Prostate Cancer Biomarkers: what is relevant for my practice nowadays and what is coming up next?

Adam B. Weiner, MD
Assistant Professor, Department of Urology
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
Adjunct Assistant Professor, Department of Urology
David Geffen School of Medicine at UCLA

UpToDate

Updated prostate cancer biomarker section coming

adam.weiner@cshs.org
@adam_weiner535

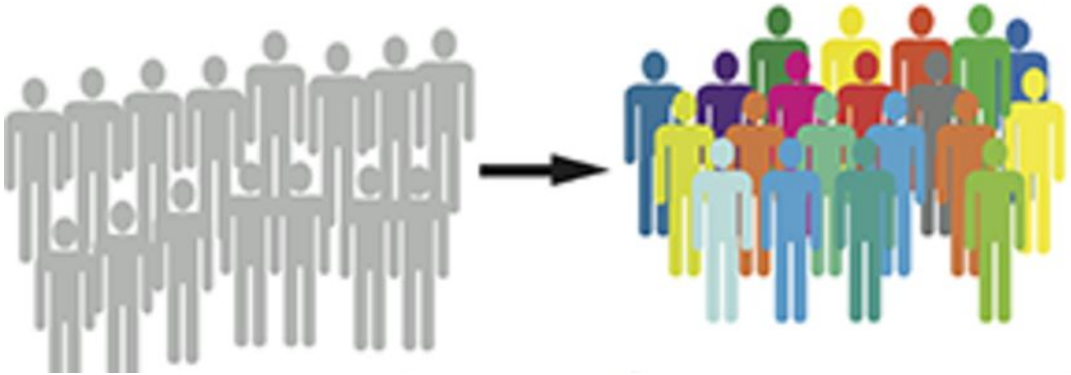
Disclosure

Veracyte Inc. - Speaker

adam.weiner@cshs.org
@adam_weiner535

Precision oncology

"Deliver the **right cancer treatment** to the **right patient** at the **right dose** and the **right time**."



Schwartzberg *et al.* 2017 ASCO Educational Book

adam.weiner@cshs.org
@adam_weiner535

Beyond risk groups

adam.weiner@cshs.org
@adam_weiner535

Biomarkers in prostate cancer: Outline

Localized

Advanced

adam.weiner@cshs.org
@adam_weiner535

Biomarkers in prostate cancer: Outline

Localized

Advanced

adam.weiner@cshs.org
@adam_weiner535

Genomic classifiers for localized prostate cancer

Test (Company)	Sample Type	Gene Content / Platform	Intended Use	Key Evidence
Decipher (Veracyte)	RP or biopsy tissue	22 RNA expression signature	Prognostic: risk of metastasis & PCa-specific mortality; guides adjuvant vs salvage RT	Multiple RCT secondary analyses (RTOG 9601, GETUG-AFU16); high-level validation
Oncotype DX Genomic Prostate Score (Exact Sciences)	Biopsy tissue	17-gene qRT-PCR panel	Prognostic: adverse pathology at RP; long-term risk of recurrence	Validated in biopsy cohorts, integrated with NCCN risk categories
Prolaris (Myriad Genetics)	Biopsy or RP tissue	46-gene cell cycle progression (CCP) score	Prognostic: disease-specific mortality in conservatively managed pts; assists ADT decision with RT	Multiple cohort validations; less RCT integration
ProMark (Metamark Genetics)	Biopsy tissue	8 protein biomarkers (immunofluorescence)	Prognostic: adverse pathology, early recurrence	Validated in biopsy tissue; FDA-approved as risk stratifier
ArteraAI Prostate Test (ArteraAI, Veracyte partnership)	Biopsy tissue, digital H&E plus clinical features	AI/ML model (digital pathology + clinico-genomics training)	**Predictive**: identifies men who benefit from ADT with RT (short- vs long-term, or omission)	Validated on >5,000 pts from RTOG trials; first AI-based predictive test in PCa

adam.weiner@cshs.org
@adam_weiner535

Genomic classifier use in the US

2013 to 2022

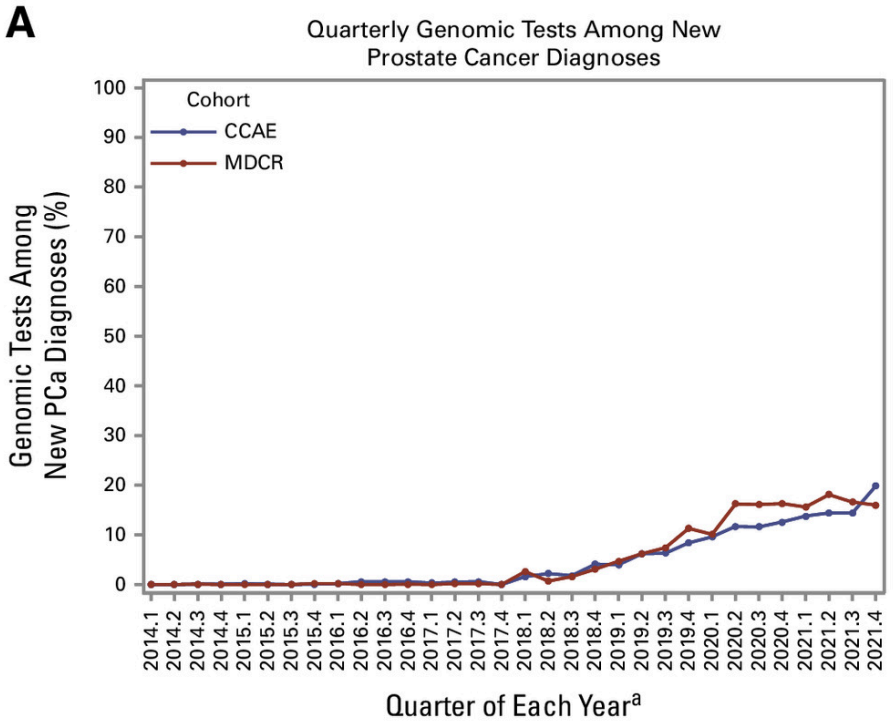
<1% ➡ 17%

2025

~30%

Use associated with

Surveillance



Janopaul-Naylor et al, JCO PO 2025

adam.weiner@cshs.org
@adam_weiner535

Genomic classifiers for localized prostate cancer

Test (Company)	Sample Type	Gene Content / Platform	Intended Use	Key Evidence
Decipher (Veracyte)	RP or biopsy tissue	22 RNA expression signature	Prognostic: risk of metastasis & PCa-specific mortality; guides adjuvant vs salvage RT	Multiple RCT secondary analyses (RTOG 9601, GETUG-AFU16); high-level validation
Oncotype DX Genomic Prostate Score (Exact Sciences)	Biopsy tissue	17-gene qRT-PCR panel	Prognostic: adverse pathology at RP; long-term risk of recurrence	Validated in biopsy cohorts, integrated with NCCN risk categories
Prolaris (Myriad Genetics)	Biopsy or RP tissue	46-gene cell cycle progression (CCP) score	Prognostic: disease-specific mortality in conservatively managed pts; assists ADT decision with RT	Multiple cohort validations; less RCT integration
ProMark (Metamark Genetics)	Biopsy tissue	8 protein biomarkers (immunofluorescence)	Prognostic: adverse pathology, early recurrence	Validated in biopsy tissue; FDA-approved as risk stratifier
ArteraAI Prostate Test (ArteraAI, Veracyte partnership)	Biopsy tissue, digital H&E plus clinical features	AI/ML model (digital pathology + clinico-genomics training)	**Predictive**: identifies men who benefit from ADT with RT (short- vs long-term, or omission)	Validated on >5,000 pts from RTOG trials; first AI-based predictive test in PCa

