Impact of genomic classifiers on *postoperative* treatment

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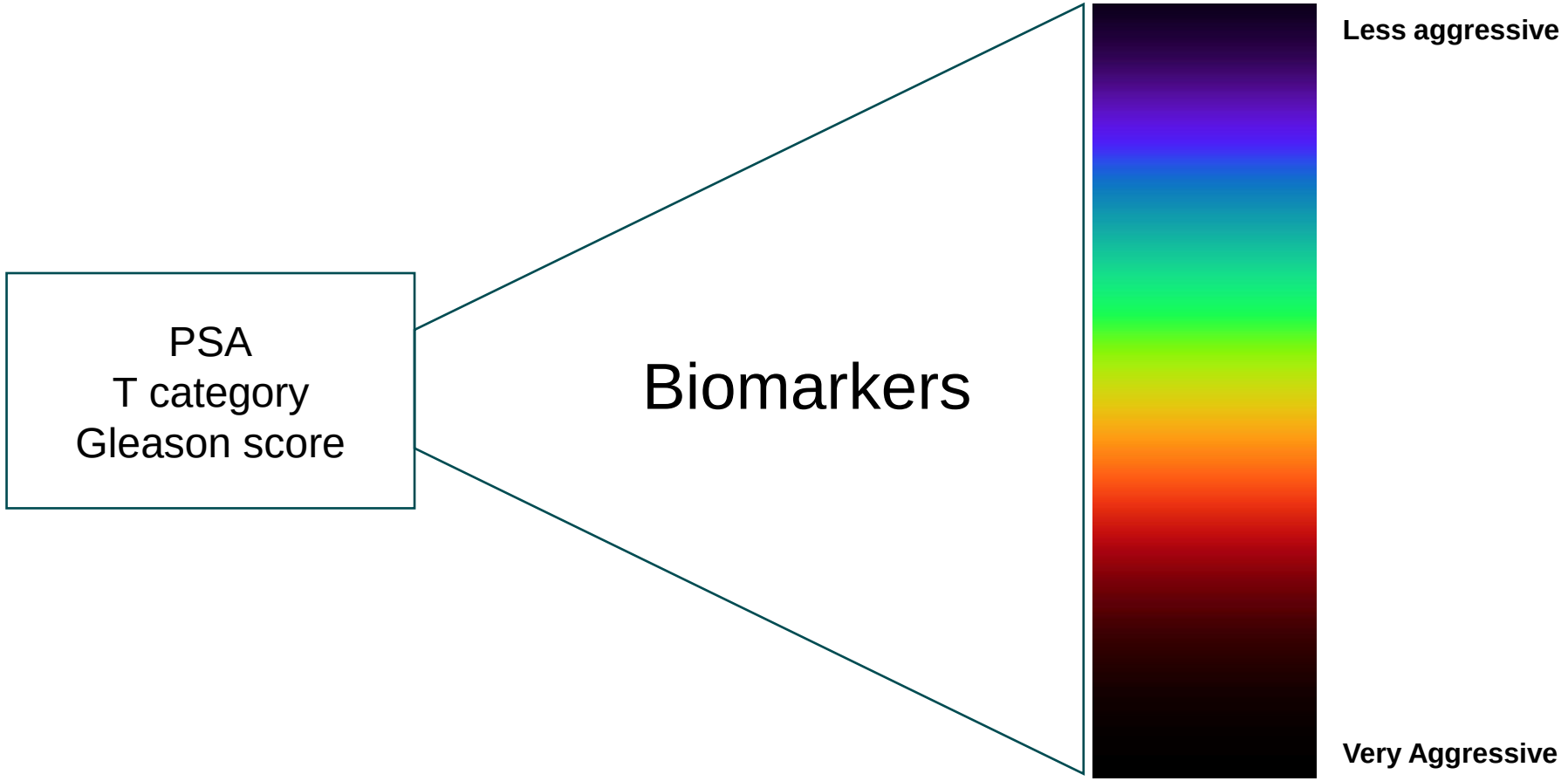
Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	Veracyte/Decipher (institutional/sponsor research support)
Receipt of honoraria or consultation fees	Merck
Stock shareholder	None
Other support (please specify):	University of Miami (employment/leadership)

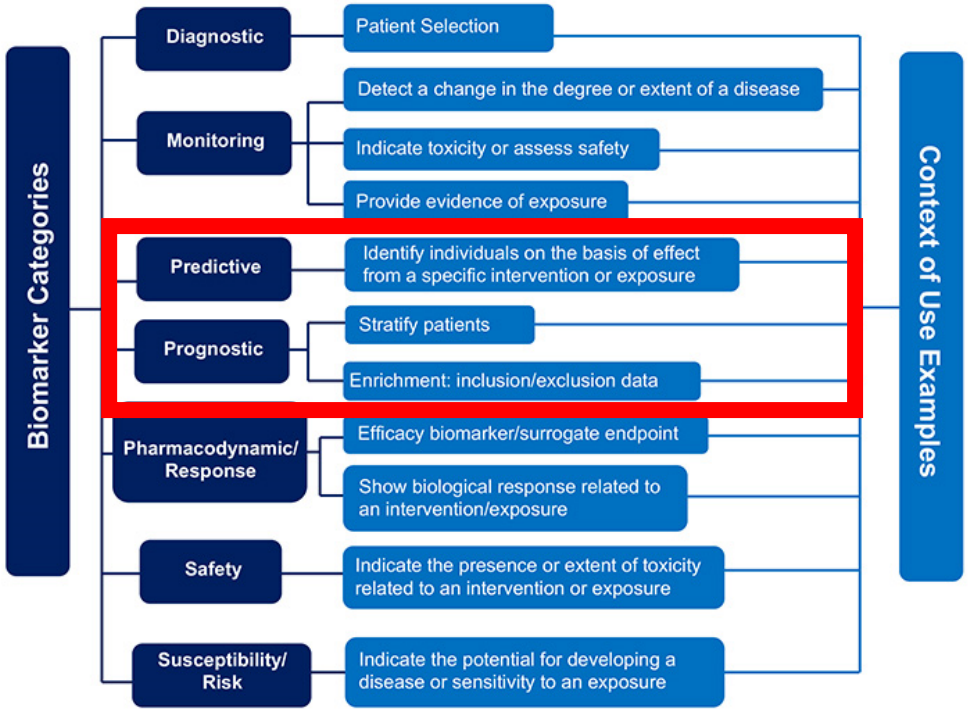
Prostate cancer is a (dynamic) *spectrum* of diseases



Conventional clinicopathologic factors DO NOT tell us the whole story!

*Spec.trum = used to classify something, **or suggest that it can be classified**, in terms of its position on a scale between two extreme or opposite points.*

Prognostic vs predictive biomarkers



https://www.fda.gov/drugs/biomarker-qualification-program/context-use

Prognostic Biomarkers:

- Measured before treatment to indicate long-term outcome for patients untreated or receiving SOC treatment (**independent of treatment received**).

Predictive Biomarkers:

- Measured before treatment to identify who is likely or unlikely to **benefit from a specific treatment.**

NCCN Prostate 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

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PRINCIPLES OF RISK STRATIFICATION

Table 1. Initial Risk Stratification for Clinically Localized Disease

Category	Tool	Predictive	Prognostic	Endpoint Trained For[a]	Level of Evidence for Validation[b]
Clinical	NCCN	No	Yes	See note[c]	1
	STAR-CAP[2]	No	Yes	PCSM	3
	CAPRA[11,d]	No	Yes	BCR	3
	MSKCC[12]	No	Yes	BCR and PCSM[f]	3
AI	ArteraAI Prostate (category 2B)[5,e]	No	Yes	BCR, DM, PCSM[g]	1
Gene Expression Testing	Decipher[13]	No	Yes	DM	1
	Prolaris[14]	No	Yes	See note[h]	3
	Oncotype[15]	No	Yes	Adverse pathology	3
Germline	HRR	No	Uncertain	See note[i]	4

- **No predictive biomarker** currently available
- Decipher is the first gene expression test considered to have level 1 of evidence

European Association of Urology

Review – Prostate Cancer

A Systematic Review of the Evidence for the Decipher Genomic Classifier in Prostate Cancer

Neil K. Jairath[a,†], Alan Dal Pra[b,†], Randy Vince Jr.[c], Robert T. Dess[a], William C. Jackson[a], Jeffrey J. Tosoian[c], Sean M. McBride[d], Shuang G. Zhao[a], Alejandro Berlin[e], Brandon A. Mahal[b,f], Amar U. Kishan[g], Robert B. Den[h], Stephen J. Freedland[i,j], Simpa S. Salami[c], Samuel D. Kaffenberger[c], Alan Pollack[b], Phuoc Tran[k], Rohit Mehra[l], Todd M. Morgan[c], Adam B. Weiner[m], Osama Mohamad[n], Peter R. Carroll[o], Matthew R. Cooperberg[o], R. Jeffrey Karnes[p], Paul L. Nguyen[q], Jeff M. Michalski[r], Jonathan D. Tward[s], Felix Y. Feng[n], Edward M. Schaeffer[m], Daniel E. Spratt[a,]*

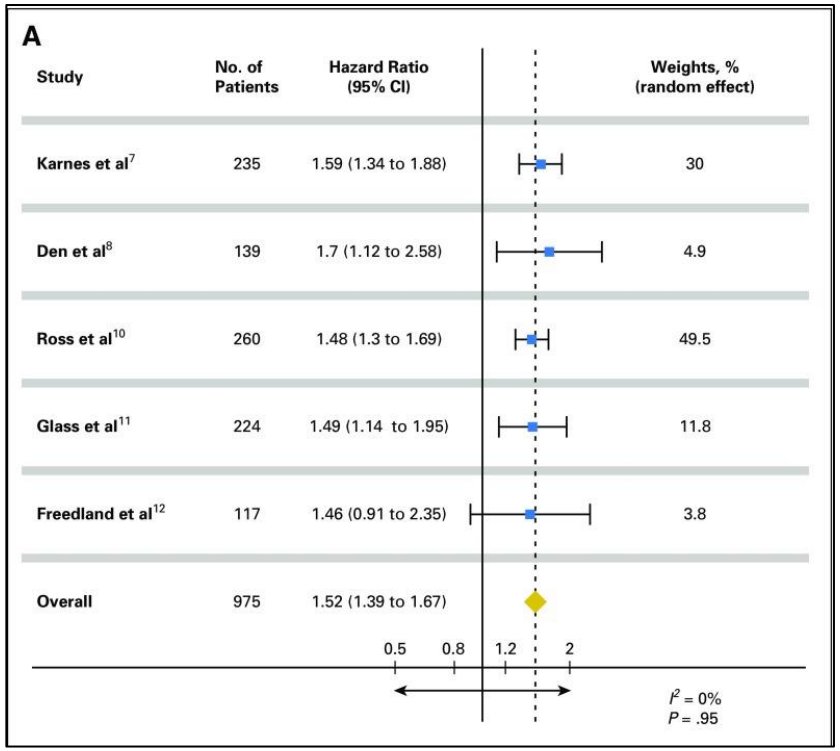
Setting	Indication	# Studies	# Patients
Biopsy	Active Surveillance	5	10,456
	Definitive Therapy	12	8,737
	Non-Metastatic Castrate Resistant	1	233
	Metastatic Hormone Sensitive	2	382
Post-RP	Early vs. Salvage Radiation	18	9,515
	Salvage Therapy Intensity	4	1,084
	TOTAL	**42**	**30,407**

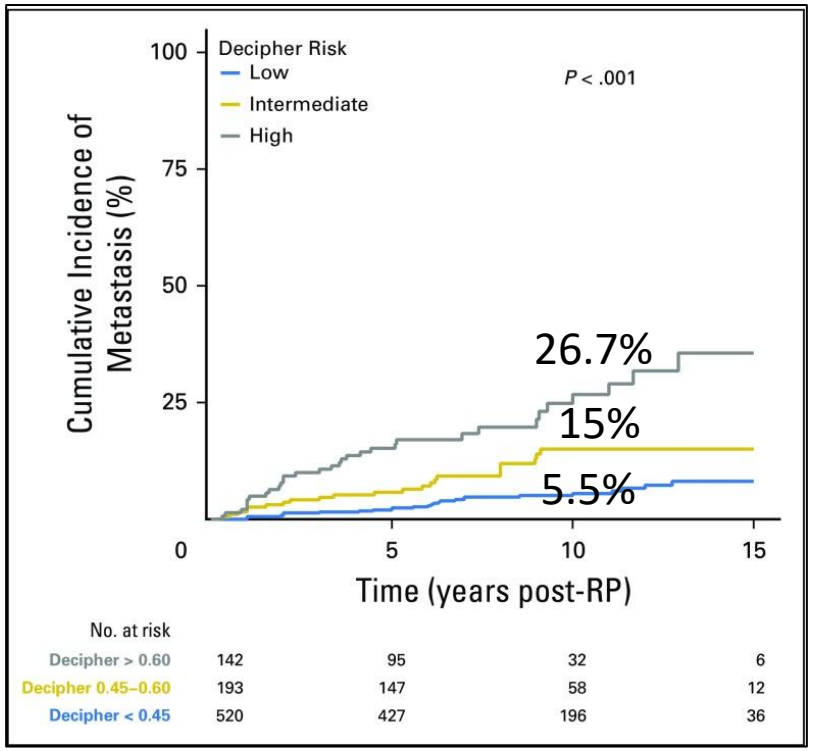
42 studies and more than 30,000 patients demonstrated that Decipher:

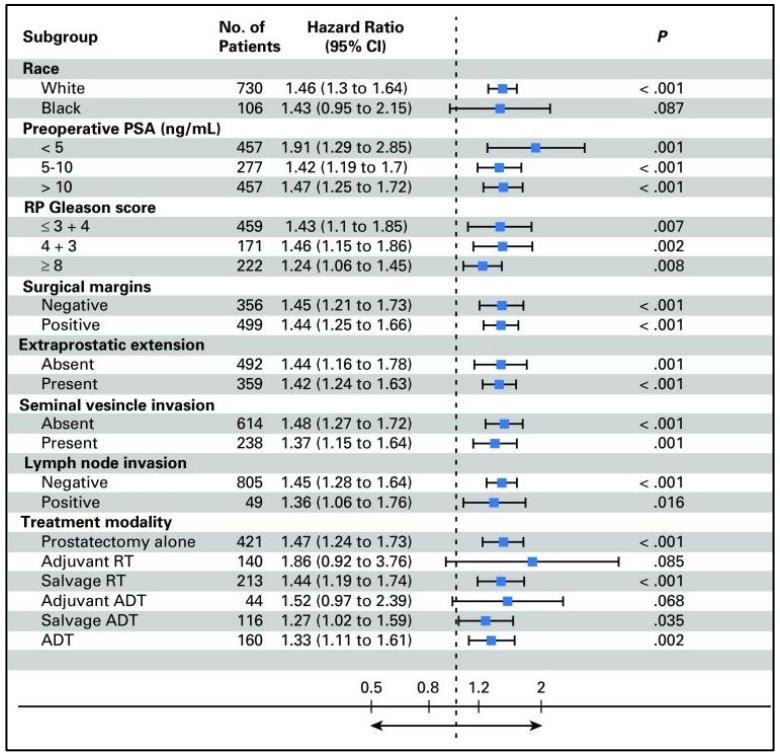
- is independently prognostic for overall survival, metastasis, PCSM, adverse pathology, and biochemical failure.
- is more accurate in stratifying patient risk than clinicopathologic variables alone.

