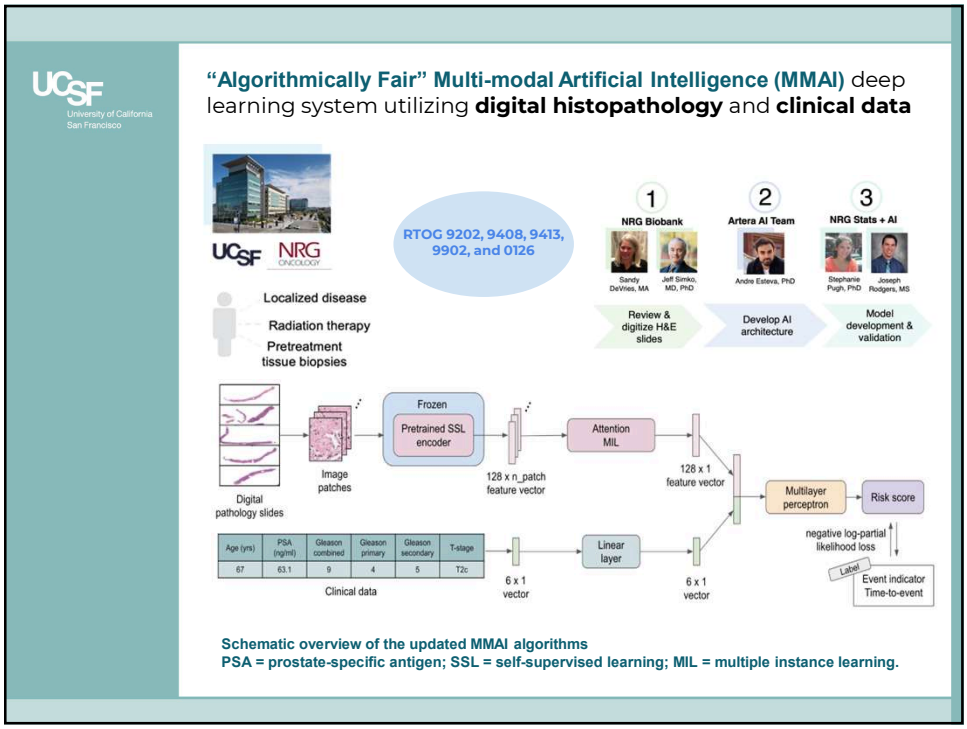
Metastasis-Free Survival





NRG ONCOLOGY



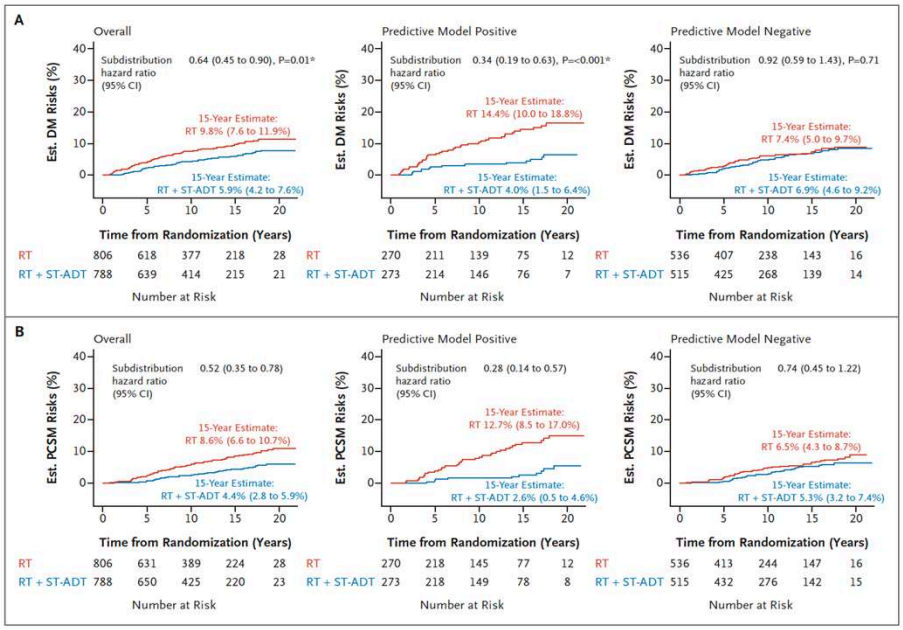


Figure 2. Cumulative Incidence in the Validation Cohort (NRG/RTOG 9408) of Histopathology-Imaged Patients by Artificial Intelligence–Predictive Model Subgroups for (Panel A) Distant Metastasis and (Panel B) Prostate Cancer–Specific Mortality. *Spratt et al. NEJM 2023*