adam.weiner@cshs.org
@adam_weiner535

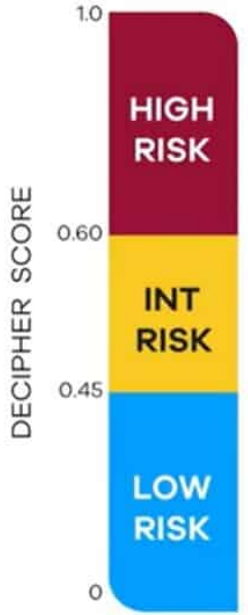
Decipher

22-gene, tissue-based risk score

Biopsy or from surgery

Designed to predict metastatic recurrence after surgery

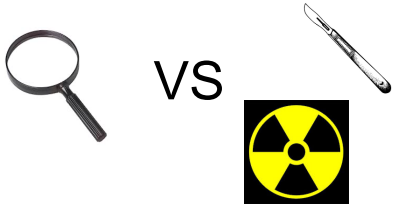
Assessed in MANY other settings



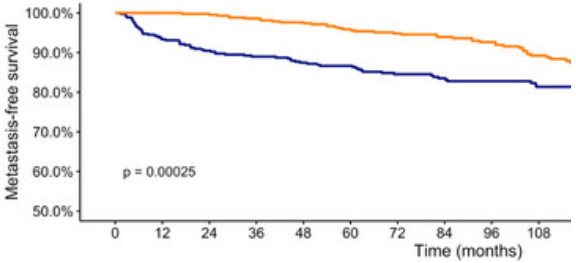
adam.weiner@cshs.org
@adam_weiner535

Decipher

Surveillance or definitive treatment

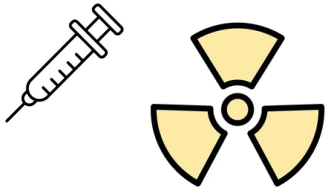


Recurrence after surgery or radiation



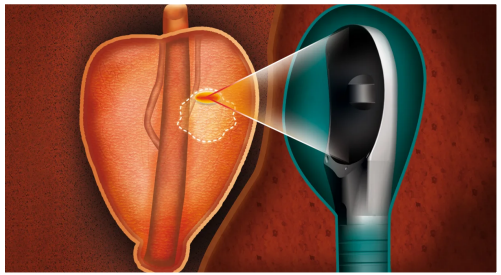
Hormone therapy with primary radiation

ADT or intensity of radiation after surgery

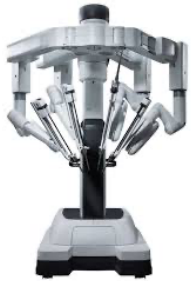


adam.weiner@cshs.org
@adam_weiner535

Focal therapy for prostate cancer

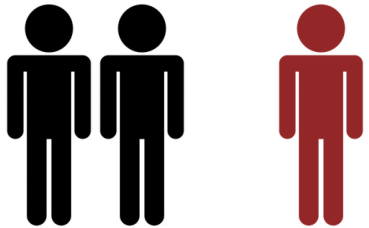


VS



Reduced side effects

High recurrence rate



Aker et al. Cancer Med 2023; Ehdaie et al. Lancet Oncol 2022

adam.weiner@cshs.org
@adam_weiner535

Focal therapy for prostate cancer: candidacy?

Summary of consensus statements

Low risk –but surveillance preferred

Int risk - largely GG2 (3+4=7)

High risk- rarely (PSA>20 but GG1-2)

Utility of genomic biomarkers is unknown

Ghoreifi et al PCAN, 2024

adam.weiner@cshs.org
@adam_weiner535

Focal therapy for prostate cancer: Biomarkers

ORIGINAL ARTICLE

Molecular biomarkers in the context of focal therapy for prostate cancer: recommendations of a Delphi Consensus from the Focal Therapy Society

Giancarlo MARRA [1, 2], Maria P. LAGUNA [3], Jochen WALZ [4], Christian P. PAVLOVICH [5], Fernando BIANCO [6], Justin GREGG [7], Amir H. LEBASTCHI [8], Herbert LEPOR [9], Petr MACEK [1], Soroush RAIS-BAHRAMI [10], Cary ROBERTSON [11], Daniel RUKSTALIS [12], Georg SALOMON [13], Osamu UKIMURA [14], Andre L. ABREU [15], Yann BARBE [1], Xavier CATHELINEAU [1], Giorgio GANDAGLIA [16], Arvin K. GEORGE [17], Juan GOMEZ RIVAS [18], Rajan T. GUPTA [19], Nathan LAWRENTSCHUK [20], Veeru KASIVISVANATHAN [21], Derek LOMAS [22], Bernard MALAVAUD [23], Daniel MARGOLIS [24], Yoh MATSUOKA [25], Sherif MEHRALIVAND [26], Marco MOSCHINI [16, 27], Marco ODERDA [2], Hazem ORABI [11, 28], Ardeshir R. RASTINEHAD [29], Mesut REMZI [30], Ariel SCHULMAN [31], Toshitaka SHIN [32], Takumi SHIRAISHI [14], Abhinav SIDANA [33], Sunao SHOJI [34], Armando STABILE [16], Massimo VALERIO [35], Varaha S. TAMMISETTI [7], Wei PHIN TAN [11], Willemien VAN DEN BOS [36], Arnaud VILLERS [37], Peter-Paul WILLEMSE [38], Jean DE LA ROSETTE [3], Thomas POLASCIK [11], Rafael SANCHEZ-SALAS [1] * on behalf of the Focal Therapy Society

Statement 2.5.4

An ideal molecular biomarker should predict those at a **high-risk of recurrence**

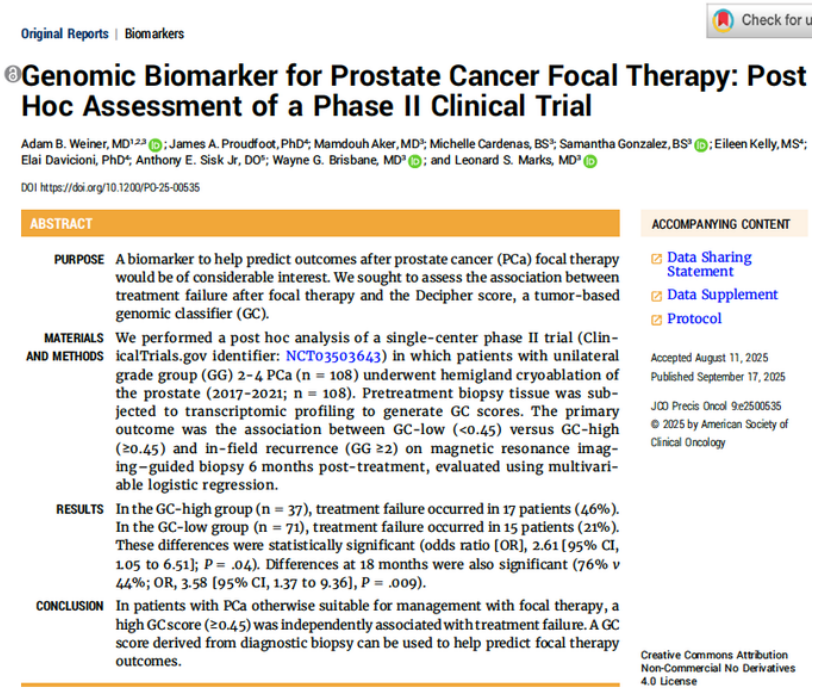
Marra Et al. Minerva Urol Nephrol. 2022

adam.weiner@cshs.org
@adam_weiner535

Post-hoc analysis of a phase II trial

JCO® Precision Oncology
An American Society of Clinical Oncology Journal

QR code will be on next few slides



Original Reports | Biomarkers

Check for u

Genomic Biomarker for Prostate Cancer Focal Therapy: Post Hoc Assessment of a Phase II Clinical Trial