Jairath, NK, Dal Pra A Vince Jr. R, et al. Eur Urol 2021

Individual Patient-Level Meta-Analysis After Prostatectomy to Predict Development of Metastatic Disease







N= 855
Median follow-up= 8 years

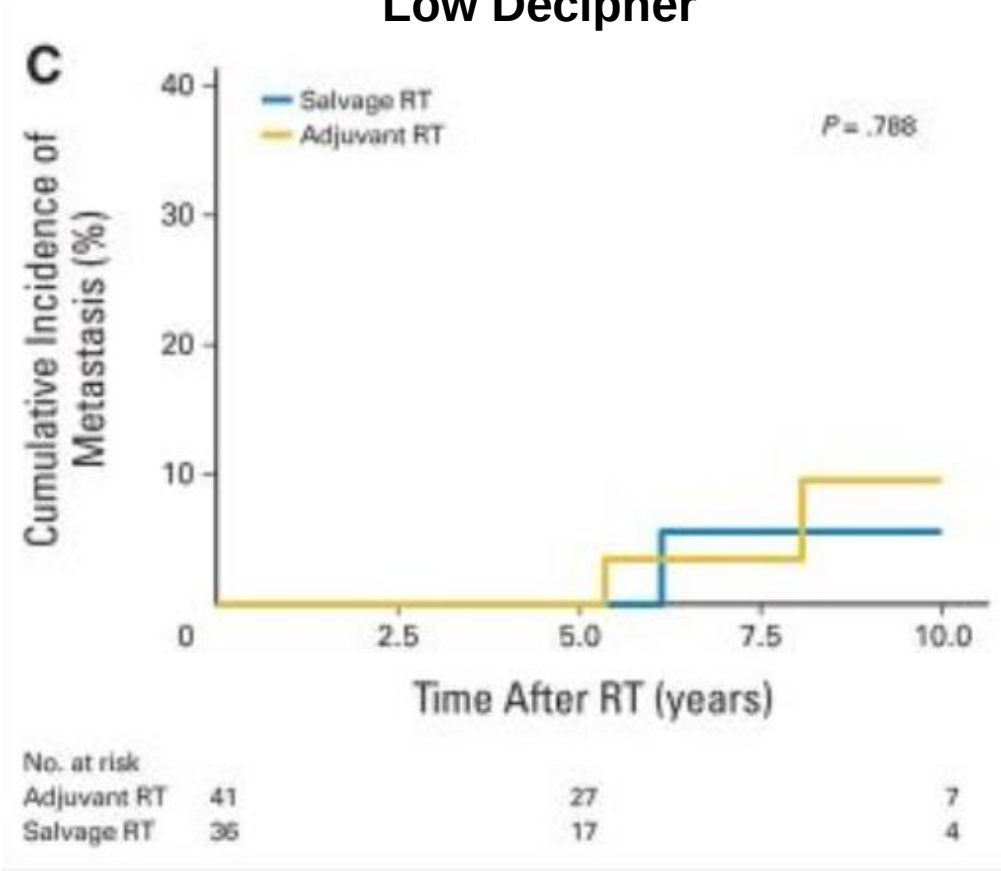
Spratt et al., JCO 2017

Personalizing Postoperative RT using Genomic Classifiers

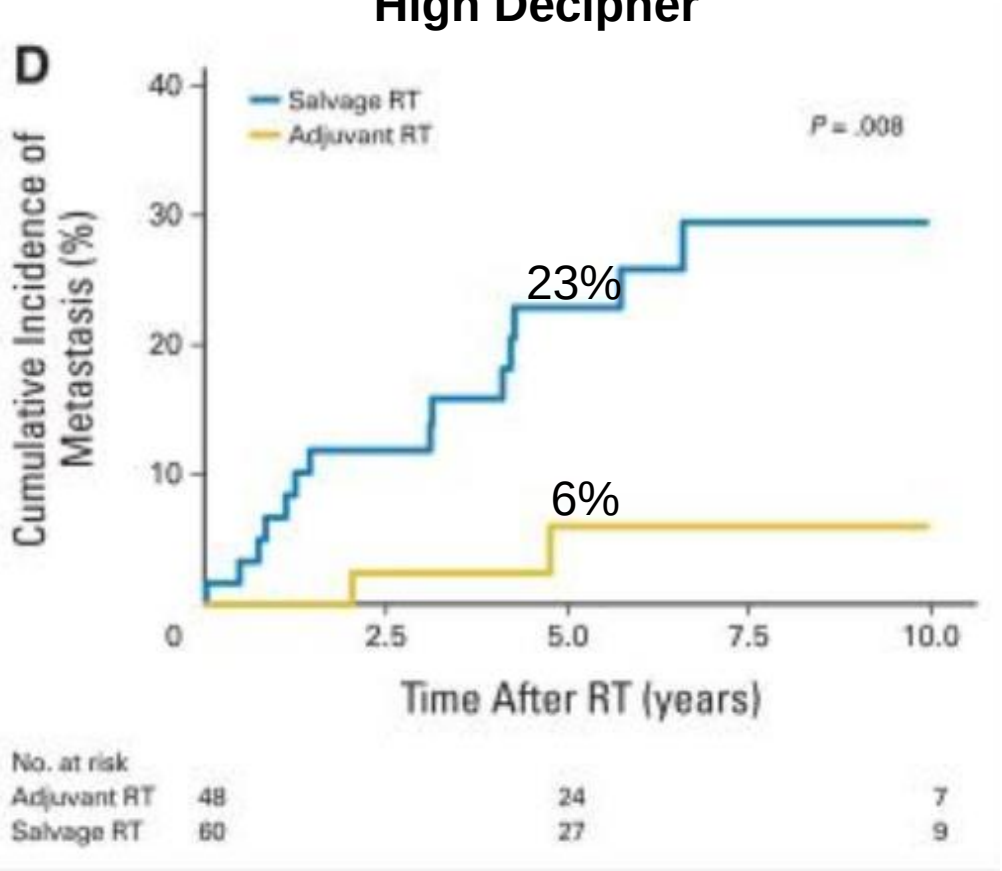
Question	Trial	Findings
RT timing	RADICALS-RT/RAVES/GETUG-AFU 17	adjuvant RT = early SRT
RT +/- ADT	RTOG 9601/GETUG-16/RTOG 0534	SRT + STADT > SRT
RT dose	SAKK 0910	64Gy = 70Gy
RT volume	RTOG 0534	SRT + STADT + PNRT > SRT
RT + ADT duration	RADICALS-HD	RT + LTADT > RT +STADT

RT timing - Adjuvant vs Salvage RT

Low Decipher



High Decipher

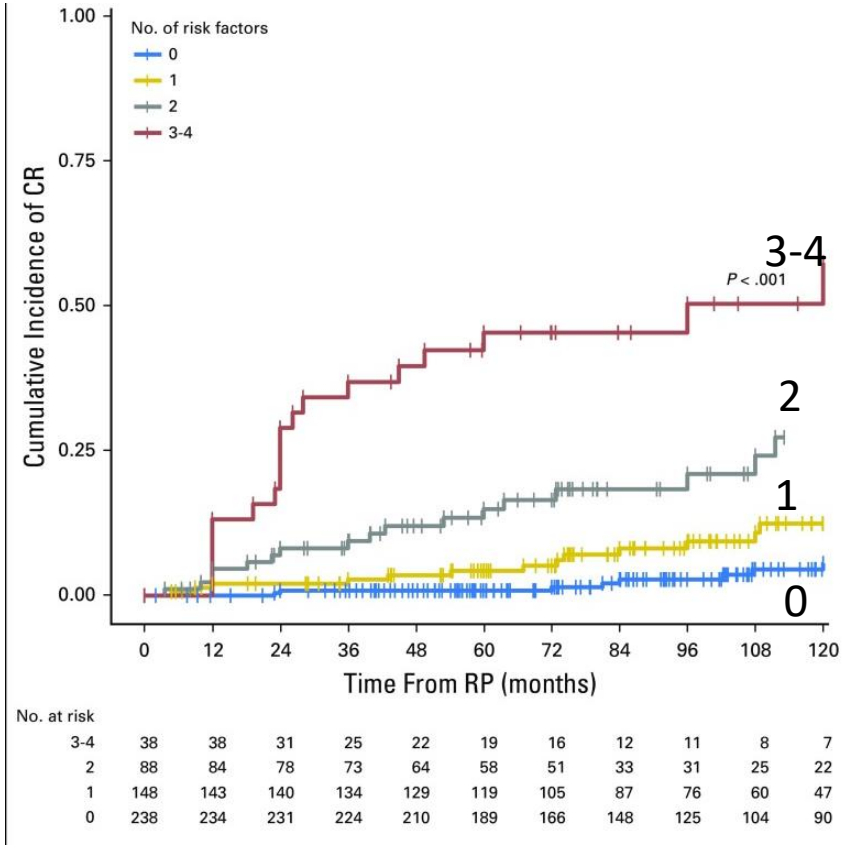


Den et al, JCO 2015

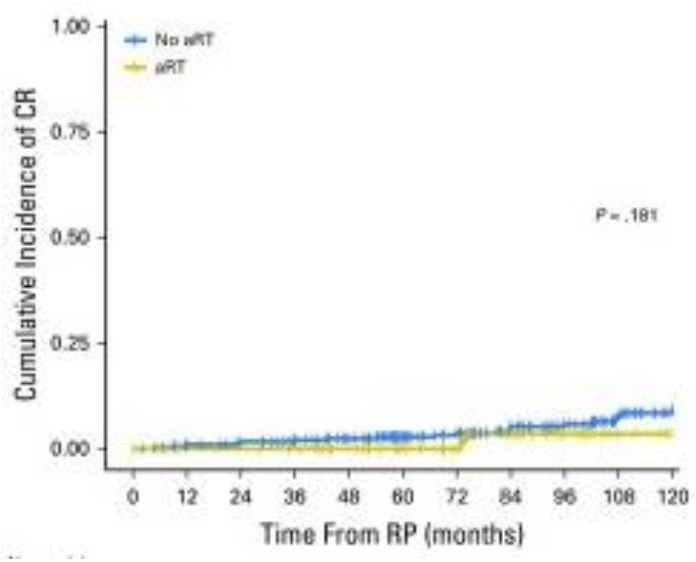
RT timing - Adjuvant vs No Adjuvant RT

Risk Factors:

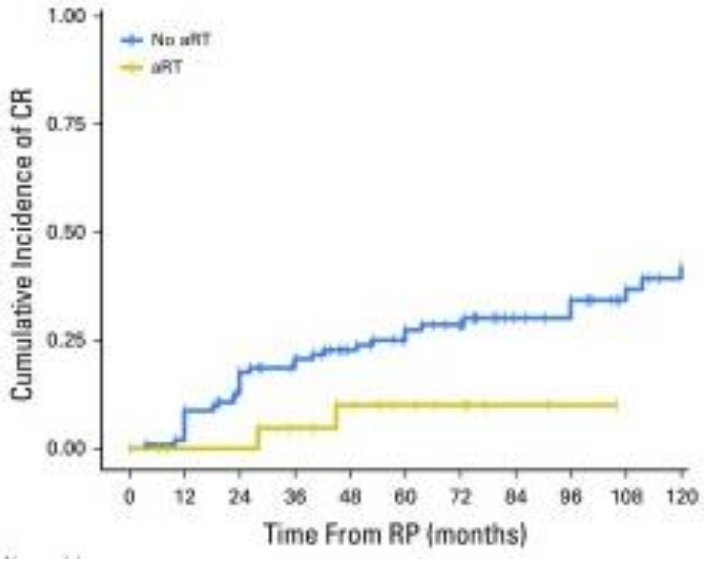
pT3b/T4, GS 8-10, N+, and high Decipher score