Summary

- **Five NRG phase III RCT** used for model training and validation
- Novel AI architecture learns from digital pathology of **biopsies without slide annotations and without consuming tissue**
- **ArteraAI MMAI prognostic model** successfully developed to predict long-term, clinically relevant outcomes
- **First predictive biomarker** to guide ADT use in localized prostate with validation in a phase III randomized trial of +/- ADT

AI models vs genomic biomarkers

	AI models	Genomic biomarkers
Prognostic tools	Yes	Yes
Predictive tools	Yes	No
Adaptive learning	Yes	No
Cost	Cheap	Expensive
Time	Fast	Slow
Global adoption feasibility	Fast	Slow

Courtesy of Osama Mohamad

Radiotherapy and Oncology 167 (2022) 226–232

Contents lists available at ScienceDirect

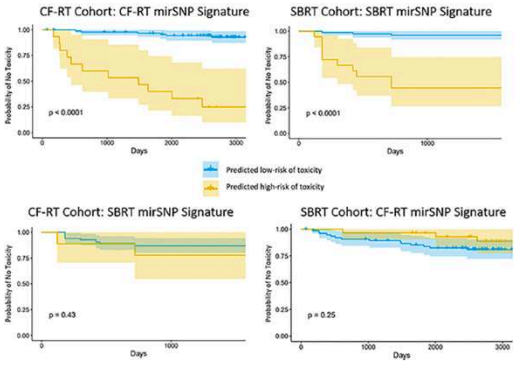
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

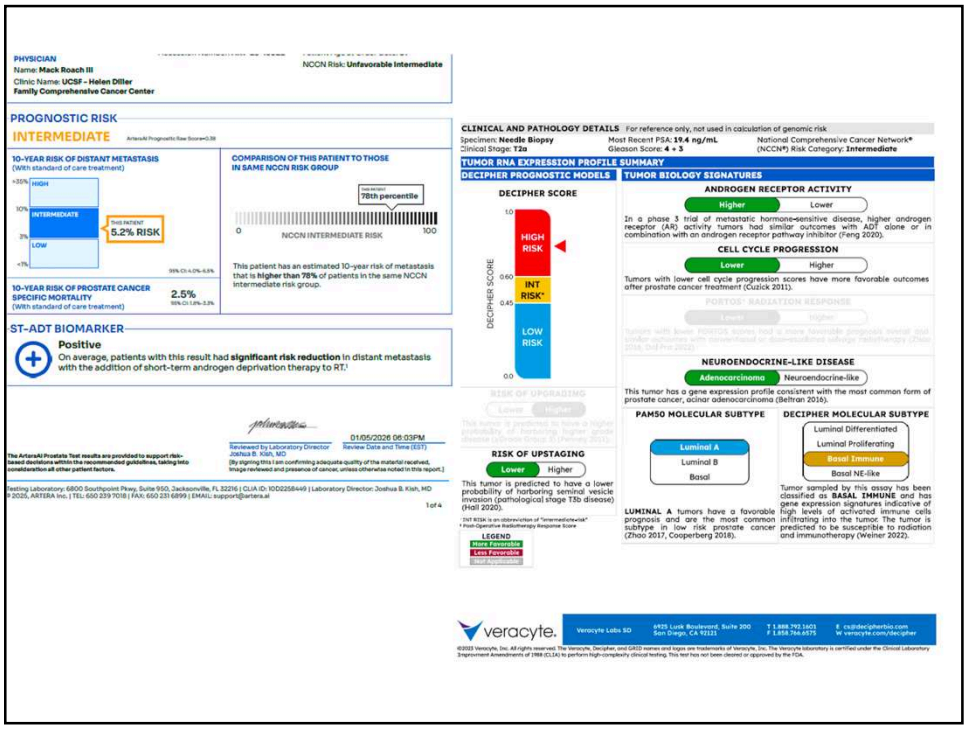
Germline variants disrupting microRNAs predict long-term genitourinary toxicity after prostate cancer radiation