Adam B. Weiner, MD[1,2,3]; James A. Proudfoot, PhD[4]; Mamdouh Aker, MD[5]; Michelle Cardenas, BS[5]; Samantha Gonzalez, BS[3]; Eileen Kelly, MS[4]; Elai Davicioni, PhD[4]; Anthony E. Sisk Jr, DO[6]; Wayne G. Brisbane, MD[3]; and Leonard S. Marks, MD[3]

DOI https://doi.org/10.1200/PO-25-00535

ABSTRACT

PURPOSE A biomarker to help predict outcomes after prostate cancer (PCa) focal therapy would be of considerable interest. We sought to assess the association between treatment failure after focal therapy and the Decipher score, a tumor-based genomic classifier (GC).

MATERIALS AND METHODS We performed a post hoc analysis of a single-center phase II trial (ClinicalTrials.gov identifier: NCT03503643) in which patients with unilateral grade group (GG) 2–4 PCa (n = 108) underwent hemigland cryoablation of the prostate (2017–2021; n = 108). Pretreatment biopsy tissue was subjected to transcriptomic profiling to generate GC scores. The primary outcome was the association between GC-low (<0.45) versus GC-high (≥0.45) and in-field recurrence (GG ≥2) on magnetic resonance imaging–guided biopsy 6 months post-treatment, evaluated using multivariable logistic regression.

RESULTS In the GC-high group (n = 37), treatment failure occurred in 17 patients (46%). In the GC-low group (n = 71), treatment failure occurred in 15 patients (21%). These differences were statistically significant (odds ratio [OR], 2.61 [95% CI, 1.05 to 6.51]; $P = .04$). Differences at 18 months were also significant (76% *v* 44%; OR, 3.58 [95% CI, 1.37 to 9.36], $P = .009$).

CONCLUSION In patients with PCa otherwise suitable for management with focal therapy, a high GC score (≥0.45) was independently associated with treatment failure. A GC score derived from diagnostic biopsy can be used to help predict focal therapy outcomes.

ACCOMPANYING CONTENT

- Data Sharing Statement
- Data Supplement
- Protocol

Accepted August 11, 2025
Published September 17, 2025

JCO Precis Oncol 9:e2500535

adam.weiner@cshs.org
@adam_weiner535

Post-hoc analysis of a phase II trial

Setting: Single center

Patients: Unilateral GG2-4 (n=108)

Treatment: Hemigland cryoablation

Primary outcome: In-field recurrence (GG≥2) at 6 months

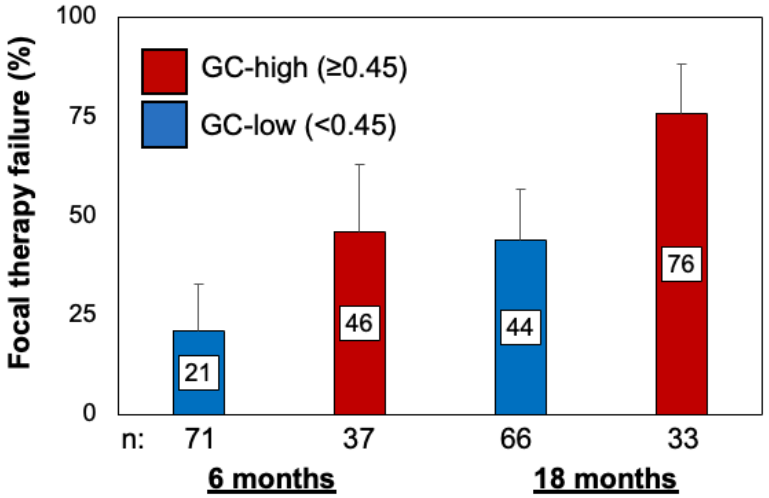
Secondary outcome: In-field or template recurrence at either 6 or 18 months

Biomarker: Commercially available, biopsy tissue-based RNA-signature
(Genomic classifier) GC-Low v GC-High

Characteristic	n (%) / Median IQR
Total	108 (100)
Age (years)	68 (63-74)
PSA (ng/mL)	6.7 (4.7-10.4)
PSA density	0.16 (0.11-0.24)
Grade group	
2	70 (65)
3-4	38 (35)
PIRADS	
1-3	19 (18)
4-5	89 (82)
Months between MRI and Cryotherapy	4.0 (2.8-7.1)
Genomic classifier	0.34 (0.20-0.50)
GC-low (<0.45)	71 (66)
GC-high (≥0.45)	37 (34)

adam.weiner@cshs.org
@adam_weiner535

Post-hoc analysis of a phase II trial



Covariate	6 months OR (95%CI)	OR	P	18 months OR (95%CI)	OR	P
GC-high vs GC-low		2.61	0.039		3.58	0.009
PSAD (per +0.1)		1.41	0.043		1.38	0.098
GG 3-4 vs GG2		1.15	0.8		0.96	0.9
PIRADS 4-5 vs 1-3		3.29	0.118		2.01	0.210