<2 risk factors



>=2 risk factors

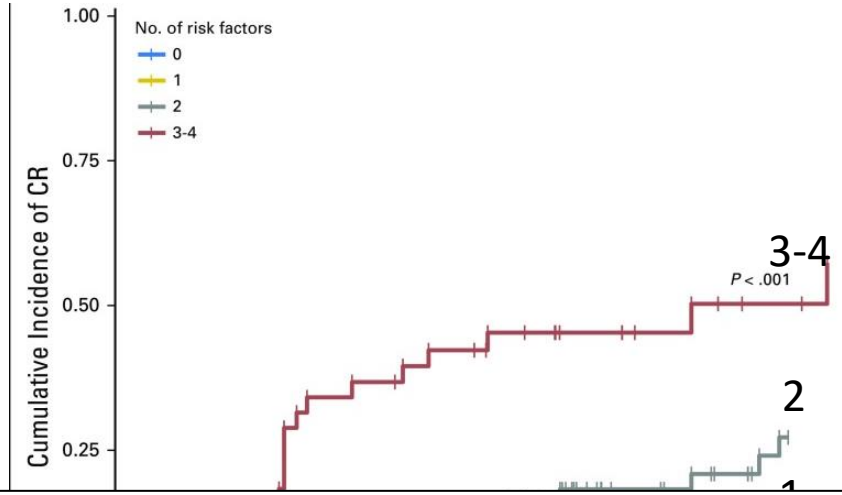


Dalela et al., JCO 2017

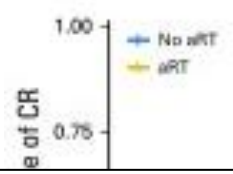
RT timing - Adjuvant vs No Adjuvant RT

Risk Factors:

pT3b/T4, GS 8-10, N+, and high Decipher score



<2 risk factors



>=2 risk factors

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Prostate Cancer

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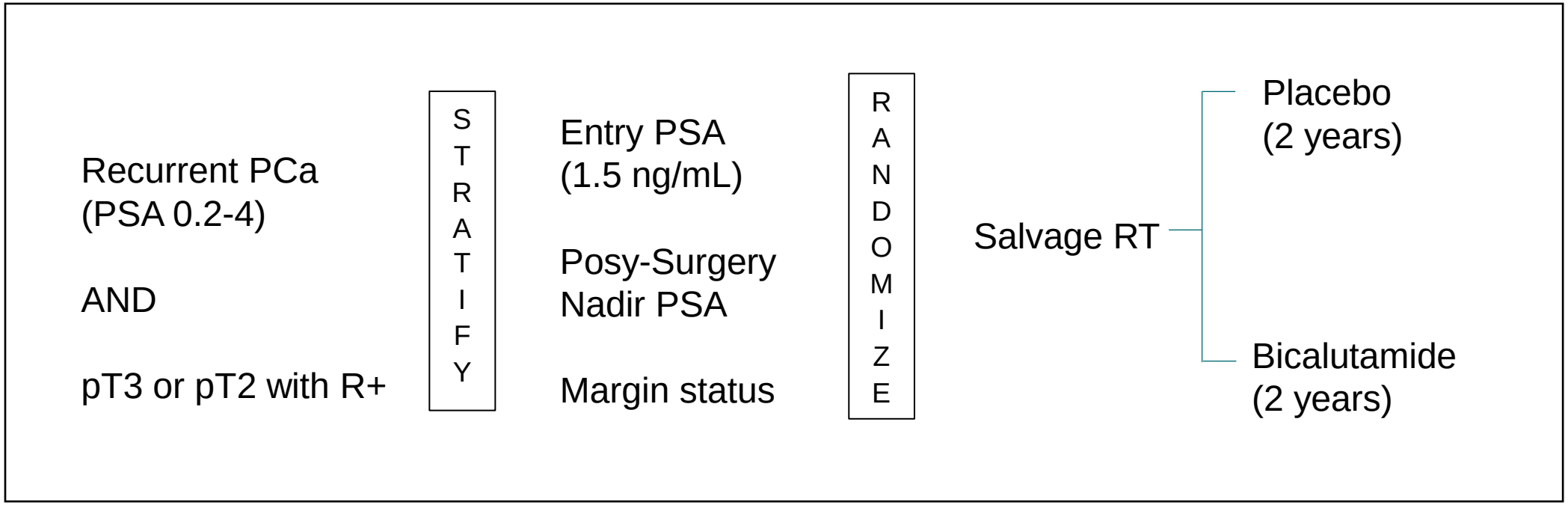
Updates in Version 1.2023 of the NCCN Guidelines for Prostate Cancer from Version 4.2022 include:

PROS-8A

- Footnote o modified: If higher grade and/or higher T stage is found *during confirmatory testing*, see PROS-2.
- Footnote t modified: Decipher molecular assay ~~is recommended~~ *should be considered* if not previously performed to inform adjuvant treatment if adverse features are found post-RP.

RT +/- ADT

NRG/RTOG 9601: A Phase 3 Trial



Sample size: 760 patients
Median follow up: 13 years

Primary endpoint: Overall survival (HR 0.77, p=0.04)

Shipley et al., NEJM 2017

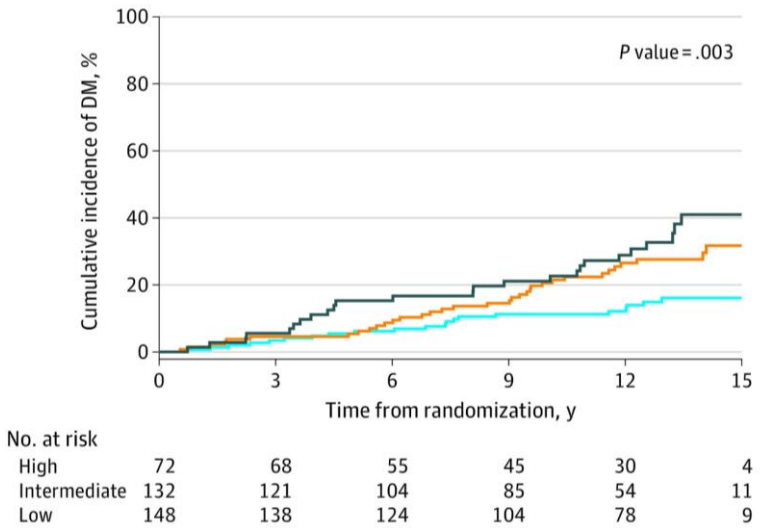
JAMA Oncology
View Article

JAMA Oncol. 2021 Apr; 7(4): 544–552.
Published online 2021 Feb 11. doi: 10.1001/jamaoncol.2020.7671
PMCID: PMC7879385
PMID: 33570548

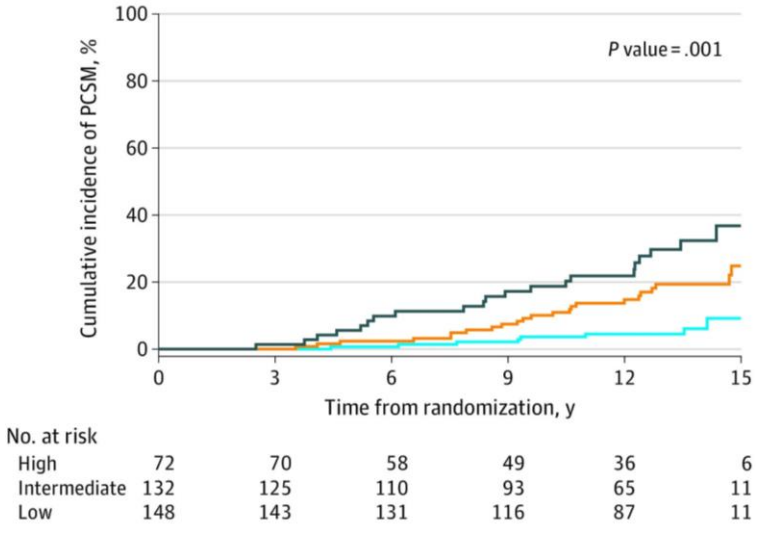
Validation of a 22-Gene Genomic Classifier in Patients With Recurrent Prostate Cancer

An Ancillary Study of the NRG/RTOG 9601 Randomized Clinical Trial

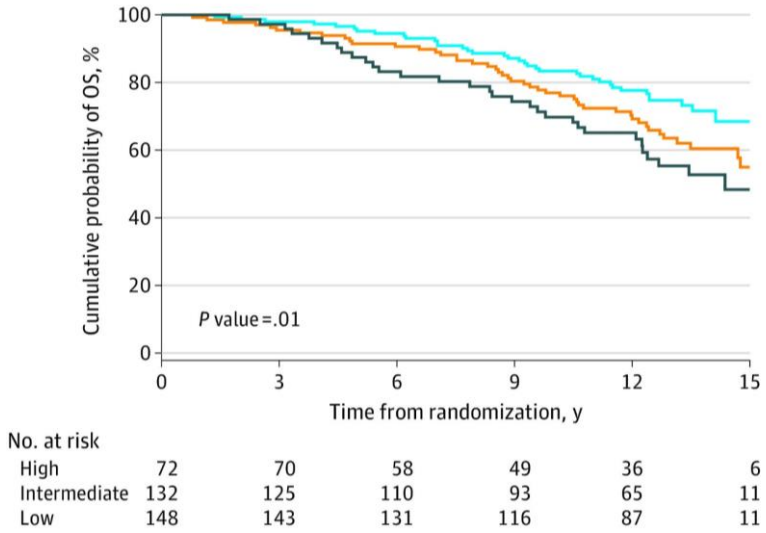
Distant metastasis



Prostate Cancer Specific Mortality



Overall Survival



Feng et al., JAMA Oncol 2021

Decipher was independently prognostic for DM, PCSM and OS

Variable	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
	Distant Metastases		**PCSM**		**OS**	
Decipher score	**1.17 (1.05 - 1.32)**	**0.006***	**1.39 (1.20 - 1.63)**	**<0.001***	**1.17 (1.06 - 1.29)**	**0.002***
Treatment vs. Placebo	0.62 (0.39 - 0.97)	0.037*	0.53 (0.30 - 0.92)	0.024*	0.82 (0.57 - 1.19)	0.293
Age 65+ vs. 65-	1.30 (0.83 - 2.06)	0.247	1.52 (0.88 - 2.66)	0.136	1.95 (1.33 - 2.91)	<0.001*
Black vs. non-Black	0.88 (0.28 - 2.13)	0.798	0.86 (0.17 - 2.73)	0.827	1.35 (0.57 - 2.77)	0.467
Gleason 8-10 vs. ≤7	2.11 (1.24 - 3.47)	0.007*	2.53 (1.38 - 4.49)	0.003*	1.87 (1.20 - 2.85)	0.007*
T3 vs. T2	1.42 (0.82 - 2.58)	0.220	2.01 (0.97 - 4.62)	0.061	1.24 (0.79 - 1.97)	0.350
Entry PSA	1.16 (0.88 - 1.49)	0.264	1.37 (1.01 - 1.80)	0.041*	1.08 (0.84 - 1.35)	0.530
Positive surgical margins	0.71 (0.44 - 1.16)	0.167	1.26 (0.68 - 2.44)	0.465	0.98 (0.64 - 1.53)	0.919
Non-nadir vs. nadir PSA (<0.5ng/ml)	1.31 (0.62 - 2.51)	0.456	2.10 (0.92 - 4.26)	0.074	1.98 (1.13 - 3.30)	0.019*

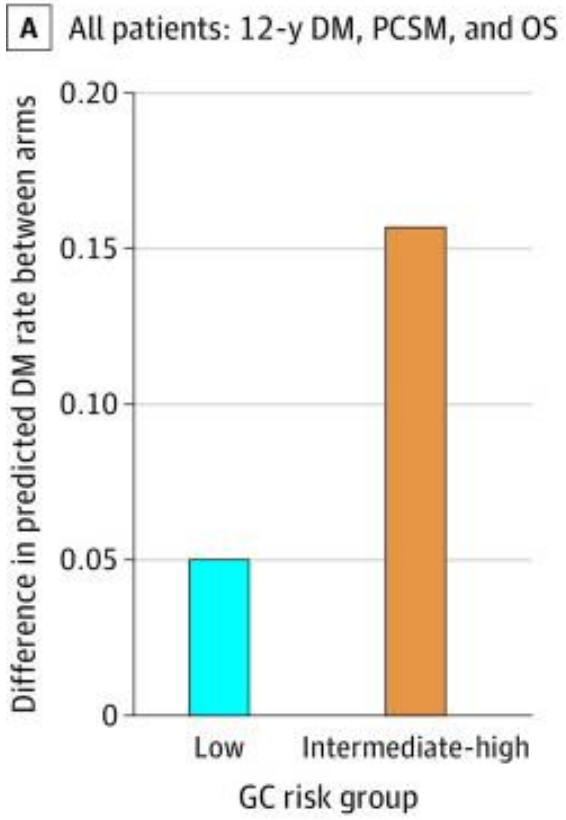
Hazard ratios of GC were per 0.1 unit increased.