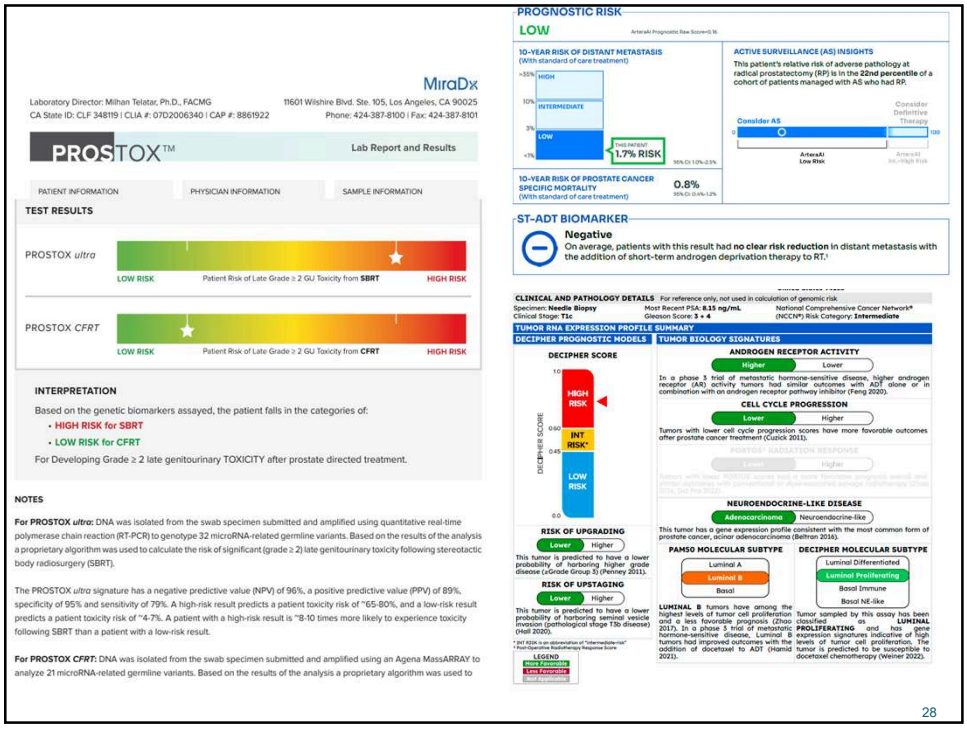
Associations between late grade 2 genitourinary toxicity and single nucleotide polymorphisms disrupting microRNA targets (mirSNPs) in patients receiving conventionally fractionated radiotherapy.



Associations between late grade 2 genitourinary toxicity and single nucleotide polymorphisms disrupting microRNA targets (mirSNPs) in patients receiving stereotactic body radiotherapy.

Fig. 2.
Toxicity-Free Survival Curves. Curves depict the predicted toxicity over time for men predicted to have a low or high risk of toxicity by the indicated mirSNP signature. p-values derived from the log-rank test.





Predicting 15-Year Prostate Cancer Specific Mortality After Radical Prostatectomy.
Scott E. Eggener et al. THE J of UROLOGY. Vol. 185, 869-875, March 2011

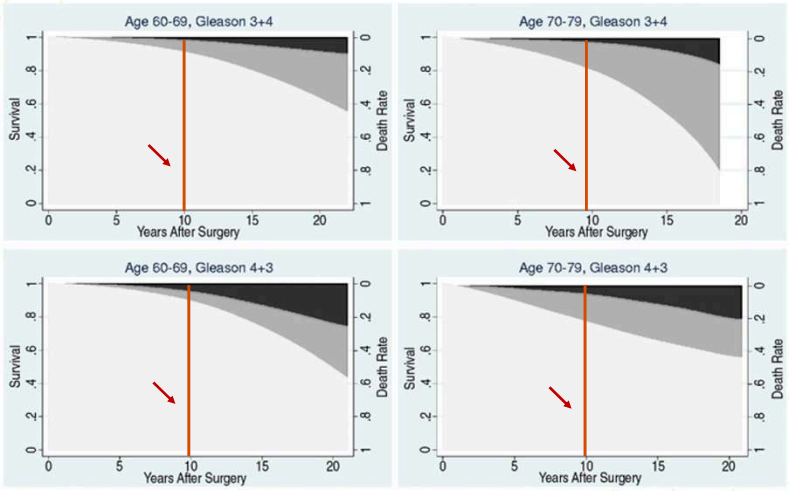


Figure 3. PCSM (black areas) and mortality from competing causes (gray areas) by pathological Gleason score and patient age at diagnosis.