Weiner et al JCO Precision Oncology, 2025

adam.weiner@cshs.org
@adam_weiner535

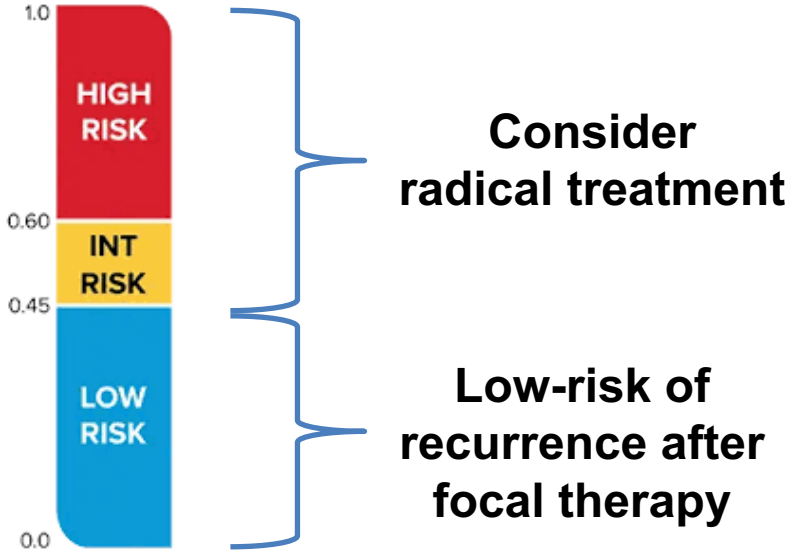
A potential biomarker for focal therapy

Conclusion
With other risk factors, GC score can help counsel for focal therapy

Future work
Validation in other cohorts ongoing

Multi-institutional RCT: Focal vs Surveillance on USA West-Coast

For focal therapy candidates



Weiner et al JCO Precision Oncology, 2025

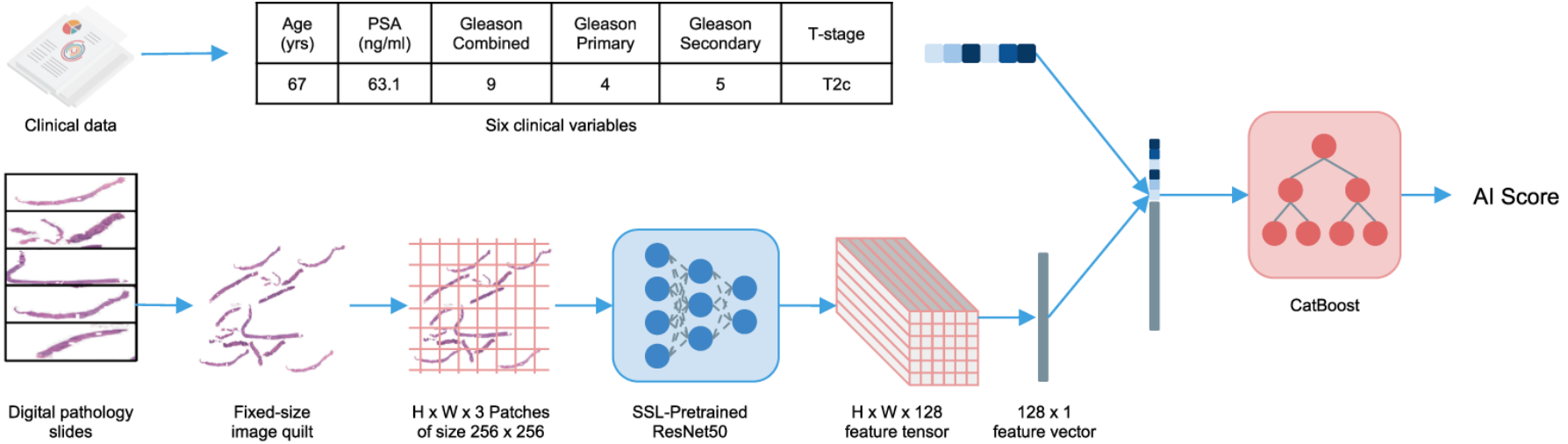
adam.weiner@cshs.org
@adam_weiner535

Forthcoming with Decipher

Trial	Risk Group	Accrual	Intervention Comparison by Decipher
NRG GU-010 GUIDANCE	Unfavorable intermediate	2050	RT ± short-term ADT (low risk) RT+ADT ± darolutamide (high risk)
NRG GU-009 PREDICT RT	High-risk / node-positive	2478	RT+ADT (12 vs 24 mo) (low risk) RT+ADT (24 mo) ± apalutamide (high risk)

adam.weiner@cshs.org
@adam_weiner535

Artera AI



Esteva npj dig med, 2022

adam.weiner@cshs.org
@adam_weiner535

Artera AI

NEJM Evidence

Published June 29, 2023
NEJM Evid 2023; 2 (8)
DOI: 10.1056/EVIDoa2300023

ORIGINAL ARTICLE

Artificial Intelligence Predictive Model for Hormone Therapy Use in Prostate Cancer

Daniel E. Spratt, M.D.,[1] Siyi Tang, Ph.D.,[2,3] Yilun Sun, Ph.D.,[1,4] Huei-Chung Huang, M.A.,[3] Emmalyn Chen, Ph.D.,[3] Osama Mohamad, M.D., Ph.D.,[5] Andrew J. Armstrong, M.D.,[6] Jonathan D. Tward, M.D., Ph.D.,[7] Paul L. Nguyen, M.D.,[8] Joshua M. Lang, M.D., M.Sc.,[9] Jingbin Zhang, M.Sc.,[3] Akinori Mitani, M.D., Ph.D.,[3] Jeffry P. Simko, M.D., Ph.D.,[5] Sandy DeVries, M.A.,[10] Douwe van der Wal, M.Sc.,[3] Hans Pinckaers, M.D., M.Sc.,[3] Jedidiah M. Monson, M.D.,[11] Holly A. Campbell, M.D.,[12] James Wallace, M.D.,[13] Michelle J. Ferguson, M.D.,[14] Jean-Paul Bahary, M.D.,[15] Edward M. Schaeffer, M.D., Ph.D.,[16] Howard M. Sandler, M.D.,[17] Phuoc T. Tran, M.D., Ph.D.,[18] Joseph P. Rodgers, M.S.,[19,20] Andre Esteva, Ph.D.,[3] Rikiya Yamashita, M.D., Ph.D.,[3] and Felix Y. Feng, M.D.,[5] on behalf of NRG Prostate Cancer AI Consortium*

Five RCTs (n=5727)
High risk patients benefit from ADT (MFS)

Original Reports | Genitourinary Cancer

Check for updates

Development and Validation of an Artificial Intelligence Digital Pathology Biomarker to Predict Benefit of Long-Term Hormonal Therapy and Radiotherapy in Men With High-Risk Prostate Cancer Across Multiple Phase III Trials

Andrew J. Armstrong, MD, ScM[1]; Vinnie Y.T. Liu, MSc[2]; Ramprasaath R. Selvaraju, PhD[2]; Emmalyn Chen, PhD[2]; Jeffry P. Simko, MD, PhD[3]; Sandy DeVries, MA[3]; Oliver Sartor, MD[4]; Howard M. Sandler, MD[5]; Osama Mohamad, MD, PhD[3]; Huei-Chung Huang, MA[2]; Jacqueline Griffin, PhD[2]; Rikiya Yamashita, MD, PhD[2]; Andre Esteva, PhD[2]; Phuoc T. Tran, MD, PhD[6]; Daniel E. Spratt, MD[7]; John Hi Carson, MD[8]; Christopher Peters, MD[9]; Elizabeth Gore, MD[10,11]; Steve P. Lee, MD, PhD[12]; Jedidiah M. Monson, MD[13]; Mark E. Augspurger, MD[14]; Ali El-Gayed, MD[15]; Joseph P. Rodgers, MS[16,17]; Rana McKay, MD[18]; Todd Morgan, MD[19]; Felix Y. Feng, MD[3]; and Paul L. Nguyen, MD[20]

DOI https://doi.org/10.1200/JCO.24.00365

Prior RCT (n=1192)
High risk patients benefit from LT vs ST ADT (MFS)

Spratt NEJM Evid 2023; Armstrong JCO 2025

adam.weiner@cshs.org
@adam_weiner535

PORTOS

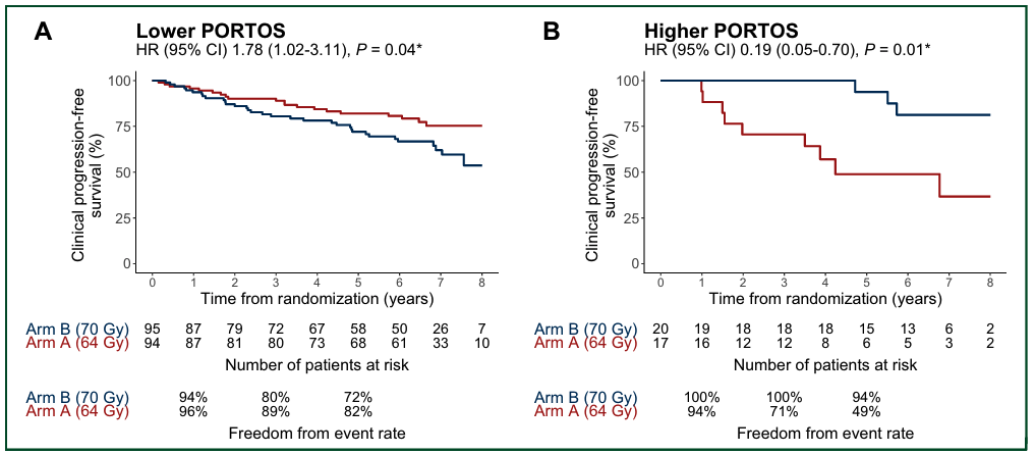
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Predicting dose response to prostate cancer radiotherapy: validation of a radiation signature in the randomized phase III NRG/RTOG 0126 and SAKK 09/10 trials