Feng et al., JAMA Oncol 2021

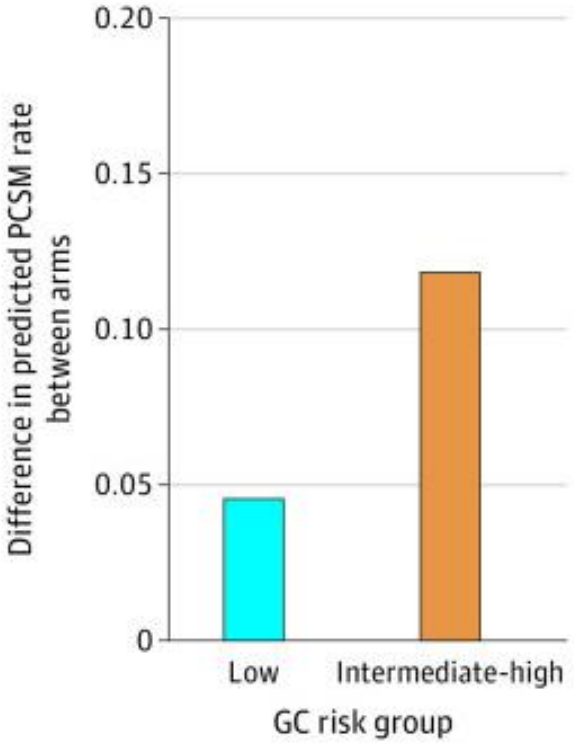
Less ADT benefit in Low Decipher patients

Full cohort

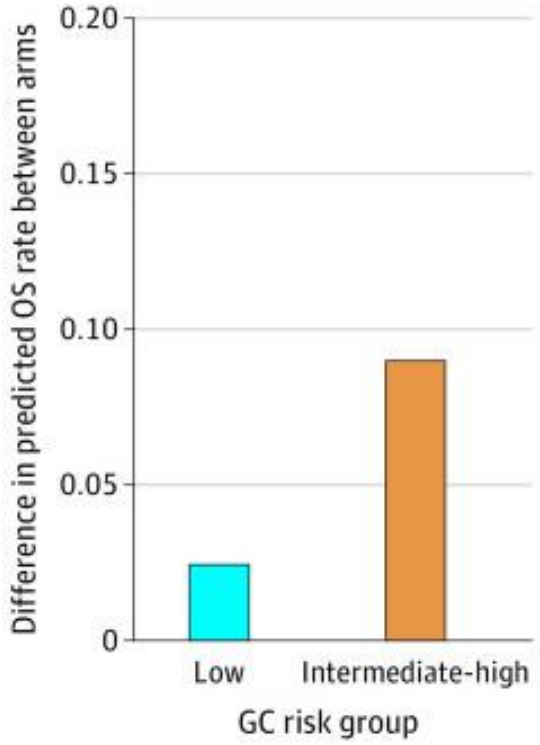
DM



PCSM



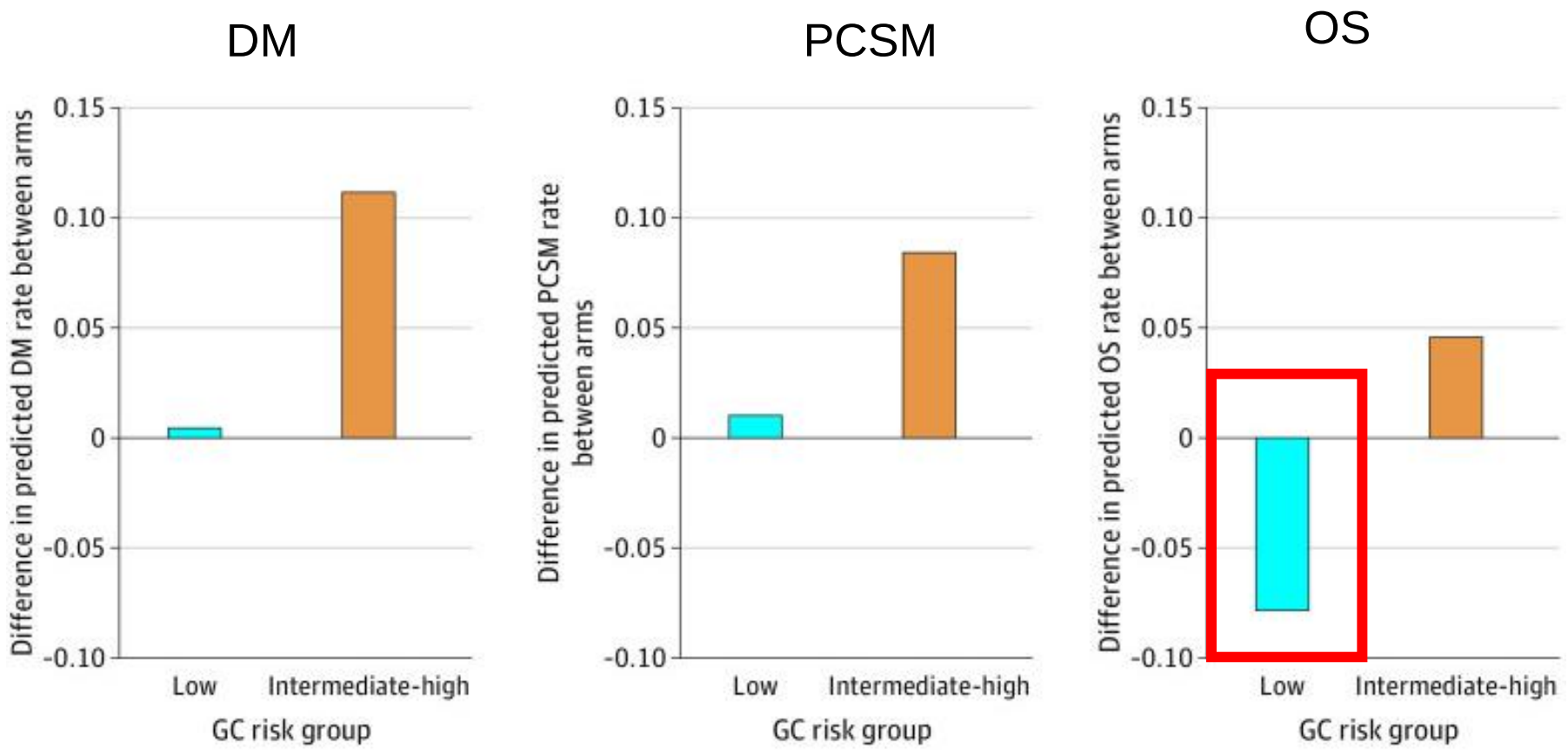
OS



Feng et al., JAMA Oncol 2021

Less ADT benefit in Low Decipher patients

Early salvage, PSA < 0.7 ng/mL



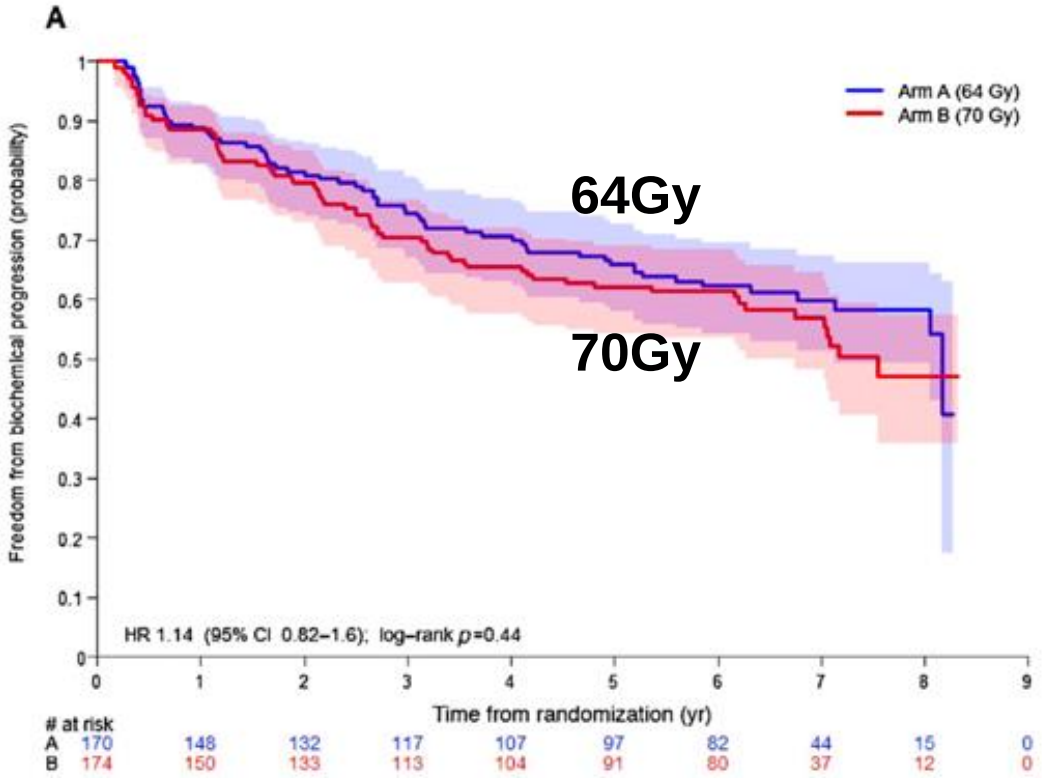
- PSA < 0.7 ng/ml was not a stratification factor
- small sample size, no SS interaction between Decipher and ADT use

Feng et al., JAMA Oncol 2021

RT dose

SAKK 09/10, Phase 3 Trial

- N= 350 patients
- 24 centers in Switzerland, Germany, and Belgium.
- Patients with biochemical progression (PSA >0.1 to 2 ng/mL at randomization)
- 64 Gy vs 70 Gy to the prostate bed
- No ADT or pelvic nodal radiotherapy



No difference in FFBP at median FU 6 yrs

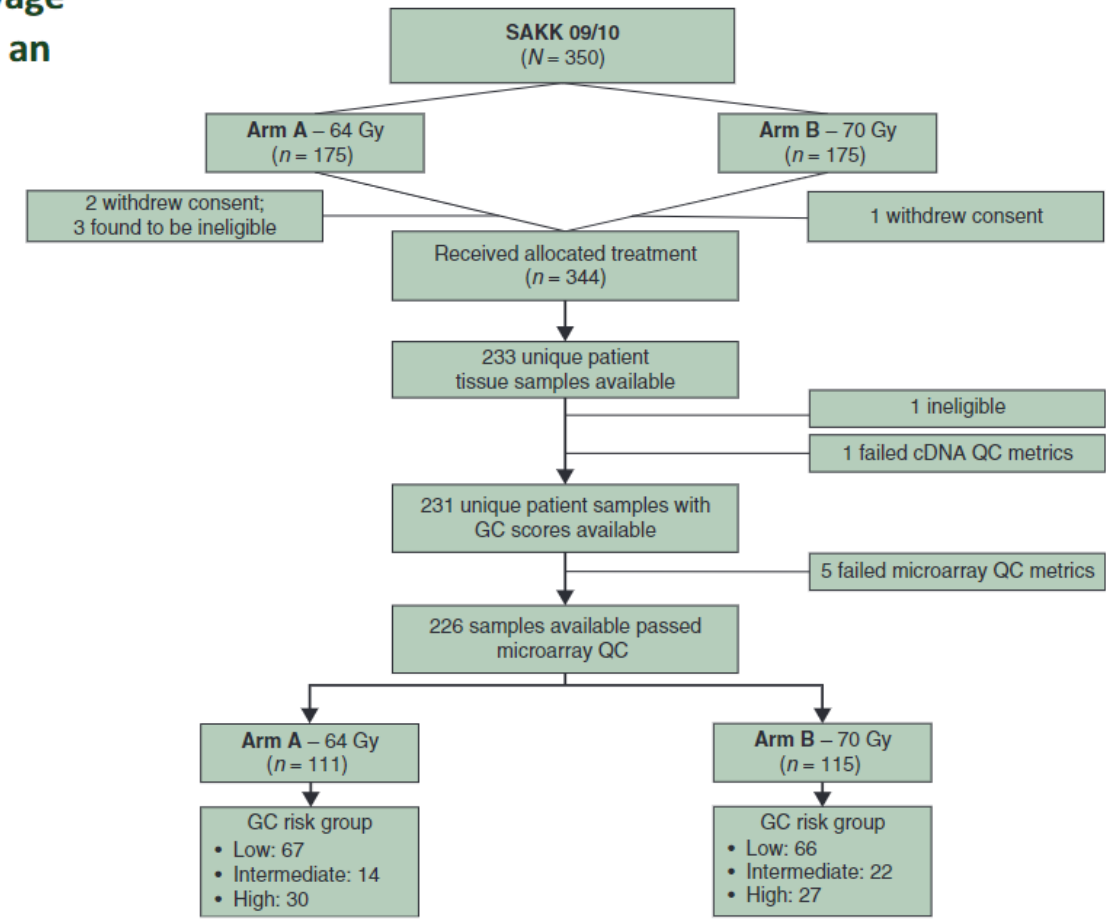
Ghadjar et al., Eur Urol 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Validation of the Decipher genomic classifier in patients receiving salvage radiotherapy without hormone therapy after radical prostatectomy – an ancillary study of the SAKK 09/10 randomized clinical trial☆