NRG ONCOLOGY

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"Not everything that counts can be counted,
and not everything that can be counted counts."

Albert Einstein

(Sign in his office at Princeton)

"Count what you can count and hope that it counts!"

Mack Roach III

AUA 2026 MAY 15-18 Washington, DC

Biomarker and Advanced Imaging-Integrated Management of Metastatic Prostate Cancer

Michael A. Carducci, MD, FACP, FASCO
AEGON Professor in Prostate Cancer Research
Hopkins Kimmel Cancer Center
Baltimore, MD

Disclosures

Consultant

- Acrivon	DSMB Chair
- Amgen	DSMB Chair
-Astra Zeneca	DSMB Member

AUA2026 Washington, DC MAY 15-18

Learning Objectives

Review the natural history of advanced prostate cancer and introduce Prostate Cancer Working Group 4 (PCWG4) recommendations

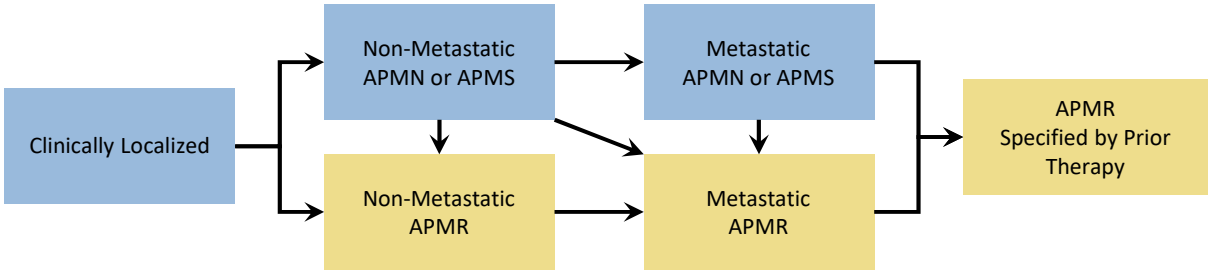
Examine how novel imaging impacts clinical decisions for better or for worse

Understand need for genetic testing/genomic evaluation to tailor treatment options with PARP inhibitors/other agents

Why Are New Trial Guidelines Needed?

1. Multiple new agents approved with a diverse set of mechanisms and indications over the past 10 years
   - ARPis, PARPis and precision therapies, PSMA RLT and radium-223
   - Movement of therapies into earlier hormone-responsive disease settings
2. Common use of novel PSMA PET imaging to diagnose, classify, and track disease over time **without clear guidance on how to do this**
3. Desire for a nomenclature and disease states model that is patient centric and that does not pre-suppose outcomes
4. Need for applications of endpoints and guidance to earlier settings
5. Further need to conform to biomarker guidance provided by the FDA
   - Patient and tumor genotype and phenotypes, changes over time
   - More evidence-based biomarker criteria and trial designs to optimize therapies for those most likely to benefit
6. Observations of clear disconnect between imaging progression without PSA progression, especially with potent AR inhibition

PCWG4: new indications model and terminology



Androgen Pathway Modulation Sensitive (APMS) or Naïve (APMN)

Androgen Pathway Modulation Resistant (APMR)

Within each state, specify where relevant: 1) genotype (germline, somatic), 2) imaging modality used to define metastasis (PET, CT/MRI/bone scan), 3) disease characteristics and biomarkers critical for risk stratification, and 4) prior therapies.

APMN/S is the preferred term for hormone/castration naïve/sensitive disease (HSPC, CSPC) while APMR is the preferred term for castration/hormone resistant prostate cancer (CRPC/HRPC).