A. Dal Pra[1*†], P. Ghadjar[2†], H. M. Ryu[3], J. A. Proudfoot[3], S. Hayoz[4], J. M. Michalski[5], D. E. Spratt[6], Y. Liu[3], C. Schär[4], A. M. Berlin[7], D. R. Zwahlen[8], J. P. Simko[9], T. Hölscher[10], J. A. Efstathiou[11], B. Polat[12], H. M. Sandler[13], G. Hildebrandt[14], M. B. Parliament[15], A.-C. Mueller[16], I. S. Dayes[17], L. Plasswilm[18], R. J. M. Correa[19], J. M. Robertson[20], T. G. Karrison[21], E. Davicioni[3], W. A. Hall[22], F. Y. Feng[9], A. Pollack[1], G. N. Thalmann[23], P. L. Nguyen[24], D. M. Aebersold[25], P. T. Tran[26*‡] & S. G. Zhao[27*‡]



Transcriptomic-based signature from tumor tissue

Two RCTs (n=441)

Higher PORTOS benefit from radiation dose-escalation in the primary and salvage setting

Needs validation

Dal Pra Ann Oncol, 2025

adam.weiner@cshs.org
@adam_weiner535

Polygenic risk score and surveillance patients

JAMA Oncology | Brief Report

Polygenic Risk Score and Upgrading in Patients With Prostate Cancer Receiving Active Surveillance

Louisa B. Goss, MS; Menghan Liu, MS; Yingye Zheng, PhD; Boya Guo, PhD; David V. Conti, PhD; Christopher A. Haiman, ScD; Linda Kachuri, PhD; William J. Catalona, MD; John S. Witte, PhD; Daniel W. Lin, MD; Lisa F. Newcomb, PhD; Burcu F. Darst, PhD

Prospective Canary PASS cohort study (n=1220)

Increasing PRS associated with tumor upgrading

Goss JAMA Oncology, 2024

adam.weiner@cshs.org
@adam_weiner535

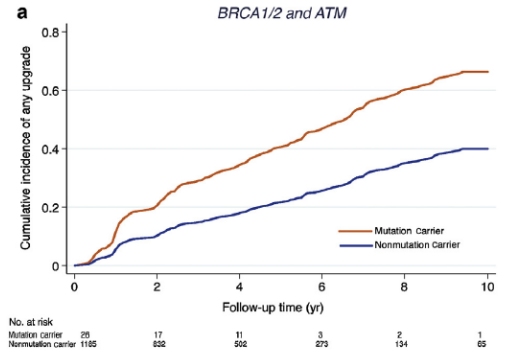
Germline and surveillance: HRD

BRCA1/2 and ATM

Risk of grade reclassification: HR 95% CI)

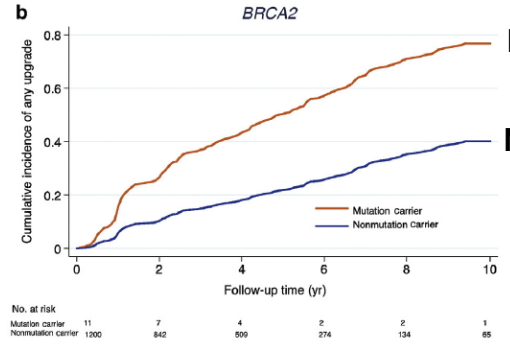
Any: 1.96 (1.004-3.84)
BRCA2: 5.01 (2.22-11.61)

Frequency in Low-int risk: ~<3%



BRCA1/2 or ATM

No mutation



BRCA2

No mutation

Carter EU, 2019

adam.weiner@cshs.org
@adam_weiner535

Localized prostate cancer: Biomarkers

HRD mutations and PRS

Prognosticate for surveillance if present/available

Decipher

Prognostic at many points

ArteraAI

Predictive of benefit for ST vs no ADT and ST vs LT ADT

Forthcoming

Prospective trials stratifying by biomarkers and clinical implementation

adam.weiner@cshs.org
@adam_weiner535

Biomarkers in prostate cancer: Outline

Localized disease: Genomic classifiers & AI tools help guide intensity of local therapy.

Advanced

adam.weiner@cshs.org
@adam_weiner535

Biomarkers in prostate cancer: Outline

Localized disease: Genomic classifiers & AI tools help guide intensity of local therapy.

Advanced

adam.weiner@cshs.org
@adam_weiner535

Transcriptomic signatures

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

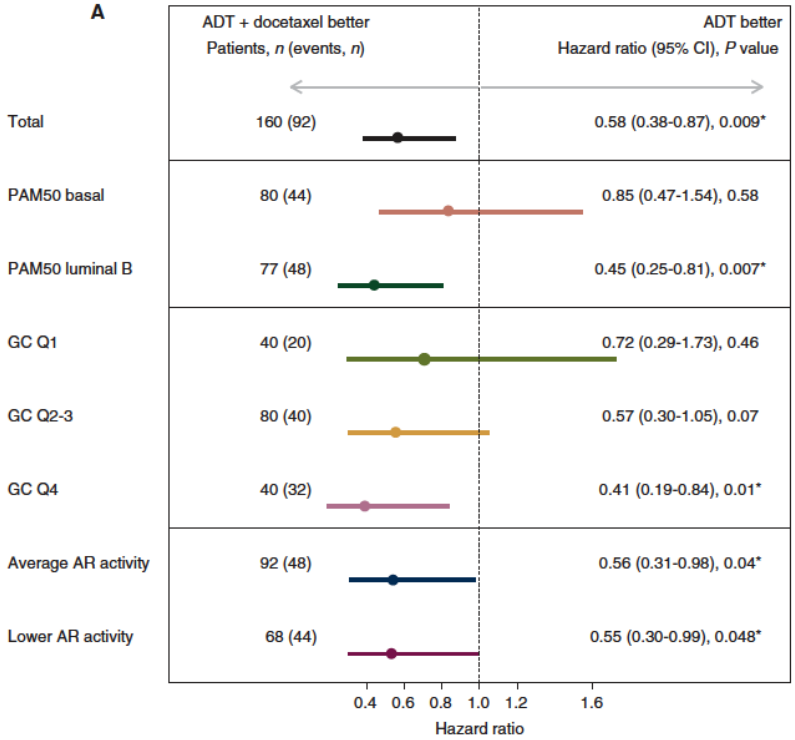
Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial☆

A. A. Hamid[1,2], H.-C. Huang[3], V. Wang[4], Y.-H. Chen[4], F. Feng[5], R. Den[6], G. Attard[7], E. M. Van Allen[1], P. T. Tran[8], D. E. Spratt[9], R. Dittamore[3], E. Davicioni[3], G. Liu[10], R. DiPaola[11], M. A. Carducci[8] & C. J. Sweeney[1]*

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA; [2]University of Melbourne, Melbourne, Australia; [3]Decipher Biosciences, San Diego; [4]Department of Data Science, Dana-Farber Cancer Institute, Boston; [5]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco; [6]Department of Radiation Oncology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, USA; [7]University College London Cancer Institute, London, UK; [8]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore; [9]Department of Radiation Oncology, University of Michigan, Ann Arbor; [10]University of Wisconsin Carbone Cancer Center, Madison; [11]University of Kentucky Medical Center, Lexington, USA