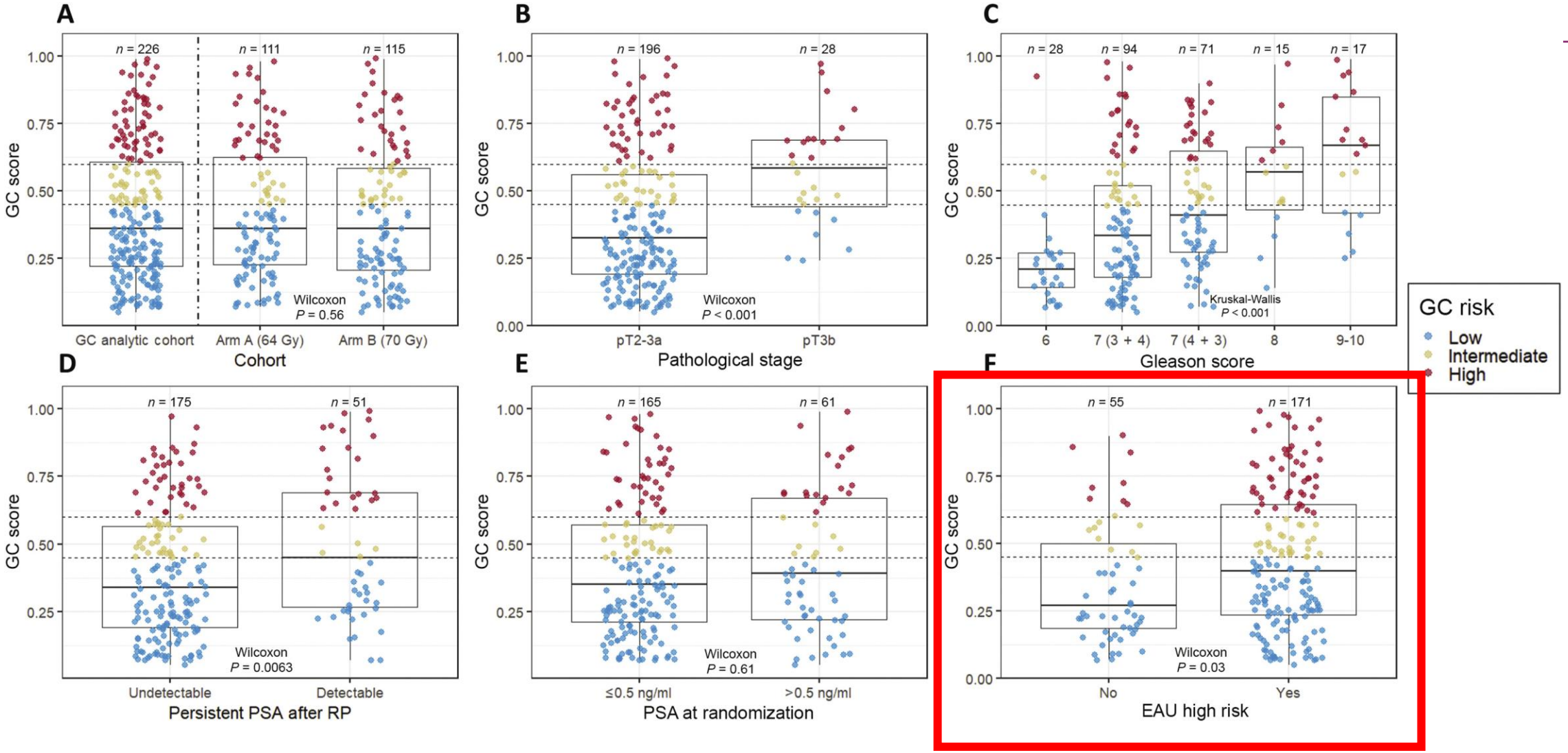


***Pre-specified analysis**

*Contemporary samples, high lab QC passing rate (>97%)

Dal Pra et al., Ann Oncol 2022

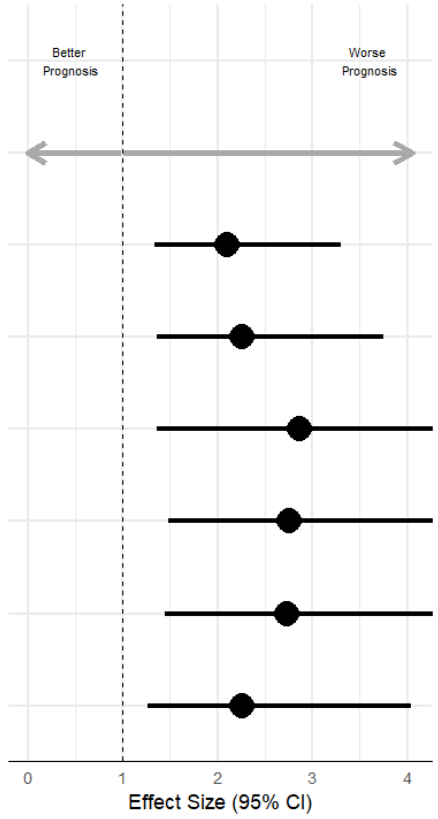
Correlation of Decipher vs. other clinicopathologic variables



Dal Pra et al., Ann Oncol 2022

Decipher is a strong prognostic biomarker

	N (event)			5 yr Event-Free Est.			GC Risk Group	Effect Size
	Decipher Analytic Cohort	Decipher Low-Int	Decipher High	Decipher Analytic Cohort	Decipher Low-Int	Decipher High	(High vs Low-Intermediate)	(95% CI), p-val
Freedom from Biochemical Progression†	226 (88)	169 (57)	57 (31)	65% (58%-71%)	71% (64%-78%)	45% (32%-59%)		2.10 (1.34 - 3.30) 0.001*
Clinical Progression-Free Survival‡	226 (65)	169 (41)	57 (24)	76% (71%-82%)	80% (74%-86%)	65% (52%-79%)		2.26 (1.36 - 3.75) 0.002*
Rapid Biochemical Failure (≤ 18 mo)§	226 (37)	169 (21)	57 (16)	84%§§	88%§§	72%§§		2.87 (1.36 - 6.05) 0.006*
Freedom from Hormonal Treatment†	226 (40)	169 (22)	57 (18)	85% (80%-90%)	89% (84%-94%)	74% (61%-86%)		2.75 (1.48 - 5.11) 0.001*
Freedom from Distant Metastasis†	226 (38)	169 (21)	57 (17)	86% (81%-90%)	89% (84%-94%)	75% (63%-87%)		2.73 (1.45 - 5.16) 0.002*
Metastasis-Free Survival†	226 (47)	169 (28)	57 (19)	83% (77%-88%)	85% (79%-91%)	75% (63%-87%)		2.26 (1.27 - 4.04) 0.006*



Dal Pra et al., Ann Oncol 2022

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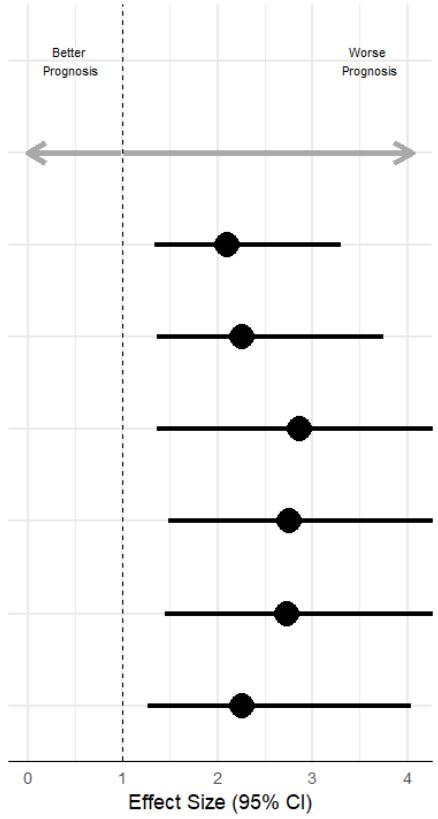
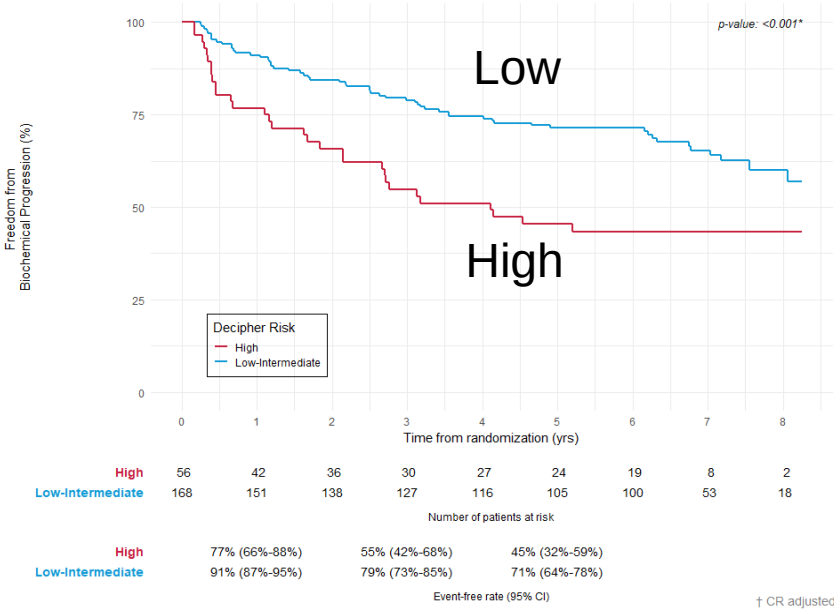