Armstrong AJ, Morris MJ…Scher HI
PCWG4; J Clin Oncol 2026

There Are No Grouped Responses in Prostate Cancer

PCWG3-4	rPFS per PCWG4	Modified RECIST	rPFS per PCWG4

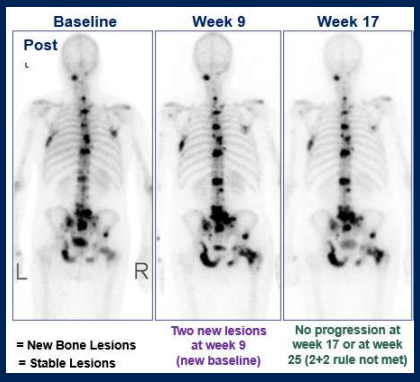
REPORT SEPARATELY: goal is simplicity, feasibility, and association with overall survival, patient benefits

Non-Imaging Response Guidance: PCWG4

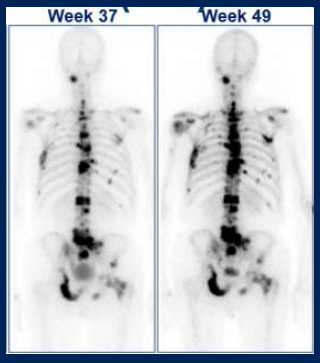
- Can be useful for early-stage trial go/no-go decisions
  - Early read-outs can accelerate decision-making
- No one feature guarantees success
- Use of multiple endpoints can improve chances of success but none are surrogates of OS
  - CTC conversion, ctDNA normalization/reduction where appropriate
  - PSA declines, PSA nadir
  - Patient reported outcomes: many validated scales (pain responses, global QOL) depends on baseline symptoms and context
  - Normalization of other adverse prognostic blood-based assays (ALP, LDH, hemoglobin, albumin)
  - Pathologic complete response

PCWG3 Approach: Highly Successful, But Always Room for Improvement

Bone scans: No changes to 2+2 at flare scan



Bone scans: New approach to confirmatory scan (2+0) in PCWG4



PCWG3: need for confirmatory scan

Progression date is backdated

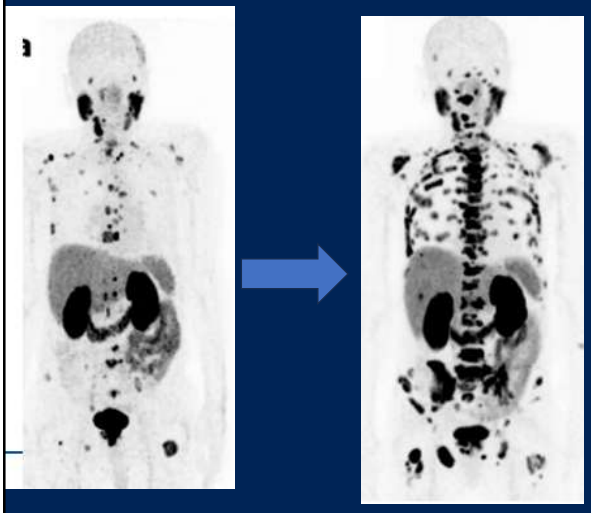
Concern: we may be keeping patients on ineffective therapies too long while watching disease burden grow!

PCWG4: Incorporates PSMA PET

PSMA PET

- If performed earlier than 8 weeks, non-actionable
- Scans with new disease at 8 weeks or beyond can be taken at face value
- Changes in disease ***volume or SUV parameters*** are ***investigational*** but highly promising. Collect these data!
  - No PR or PD by SUV's or volume
  - Report CR's
- Hence, as a bridge, the focus will *also* be on *new lesions* as PD bridging to PCWG5
- RECIST still applies to the CT component; *get contrast with the PSMA PET/CT*

Rule of 5 for PMSA PET (Bone, Nodes, Pulmonary Mets)



Rule of 5 (bone, nodes, lung):

- **≤5 new lesions: 2 new lesions that are confirmed on a subsequent scan**
- **≥6 new lesions = POD**

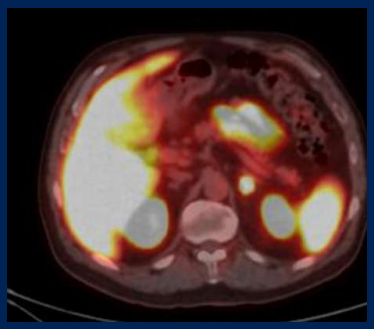
Report separately from bone scan findings