CHAARTED RCT (ADT±Docetaxel)

Benefitted from docetaxel
Luminal vs Basal signature
Higher decipher



Hamid Ann Oncol 2021

adam.weiner@cshs.org
@adam_weiner535

Transcriptomic signatures

Cell

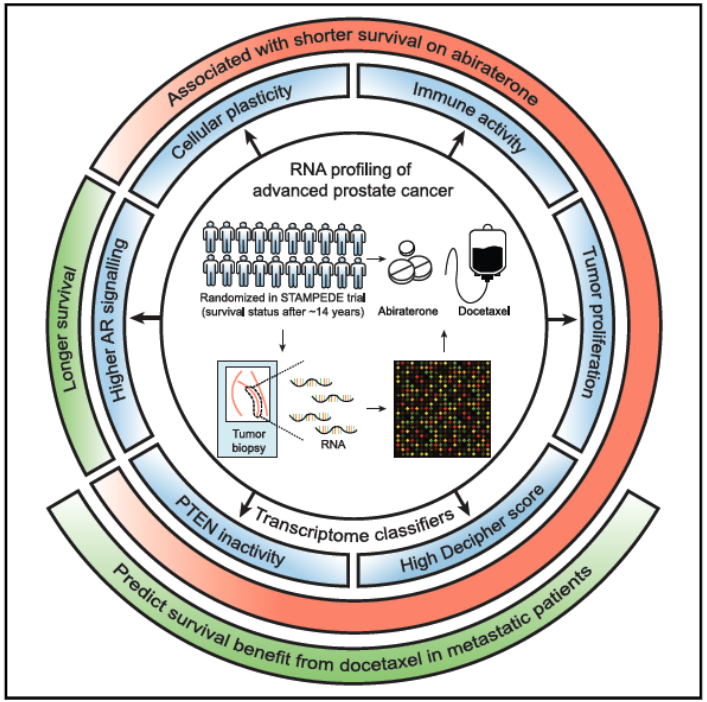
CellPress
OPEN ACCESS

Article

Tumor transcriptome-wide expression classifiers predict treatment sensitivity in advanced prostate cancers

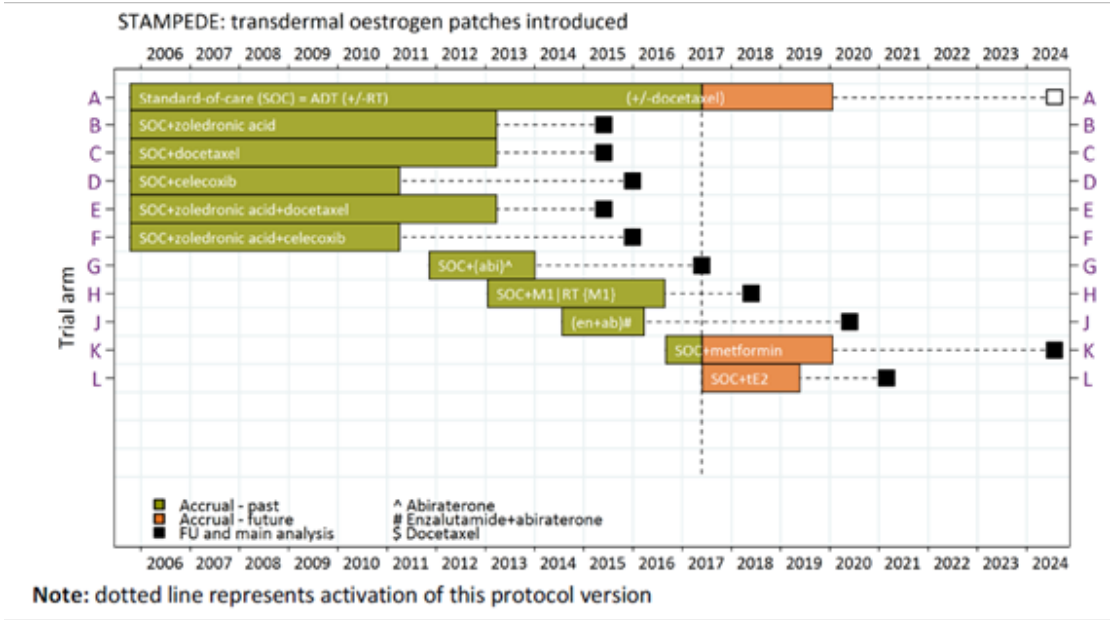
Emily Grist,[1,22] Peter Dutey-Magni,[2,22] Marina A. Parry,[1,22] Larissa Mendes,[1,22] Ashwin Sachdeva,[3,4] James A. Proudfoot,[5] Anis A. Hamid,[6] Mazlina Ismail,[1] Sarah Howlett,[1] Stefanie Friedrich,[1] Lia DePaula Oliveira,[7] Laura Murphy,[2] Christopher Brawley,[2,23] Oluwademilade Dairo,[7] Sharanpreet Lall,[1] Yang Liu,[5] Daniel Wetterskog,[1] Anna Wingate,[1]

STAMPEDE RCT (ADT ± docetaxel or abi)
N=1523 (832 metastatic [M1])