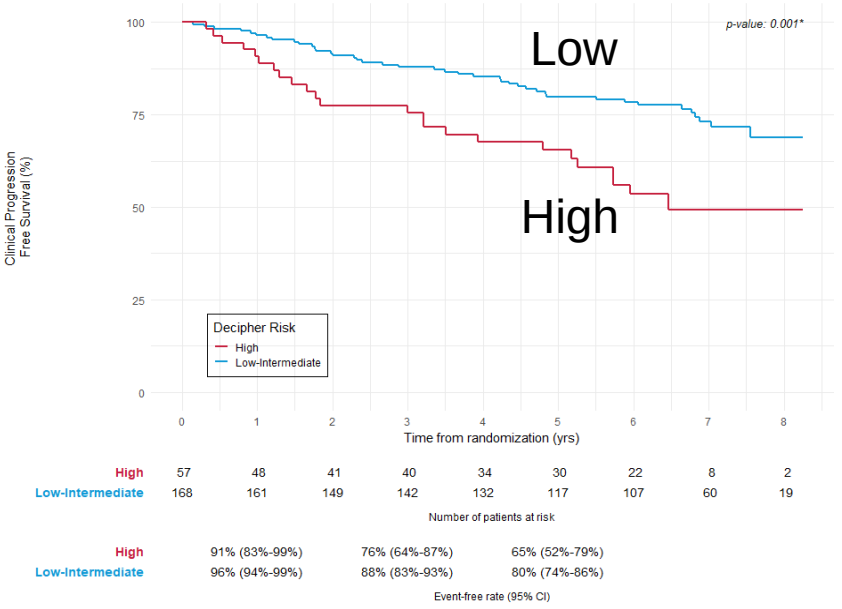
Dal Pra et al., Ann Oncol 2022

Decipher is a strong prognostic biomarker

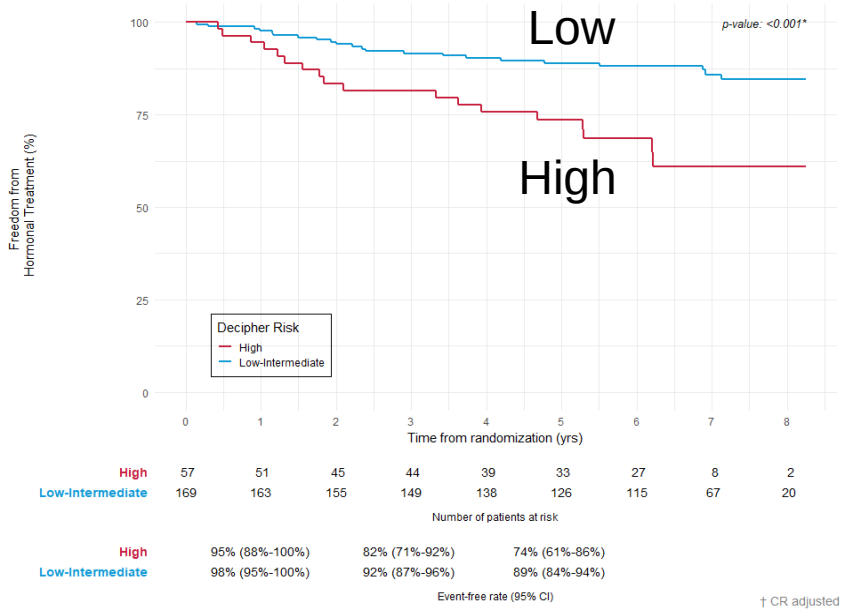
FFBP



CPFS



Salvage ADT

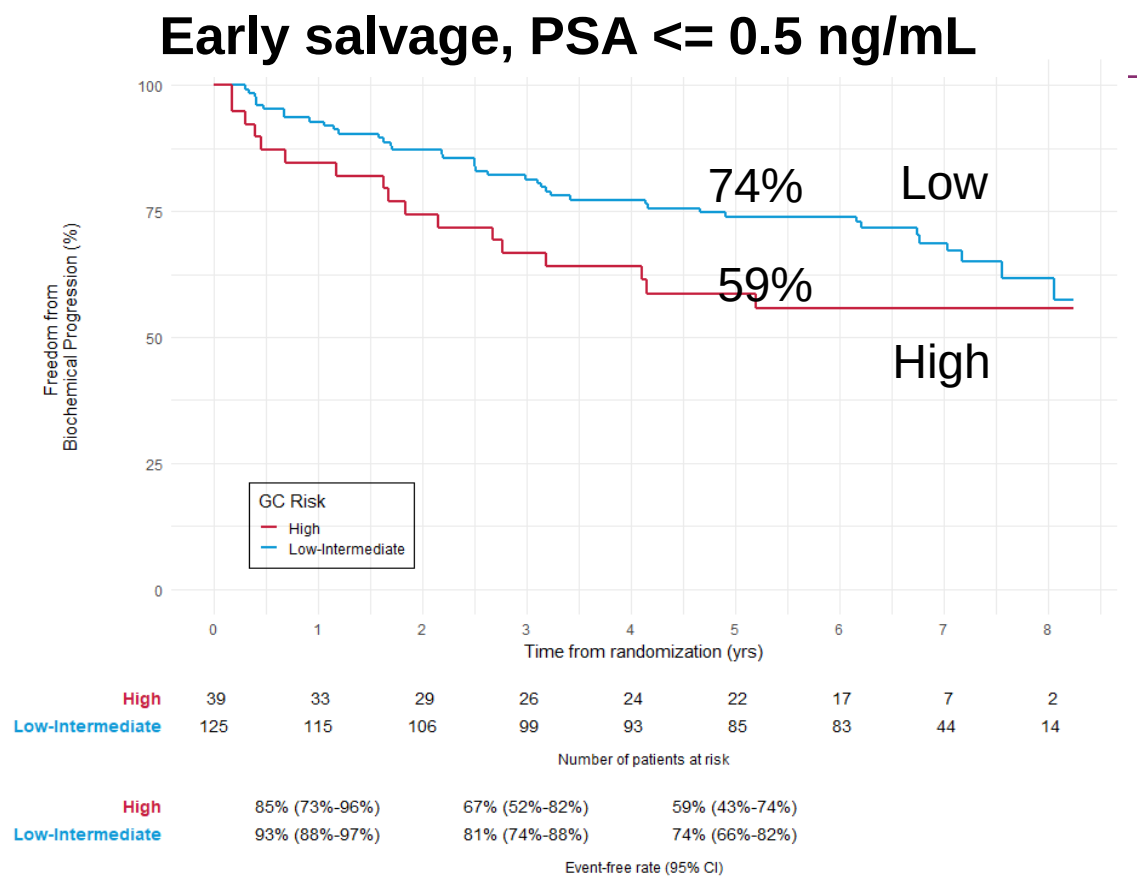


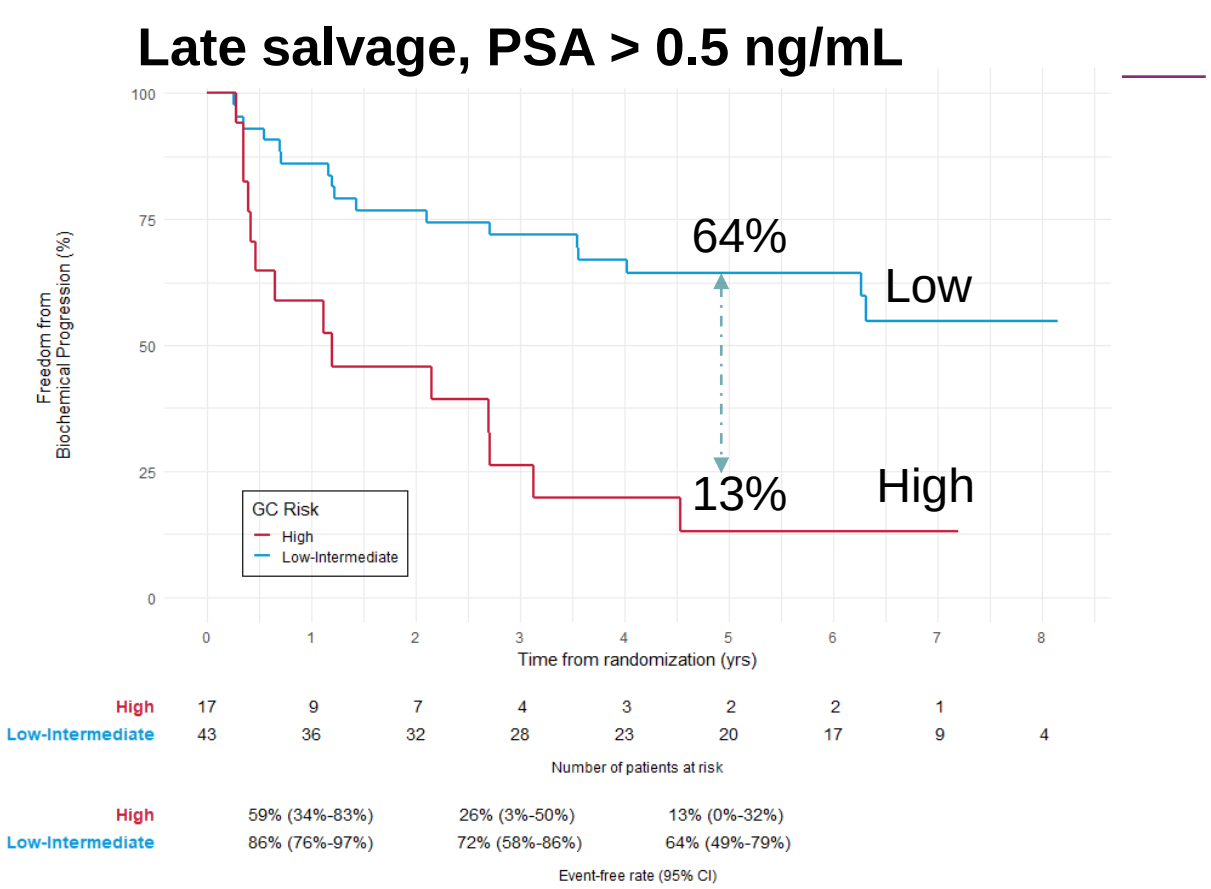
High Decipher → > 2x increased risk of progression

HR 2.1 (95% IC 1.3-3.3, p=0.002) on MVA

Dal Pra et al., Ann Oncol 2022

Decipher - Early vs Late Salvage RT





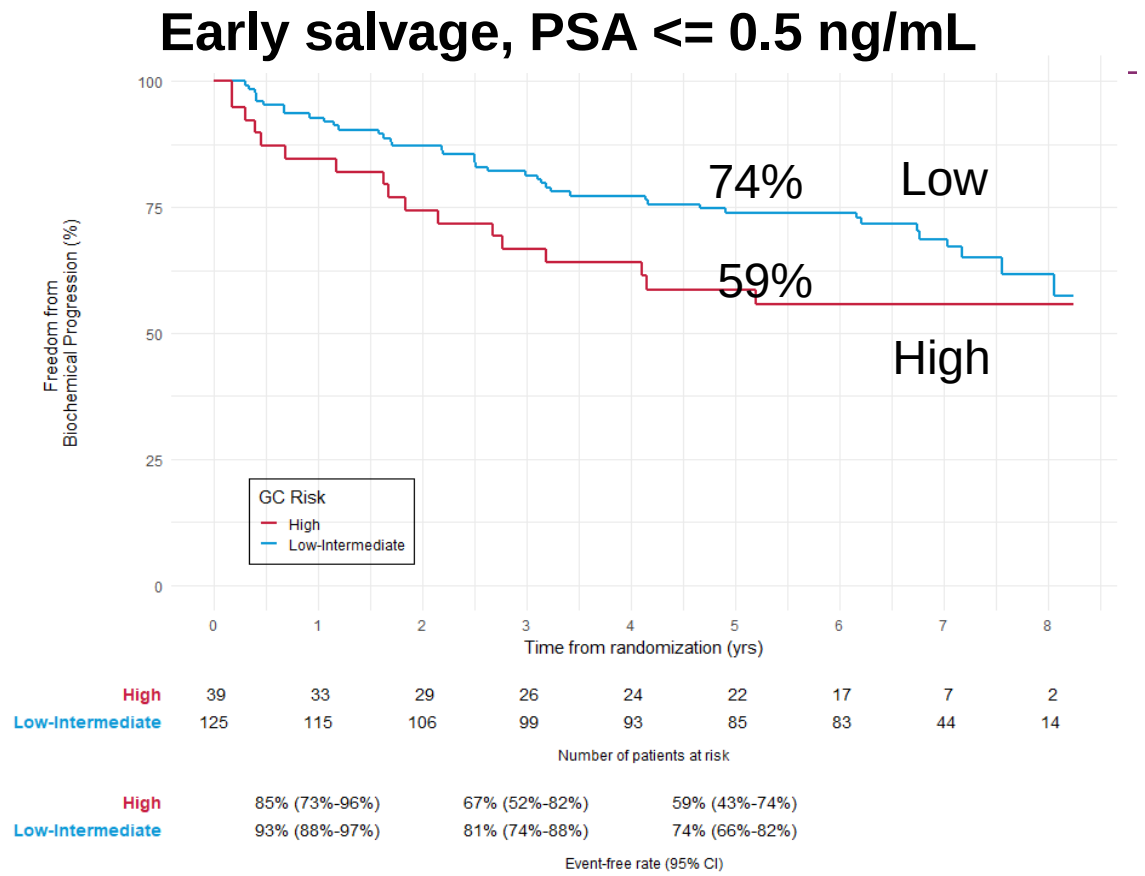
GC high- vs. low/intermediate HRs:

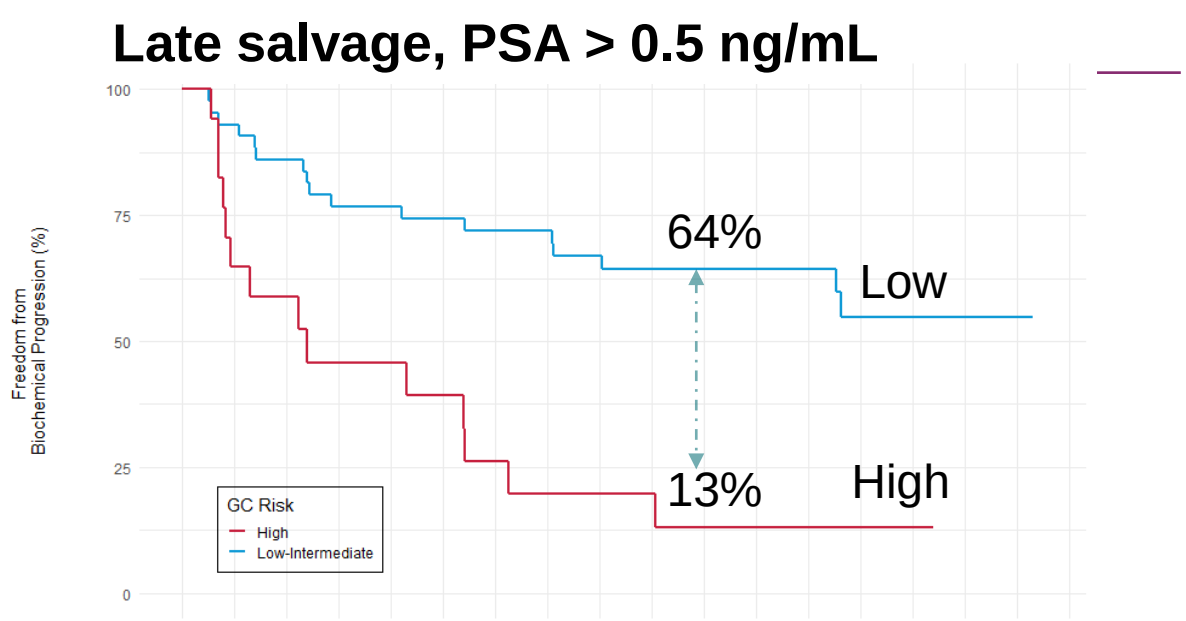
- 1.84 (95%CI 0.99-3.43, for early salvage RT (PSA ≤ 0.5 ng/mL)
- **3.07** (95%CI 1.39-6.8, for **late salvage RT (PSA > 0.5 ng/mL)**

*Cox PH MVA results adjusting for clinical variables and randomization arm as strata

Dal Pra et al., Ann Oncol 2022

Decipher - Early vs Late Salvage RT





High Decipher patients treated w/ late salvage ~ 90% risk of progression at 5 yrs.

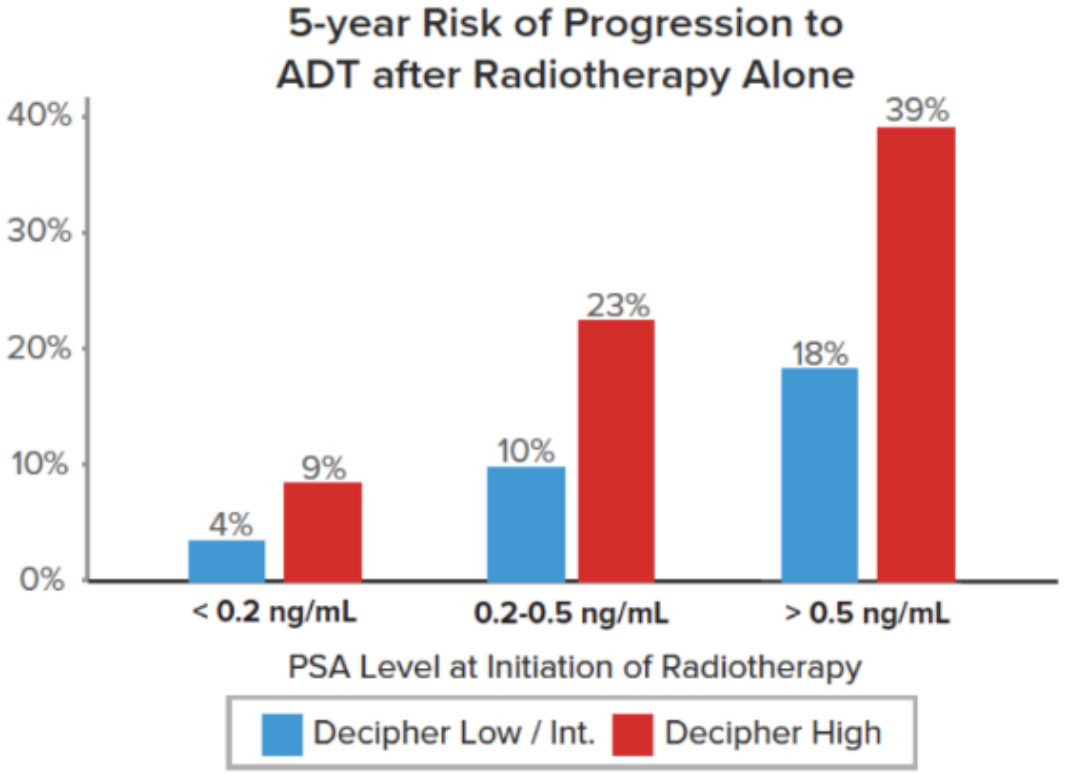
GC high- vs. low/intermediate HRs:

- 1.84 (95%CI 0.99-3.43, for early salvage RT (PSA ≤ 0.5 ng/mL)
- **3.07** (95%CI 1.39-6.8, for **late salvage RT (PSA > 0.5 ng/mL)**

*Cox PH MVA results adjusting for clinical variables and randomization arm as strata

Dal Pra et al., Ann Oncol 2022

Decipher vs. pre-SRT PSA



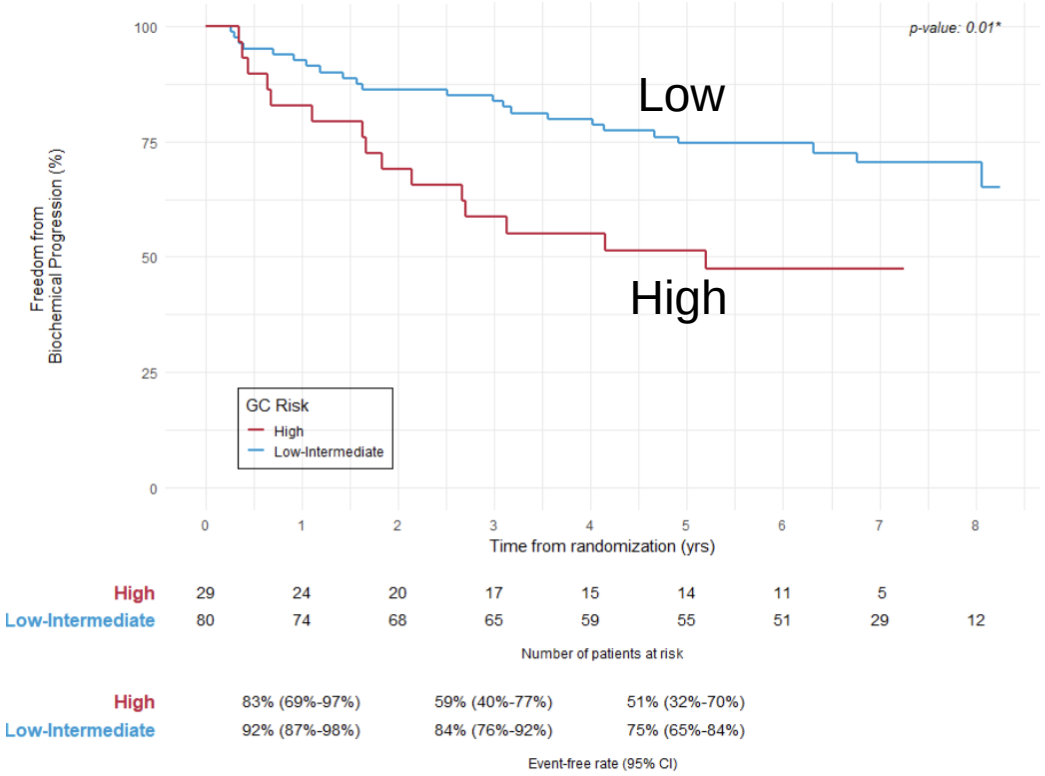
Decipher may help define subgroups associated with improved outcomes when treated with very early vs early vs late SRT

Dal Pra et al., Ann Oncol 2022

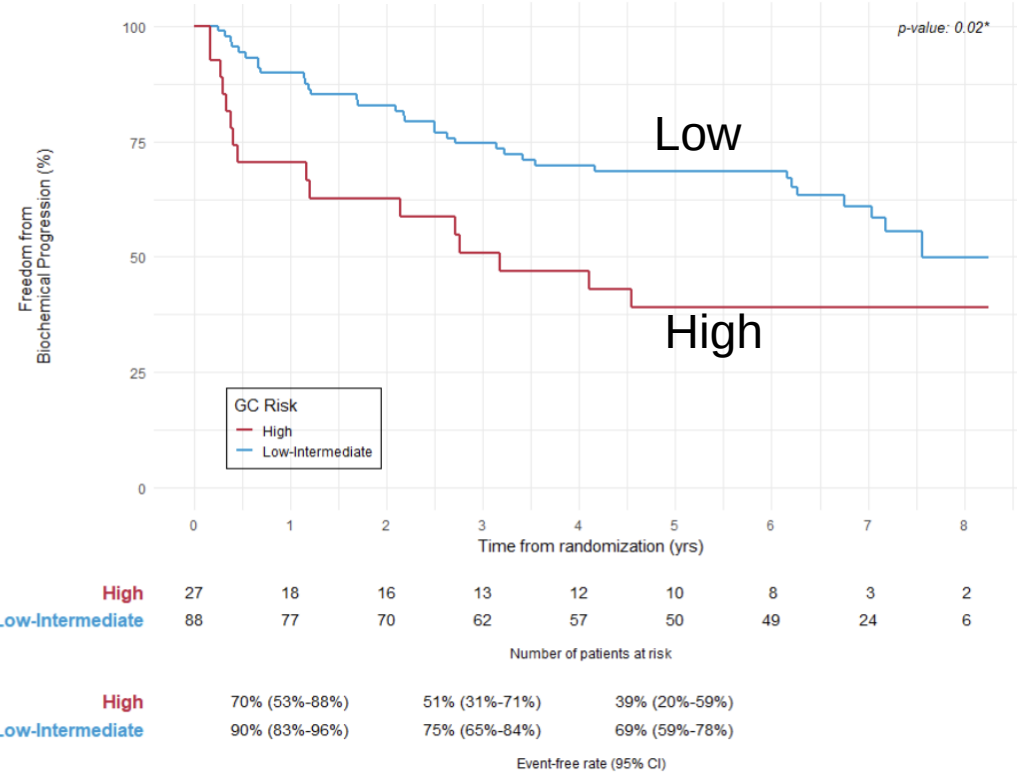
*PSA < 0.2 ng/ml was not a stratification factor

RT dose?
Decipher does not predict benefit from dose escalation

64Gy arm



70Gy arm

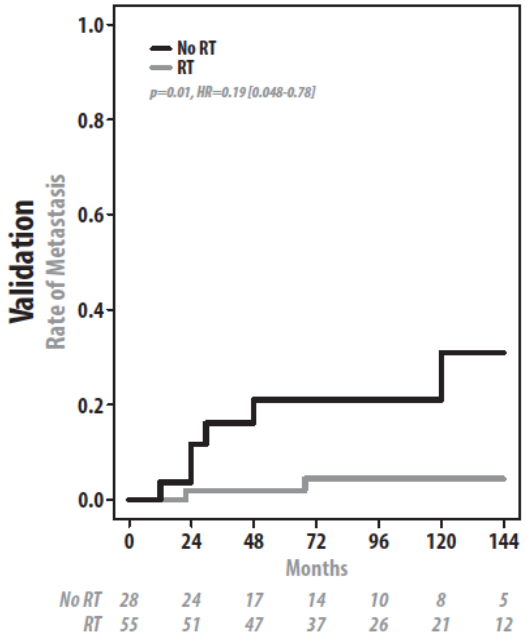


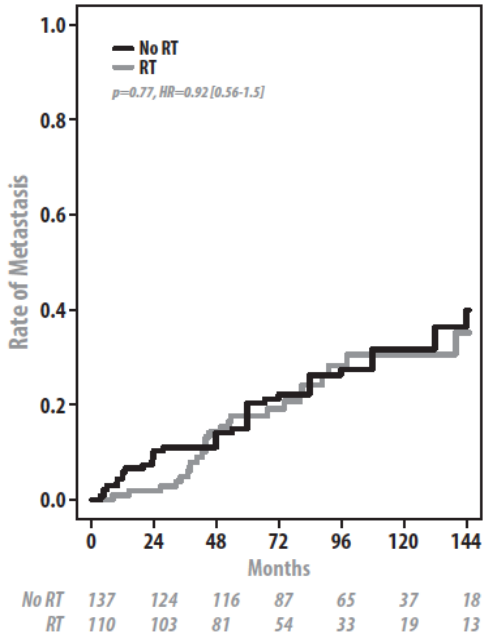
Dal Pra et al., Ann Oncol 2022

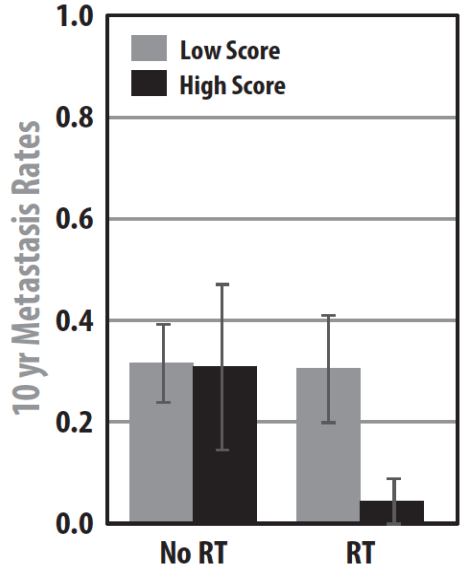
Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis

Shuang G Zhao*, S Laura Chang*, Daniel E Spratt, Nicholas Erho, Menggang Yu, Hussam Al-Deen Ashab, Mohammed Alshalalfa, Corey Speers, Scott A Tomlins, Elai Davicioni, Adam P Dicker, Peter R Carroll, Matthew R Cooperberg, Stephen J Freedland, R Jeffrey Karnes, Ashley E Ross, Edward M Schaeffer, Robert B Den, Paul L Nguyen†, Felix Y Feng†

PORTOS is an expression signature of 24 DNA damage repair, and immune pathway genes







Patients with high PORTOS scores may benefit from post-op RT

Zhao et al., Lancet Oncol 2016

? Presentation #160

Prognostic and Predictive Performance of a 24-Gene Post-Operative Radiation Therapy Outcomes Score (PORTOS) in a Phase 3 Randomized Trial of Dose-Intensified Salvage Radiotherapy after Radical Prostatectomy (SAKK 09/10)

Alan Dal Pra[1], Daniel R. Zwahlen[2], Vinnie Y. Liu[3], Stefanie Hayoz[4], Daniel E. Spratt[5], Elai Davicioni[3], Yang Liu[3], James A. Proudfoot[3], Corinne Schär[4], Tobias Hölscher[6], Philipp Gut[7], Buelent Polat[8], Guido Hildebrandt[9], Arndt-Christian Mueller[10], Ludwig Plasswilm[11], Felix Y. Feng[12], Alan Pollack[1], George Thalmann[13], Daniel M. Aebersold[14], and Pirus Ghadjar[14,15]

[1]Department of Radiation Oncology, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL
[2]Department of Radiation Oncology, Kantonsspital Graubünden, Chur, now at Kantonsspital Winterthur, Winterthur, Switzerland
[3]Veracyte Inc., San Diego, CA
[4]SAKK Coordinating Center, Bern, Switzerland
[5]University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH
[6]Department of Radiation Oncology, University Hospital Dresden, Dresden, Germany
[7]Department of Radiation Oncology, Kantonsspital Luzern, Switzerland, now at Hirslanden Hospital Group, Zürich, Switzerland
[8]University hospital Wuerzburg, Wuerzburg, Germany
[9]Department of Radiation Oncology, University Hospital Rostock, Rostock, Germany
[10]Department of Radiation Oncology, Eberhard Karls University, Tübingen, Germany
[11]Department of Radiation Oncology, Kantonsspital St. Gallen, St. Gallen, Sankt Gall, Switzerland
[12]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA
[13]Department of Urology, Bern University Hospital, Bern, Switzerland
[14]Department of Radiation Oncology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland
[15]Department of Radiation Oncology, Charité Universitätsmedizin Berlin, Berlin, Germany

RT volume

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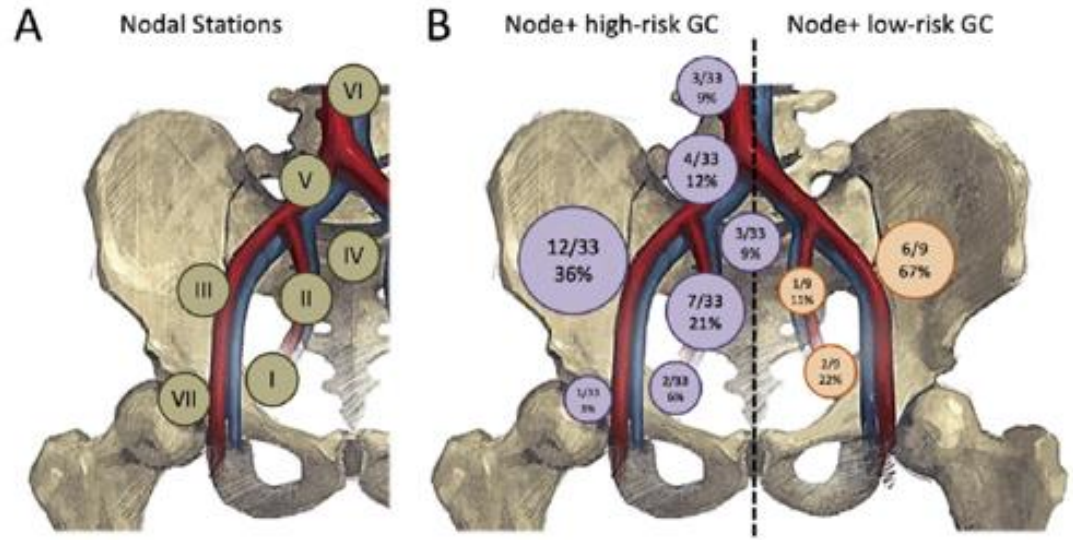
journal homepage: euoncology.europeanurology.com

European Association of Urology

Genomic Risk Predicts Molecular Imaging-detected Metastatic Nodal Disease in Prostate Cancer