Report separately from CT findings

No implications for treatment until validated

The Rule of 5 Does *NOT* Apply to Liver or Other Non-pulmonary Visceral Mets

- Any *single* liver, adrenal, or non-pulmonary visceral lesion constitutes progression



From Guidelines to the Clinic

Molecular Imaging

- 18-Fluciclovine (Axumin), DFCyL-PSMA PET (Pylarify), Ga68- PSMA PET (Locametz), Flotufolastat-F18 (Posluma)
- Able to show more metastatic sites than Bone and CT Scan
- Most studies have not shown that outcomes are improved by the changes made in response to novel imaging findings
- **Yet, clearly changes disease state with natural tendency to push additional therapy or change treatment approach**
  - Prematurely or more appropriately to improve outcomes?

Need to Ask

- How is the patient doing?
- What are the scans doing- are they needed?
- What is PSA doing?

- Changes in therapy should be based on two of three approach- if two or more of the above changing- likely need to change treatment approach
- **Need for molecular testing in all patients with metastatic/recurrent prostate cancer- Guide to additional treatment options**

CRPC – Current Management Options

- **Maintenance of ongoing ADT**
- **Secondary Hormonal Strategies**
  - Anti-androgens (bicalutamide, enzalutamide, apalutamide, darolutamide)
  - Androgen synthesis inhibitors (abiraterone)
- **Immunotherapy (sipuleucel-T)**
- **PARP Inhibitors (olaparib, rucaparib, talazoparib, niraparib)**
- **Chemotherapy**
  - Docetaxel, cabazitaxel, mitoxantrone
- **Radium-223**
- **Lu177- PSMA-617**
- **Supportive Care**
  - Bone health agents: bisphosphonates (zolendronic acid), Rank ligand inhibitors (denosumab)
  - Exercise, sunlight, vitamin D and calcium
  - Palliative radiation, palliative care

JOHNS HOPKINS MEDICINE | THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

TURNING RESEARCH INTO RESULTS

Role of Molecular Sequencing in Metastatic Prostate Cancer

- Germline and somatic mutation rates for DNA Damage Repair (DDR) approach 20% of patients
  - Higher rates of mutations in patients with Gleason 5 primary and patients with ductal features
- Can measure TMB (Tumor Mutational Burden) and MSI
  - PD1 inhibitors (pembrolizumab) on-label
- Variation in practice
  - Genetic counseling, then test
  - Test and if positive, then send to genetic counselor for cascade testing
- Most patients will NOT have actionable result

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Who needs germline testing?

- Metastatic prostate cancer *(NCCN, AUA/ASTRO/SUO, ESMO, EUA)*
- Very high-risk and high-risk localized prostate cancer *Consider:*
  Intermediate risk prostate cancer and intraductal/cribriform histology

Adapted from Carlo,Annual ASCO 2021, and PC Guidelines: NCCN 2021, AUA/ASTRO/SUO 2021, ESMO 2020, EUA 2020.

- Family or personal history of cancer:
  1) BRCA1/2 associated: *ovarian, breast, pancreas*
  2) Lynch syndrome associated: *colorectal, endometrial, upper tract urothelial, gastric…*
  3) HOXB13 associated: *prostate*

- Ashkenazi ancestry and/or family history of known germline variants*
  *Per NCCN 2021: BRCA1/2, ATM, PALB2, CHEK2, MLH1, MSH2/6, PMS2, EPCAM
- Tumor-only sequencing positive for cancer predisposition genes
  ~3%-12% are associated with actionable germline mutations

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Single agent PARP Inhibitors in Prostate Cancer

- Two US approvals- one broad for all HRD mutations (Olaparib) and one restricted to BRCA 1 / 2 mutations (rucaparib)
- Since approvals- use of PARPi has been in sequence typically after 1st line APM
- Not all HRD mutations the same in terms of likelihood of benefit- critical when counseling patients as to benefits
- Close follow-up needed for anemia, fatigue, nausea, etc

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rPFS and OS by HRR Gene Mutation