adam.weiner@cshs.org
@adam_weiner535

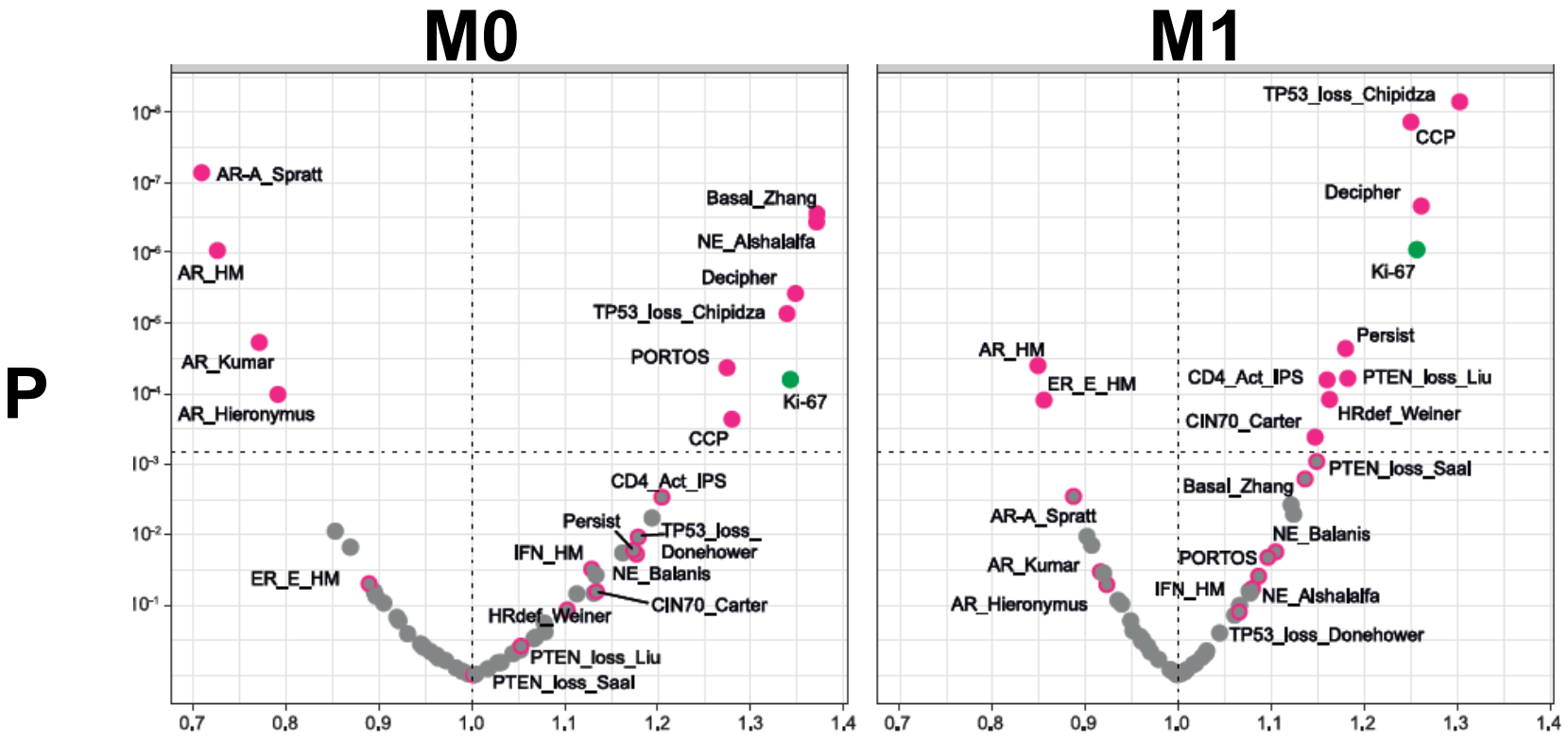
STAMPEDE TRIAL



https://www.stampedetrial.org/centres/information-on-stampede/

adam.weiner@cshs.org
@adam_weiner535

Transcriptomic signatures



Hazard ratios for overall survival

adam.weiner@cshs.org
@adam_weiner535

Transcriptomic signatures

Cell

CellPress
OPEN ACCESS

Article

Tumor transcriptome-wide expression classifiers predict treatment sensitivity in advanced prostate cancers

Emily Grist,[1,22] Peter Dutey-Magni,[2,22] Marina A. Parry,[1,22] Larissa Mendes,[1,22] Ashwin Sachdeva,[3,4] James A. Proudfoot,[5] Anis A. Hamid,[6] Mazlina Ismail,[1] Sarah Howlett,[1] Stefanie Friedrich,[1] Lia DePaula Oliveira,[7] Laura Murphy,[2] Christopher Brawley,[2,23] Oluwademilade Dairo,[7] Sharanpreet Lall,[1] Yang Liu,[5] Daniel Wetterskog,[1] Anna Wingate,[1]

STAMPEDE RCT (ADT ± docetaxel or abi)
N=1523 (832 metastatic [M1])

Key takeaways

Transcriptomic signatures from clinical grade assays can help personalize systemic therapies

Decipher was prognostic for both M0 and M1

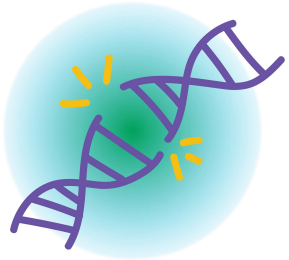
High Decipher was predictive of benefit from docetaxel for M1

PTEN loss signature associated with resistance to ADT and benefit from docetaxel

Grist Cell, 2025

adam.weiner@cshs.org
@adam_weiner535

PARP-inhibitors



mHSPC (phase 3 ongoing)

AMPLITUDE - HRR-altered Abi±niraparib
~37% risk reduction overall in rPFS (ASCO 2025)
Target accrual n=788

TALAPRO-3 – **HRR-altered** Enza±talazoparib
Target accrual n=599

mCRPC (phase 3 with OS)

PROfound - Post-ARPi mCRPC
Olaparib vs abi/enza switch
BRCA1/2 or ATM (cohort A)
OS 19.1 vs 14.7 mo; HR 0.69 (0.50-0.97)

PROpel – First line mCRPC
Abi±Olaparib
BRCA subgroup
OS HR 0.29 (0.14-0.56)

TALAPRO-2 – First line mCRPC
Enza ± Talazoparib
OS benefit for HRR deficient population

Attard ASCO 2025; Agarwal Future oncol 2025; Hussain NEJM 2020; Saad Lancet Onc 2023; Fizazi Lancet 2025; Agarwal Lancet 2025

adam.weiner@cshs.org
@adam_weiner535

TALAPRO-2: Background

BRCA mutant PCa: 10% of advanced cases and worse outcomes

PARPi: Established after ARPi progression for HRD but resistance develops quickly

Perhaps earlier use of PARPi could be more beneficial

Fizazi Lancet 2025; Agarwal Lancet 2025

adam.weiner@cshs.org
@adam_weiner535

TALAPRO-2

THE LANCET

Talazoparib plus enzalutamide in men with HRR-deficient metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

Karim Fizazi*, Arun A Azad, Nobuaki Matsubara, Joan Carles, André P Fay, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Dingwei Ye, Xun Lin, Matko Kalac, A Douglas Laird, Dana Kennedy, Neeraj Agarwal*

Design: Phase III, randomized, double-blind (n=399, 26 countries).
Population: mCRPC, prospectively tested HRR-deficient (12-gene panel); No prior life-prolonging therapy in CRPC.

Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

Neeraj Agarwal*, Arun A Azad, Joan Carles, André P Fay, Nobuaki Matsubara, Cezary Szczylik, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Fred Saad, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Xun Lin, Cynthia G Healy, Matko Kalac, Dana Kennedy, Karim Fizazi*

Design: Phase III, randomized, double-blind (n=805, 200 centers, 26 countries).
Population: mCRPC, unselected for HRR status (21% HRR-deficient, 79% HRR-non-deficient/unknown).

Arms: Talazoparib (0.5 mg daily) + Enzalutamide (160 mg daily) vs Enzalutamide + placebo.
Primary endpoint: rPFS; OS was key alpha-protected secondary.

Fizazi Lancet 2025; Agarwal Lancet 2025

adam.weiner@cshs.org
@adam_weiner535

TALAPRO-2

THE LANCET

Talazoparib plus enzalutamide in men with HRR-deficient metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

Karim Fizazi*, Arun A Azad, Nobuaki Matsubara, Joan Carles, André P Fay, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Dingwei Ye, Xun Lin, Matko Kalac, A Douglas Laird, Dana Kennedy, Neeraj Agarwal*

Results (median follow-up 44 mo):

OS: HR 0.62 (95% CI 0.48–0.81), p=0.0005

Median 45.1 mo vs 31.1 mo.

BRCA1/2 subgroup: HR 0.50

Median OS not reached vs 28.5 mo.

Non-BRCA HRR: HR 0.73 (p=0.066)

Trend toward benefit.

rPFS: HR 0.47; Median 30.7 vs 12.3 mo.

Talazoparib plus enzalutamide in men with metastatic castration-resistant prostate cancer: final overall survival results from the randomised, placebo-controlled, phase 3 TALAPRO-2 trial

Neeraj Agarwal*, Arun A Azad, Joan Carles, André P Fay, Nobuaki Matsubara, Cezary Szczylik, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Fred Saad, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Xun Lin, Cynthia G Healy, Matko Kalac, Dana Kennedy, Karim Fizazi*

Results (median follow-up 52.5 mo):

OS: HR 0.80 (95% CI 0.66–0.96), p=0.016

Median 45.8 mo vs 37.0 mo.

By HRR status:

HRR-deficient: HR 0.55 (p=0.0035) → strong benefit.

HRR-non-deficient/unknown: HR 0.88 (NS).

rPFS: HR 0.67 (p<0.0001); Median 33.1 vs 19.5 mo.

Fizazi Lancet 2025; Agarwal Lancet 2025

adam.weiner@cshs.org
@adam_weiner535

TALAPRO-2: Key themes

BRCA mutations: Poor prognosis, strong PARPi sensitivity.
Other HRR (CDK12, PALB2): Also sensitive but data weaker.
HRR-wildtype: Uncertain benefit.

BRCA: PARPi should always be given (preferably earlier)
Earlier PARPi + ARPI: Beats sequential ARPI → PARPi
For HRR-wildtype/unknown: ARPI alone remains reasonable due to unclear benefit and toxicity risk.

Future
Combinations moving into mHSPC

Fizazi Lancet 2025; Agarwal Lancet 2025

adam.weiner@cshs.org
@adam_weiner535

PSMA and FDG

PSMA uptake on PET: Predictive of response to Lu-177-PSMA

Eligible mCRPC patients: ~83% (VISION trial)
Heterogenous response: Partial or complete response in ~51%

FDG PET: + lesions associated with worse response to Lu-177-PSMA (TheraP)
PSA response: When excluded patients with FDG+/PSMA- lesions ~66% (still investigational)

Hofman Lancet Onc 2024; Hofman Lancet 2021; Sartor NEJM 2021; Azad Lancet Oncol 2024

adam.weiner@cshs.org
@adam_weiner535

PSMA and FDG

Conclusion
PSMA PET+ is critical to prioritize Lu-177-PSMA
CT with contrast is still standard for detecting PSMA- lesions

Forthcoming
UpFrontPSMA (phase II) in high volume mHSPC Docetaxel±LuPSMA (n=130)
48wk undetectable PSA 16% vs 41% (no OS difference)

PSMAddition (phase III) in mHSPC (n=1126)
Intervention:
SOC (ADT + ARPI, with or without docetaxel)
vs SOC + Lu-177–PSMA-617 (given q6 weeks × 6 cycles).
Eligibility: Required PSMA PET–positive disease (no discordant FDG+ / PSMA– lesions).
Primary Endpoints: rPFS; OS

Hofman Lancet Onc 2024; Hofman Lancet 2021; Sartor NEJM 2021; Azad Lancet Oncol 2024

adam.weiner@cshs.org
@adam_weiner535

MSI-H/dMMR and TMB-high

MSI-H/dMMR: 2-3% of advanced PCa
Response to pembrolizumab can be dramatic and durable

TMB≥10 mut/Mb: <5%, nearly all were MSI-H/dMMR
Pembrolizumab approved, tissue agnostic

Clinical practice:
Always test mCRPC for MSI/MMR (tissue or ctDNA NGS panels).
Pembrolizumab is an **option in later lines** for these biomarker-defined subsets.
Outside MSI-H/TMB-high: Pembro activity in prostate cancer is minimal.

Le Science 2017; Le NEJM 2015; Marabelle Lancet Oncol 2020; Armenia Nat Genet 2018

adam.weiner@cshs.org
@adam_weiner535

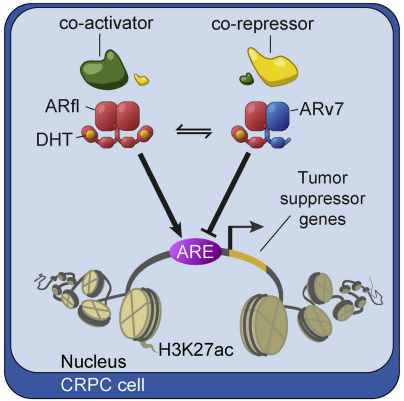
AR-V7 (Androgen Receptor Splice Variant 7)

What it is: AR splice variant lacking ligand-binding domain → constitutively active

Detection: Circulating tumor cells (CTCs), RT-PCR assays

Clinical impact:
Predicts **resistance to AR-targeted therapies (enzalutamide, abiraterone)**
AR-V7+ patients may derive more benefit from **taxane chemotherapy**

Status: Prognostic/predictive, but **not yet standard of care**
(assays not widely available/validated)



Cato Cancer Cell 2019

adam.weiner@cshs.org
@adam_weiner535

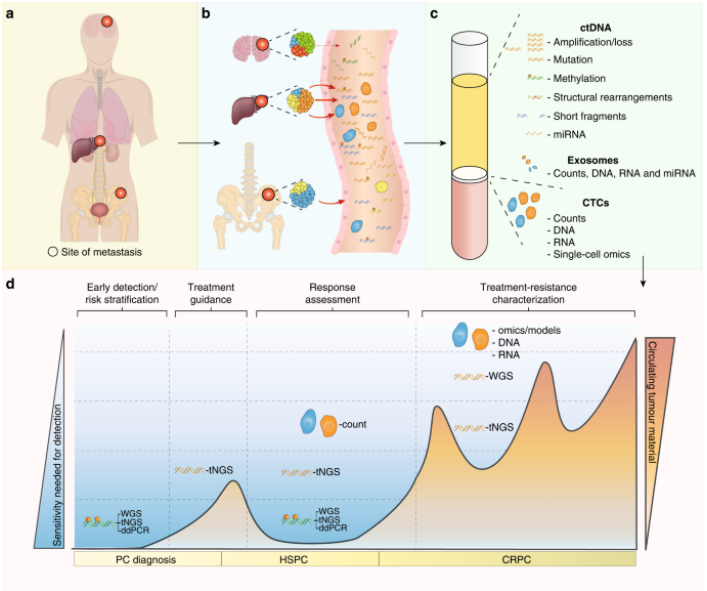
ctDNA Assays (Liquid Biopsy)

What it is: Plasma-based next-generation sequencing of tumor DNA

Clinical use:
Detects **HRR mutations, MSI-H, TMB** when tissue biopsy is inadequate
Can monitor **treatment resistance mechanisms** (e.g., BRCA reversion, AR mutations)

Advantages: Less invasive, captures tumor heterogeneity, repeatable over time

Status: Increasingly used in practice, but sensitivity varies (esp. in low tumor burden)



Trujillo BJC 2022

adam.weiner@cshs.org
@adam_weiner535

Advanced prostate cancer: Biomarkers

Biomarker	Frequency	Predicts	Therapy
HRR mutations (BRCA1/2, PALB2, CDK12, etc.)	~20–25%	PARP inhibitor sensitivity	**Olaparib, Rucaparib, Talazoparib, Niraparib**
MSI-H / dMMR	~2–3%	ICI response	**Pembrolizumab** (FDA tissue-agnostic)
TMB-High (≥10/Mb)	~3–5% (often overlaps MSI-H)	ICI response	**Pembrolizumab**
PSMA PET+	Majority of mCRPC	RLT eligibility	**Lu-177–PSMA-617**
FDG+/PSMA–	Subset of aggressive tumors	Poor RLT candidates	Guides away from PSMA RLT
AR-V7 splice variant	Research	ARPI resistance → chemo benefit	Not standard of care
Gene classifiers (Decipher, etc.)	Trials	Prognosis / ADT benefit prediction	Investigational in mHSPC/mCRPC
ctDNA assays	Expanding	Detect HRR/MSI when tissue limited	Increasing clinical use

adam.weiner@cshs.org
@adam_weiner535

Prostate cancer biomarkers

Localized disease: Genomic classifiers & AI tools help guide intensity of local therapy.

Advanced disease: Universal testing for **HRR, MSI, TMB, and PSMA PET** is essential; guides targeted use of **PARPi, immunotherapy, and radioligand therapy**.

Emerging tools (AR-V7, ctDNA) show promise but are not yet routine.

adam.weiner@cshs.org
@adam_weiner535

Beyond risk groups

adam.weiner@cshs.org
@adam_weiner535