TABLE 2. rPFS and OS by HRR Gene Mutation

Gene Mutation	End Point	Arm	No.	No. of Events	Median Survival, Months	HR[a] (95% CI)	HR[b] (95% CI)
ATMm (N = 268)	rPFS (BICR)	PARPi + ARPI	136	67	19 (16-28)	1.05 (0.74 to 1.49)	1.02 (0.71 to 1.45)
		Placebo + ARPI	132	59	19 (16-NE)		
	OS	PARPi + ARPI	136	63	33 (26-NE)	1.18 (0.82 to 1.71)	1.12 (0.77 to 1.62)
		Placebo + ARPI	132	55	33 (28-NE)		
BRCA1m (N = 64)	rPFS (BICR)	PARPi + ARPI	37	14	20 (14-NE)	0.51 (0.23 to 1.1)	0.52 (0.2 to 1.33)
		Placebo + ARPI	27	15	12 (4-NE)		
	OS	PARPi + ARPI	37	16	29 (15-NE)	0.74 (0.34 to 1.61)	0.73 (0.28 to 1.89)
		Placebo + ARPI	27	13	26 (13-28)		
BRCA2m (N = 422)	rPFS (BICR)	PARPi + ARPI	199	60	NA (22-NE)	0.31 (0.23 to 0.42)	0.27 (0.19 to 0.37)
		Placebo + ARPI	223	144	10 (8-11)		
	OS	PARPi + ARPI	199	77	33 (29-NE)	0.66 (0.49 to 0.89)	0.6 (0.44 to 0.82)
		Placebo + ARPI	223	112	24 (22-28)		
CDK12m (N = 146)	rPFS (BICR)	PARPi + ARPI	73	32	17 (16-NE)	0.5 (0.32 to 0.8)	0.51 (0.32 to 0.82)
		Placebo + ARPI	73	44	14 (8-17)		
	OS	PARPi + ARPI	73	32	36 (25-NE)	0.63 (0.39 to 0.99)	0.64 (0.4 to 1.03)
		Placebo + ARPI	73	44	27 (20-33)		
CHEK2m (N = 172)	rPFS (BICR)	PARPi + ARPI	85	37	14 (14-25)	1.06 (0.67 to 1.66)	1.00 (0.63 to 1.59)
		Placebo + ARPI	87	43	18 (13-22)		
	OS	PARPi + ARPI	85	39	26 (23-NE)	1.53 (0.95 to 2.46)	1.48 (0.92 to 2.4)
		Placebo + ARPI	87	32	34 (26-NE)		
PALB2m (N = 41)	rPFS (BICR)	PARPi + ARPI	23	12	14 (8-NE)	0.52 (0.23 to 1.17)	0.43 (0.15 to 1.21)
		Placebo + ARPI	18	13	9 (2-20)		
	OS	PARPi + ARPI	23	12	25 (15-NE)	0.78 (0.34 to 1.8)	0.59 (0.21 to 1.65)
		Placebo + ARPI	18	11	20 (11-NE)		

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Phase 3 Trials of PARPi + AR Pathway Modulators in 1st-line mCRPC Setting

PROpel: Abiraterone + Olaparib [1] Published

MAGNITUDE: Abiraterone + Niraparib [2] Published

TALAPRO-2: Enzalutamide + Talazoparib Published

1. Clarke NW et al. *NEJM Evidence.* 2022;1(9):EVIDoa2200043.
2. Chi KN et al. *J Clin Oncol.* 2022;40(suppl 6):12.

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Should we give PARPi when starting an APM?

- Very consistent data to recommend adding PARPi to APM for individuals with BRCA1/2 mutations
- Some inconsistencies and magnitude of benefit in all comers suggest caution for those who have no mutation in HRR genes
- Recent data showing benefit of PARPi/APM in metastatic androgen pathway modulation sensitive setting

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Current Approach to Metastatic Prostate Cancer

- Obtain germline and NGS early to guide therapy- and utilize combinations of PARPi and APM in mBRCA 1 / 2
- Standard to offer doublet therapy for mHSPC, with consideration for triplet in de novo, high volume disease
  - Additional data for niraparib, LU-177-PSMA 617, capivasertib in PTEN deficient tumors
- Limited impact of second line APM
- Emerging data as to timing of Lu-177-PSMA 617
- Radium and Chemotherapy remain important agents- and timing can be individualized

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Thank You

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