Melody J. Xu[a], Zachary Kornberg[b], Adam J. Gadzinski[b], Dongmei Diao[a,c], Janet E. Cowan[b], Susan Y. Wu[a], Lauren Boreta[a], Daniel E. Spratt[d], Spencer C. Behr[e], Hao G. Nguyen[b], Matthew R. Cooperberg[b], Elai Davicioni[f], Mack Roach 3rd[a], Thomas A. Hope[e], Peter R. Carroll[b], Felix Y. Feng[a,b,]*

[a] Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA; [b] Department of Urology, University of California San Francisco, San Francisco, CA, USA; [c] Department of Surgical Oncology, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [d] Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA; [e] Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA, USA; [f] GenomeDx Inc., San Diego, CA, USA



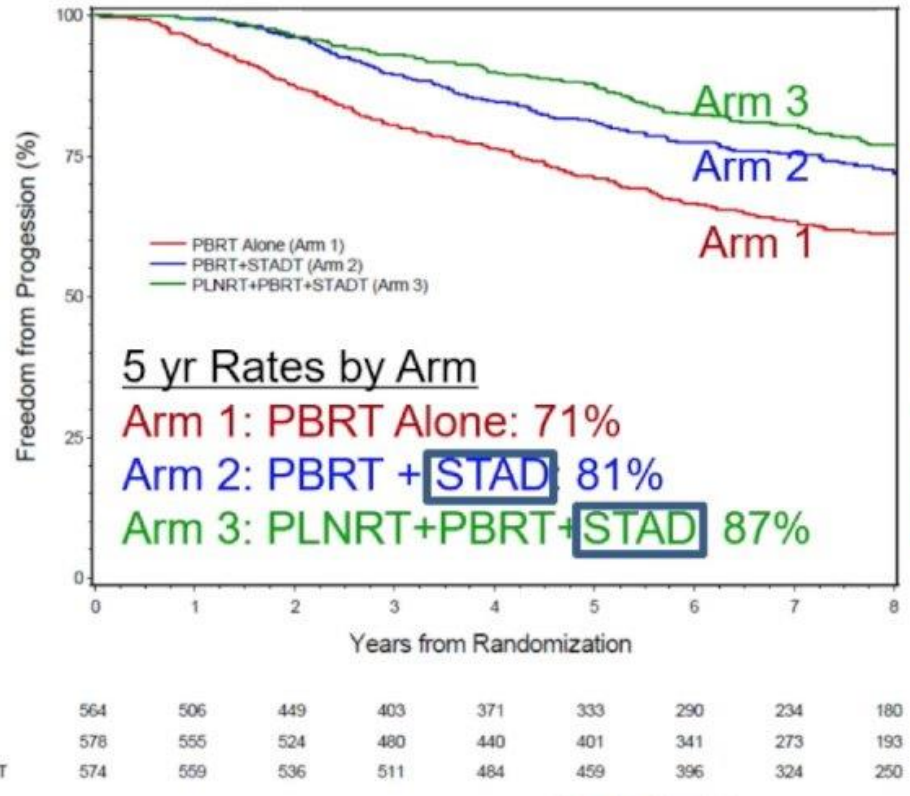
- 91 NCCN int/high-risk patients with Decipher and PSMA PET at recurrence
- Higher Decipher score associated with PSMA (+) nodal disease
- **Higher Decipher ~8x as likely to harbor PSMA (+) positive lymph nodes**

Xu et al., Eur Urol Focus 2019

RT volume

RTOG 0534 – addition of pelvic nodal RT to PBRT + ADT improves PFS

FFP
PSA: Nadir+2
Clinical Prog
Death Any Cause



5 yr Rate Comparison
Arm 3 vs Arm 1: p<0.001
Arm 2 vs Arm 1: p<0.001
Arm 3 vs Arm 2: p=0.003

Per Protocol Criteria: Arm 3 was Superior to the other arms

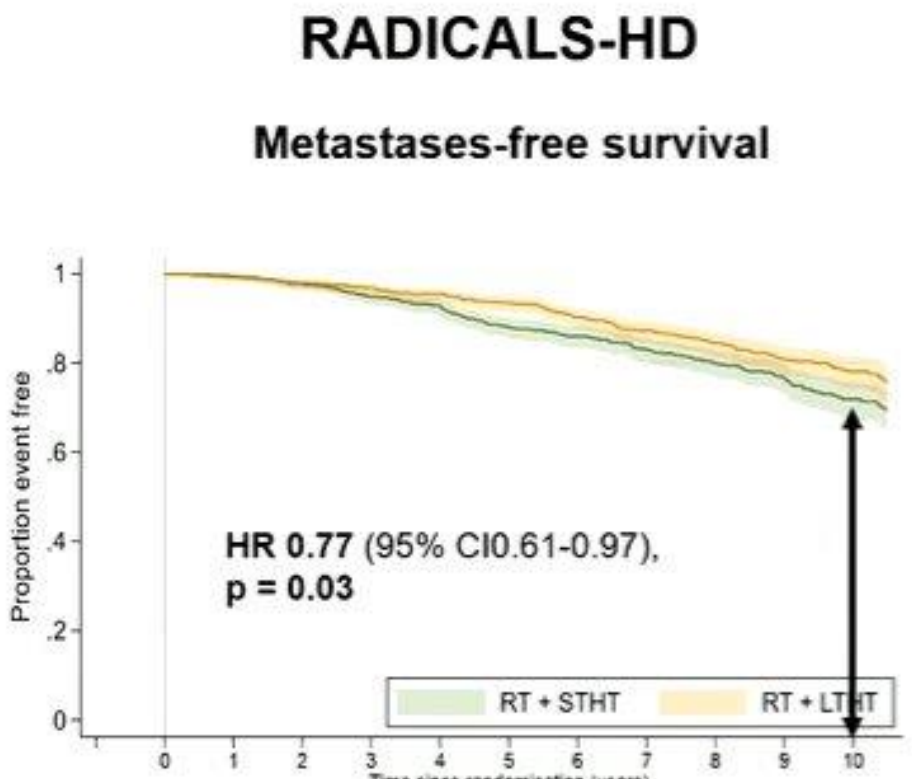
N =1,736
Median follow up = 8 yrs

Can Decipher help select patients for pelvic RT?
Correlative studies in progress

Pollack et al., Lancet 2022

SRT + ADT duration?

Which patients need long term ADT?



At **10 years**:
MFS 72% in short term
vs 78% in long term

Absolute MFS benefit 6%
No statistically significant OS benefit demonstrated

Number needed to treat: ~17

ESMO 2022

PARIS 2022 ESMO congress

Clinical qualification of transcriptome signatures for advanced prostate cancer starting androgen deprivation therapy with or without abiraterone acetate and prednisolone: **an ancillary study of the STAMPEDE trial**

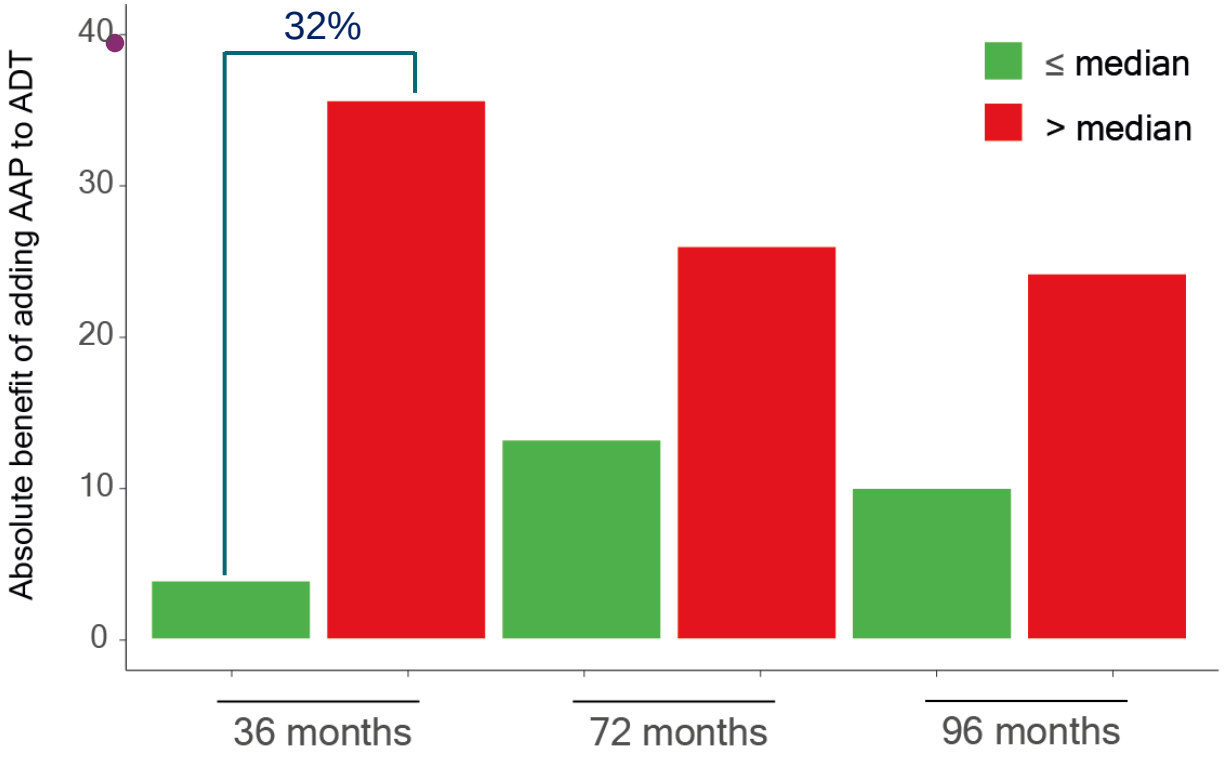
Marina Parry, Emily Grist, Christopher Brawley, James Proudfoot, Larissa Mendes, Sharan Lall, Alex Hoyle, Ashwin Sachdeva, Yang Liu, Claire Amos, Matthew Sydes, Robert Jones, Max Parmar, Felix Feng, Christopher Sweeney, Noel Clarke, Elai Davicioni, Nick James, Louise Brown, Gerhardt Attard **on behalf of the STAMPEDE investigators**

@marina_parry, @EmilyGrist1, @LarissaSTMendes, @AshwinUrol, @mattsydes, @ChrisSweens1, @Davicioni, @Prof_Nick_James, @AttardLab

ClinicalTrials.gov number, NCT00268476 & Current Controlled Trials number, ISRCTN78818544

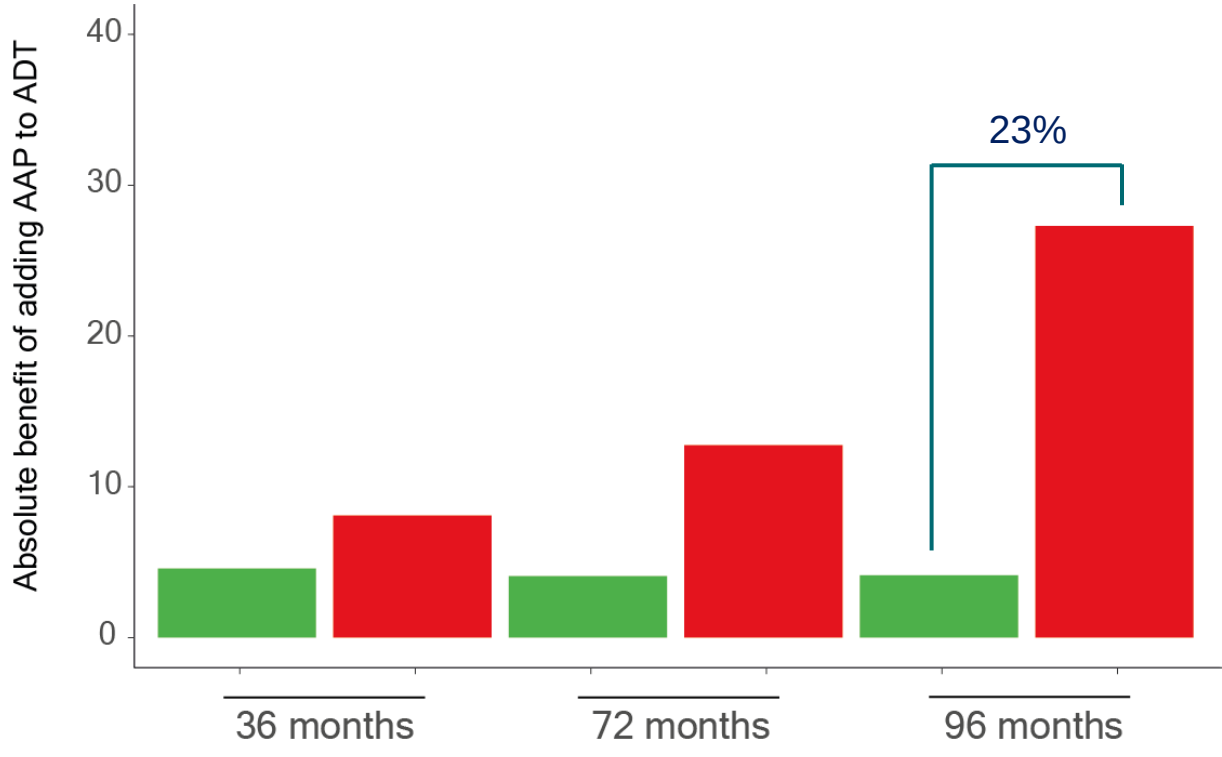
Absolute benefit of adding AAP to ADT varies by Decipher score

Metastatic



OS benefit of AAP

Localised high-risk



MFS benefit of AAP

Event rate calculated using flexible parametric modelling adjusted for baseline characteristics

Some practical scenarios

Undetectable PSA High risk features	Low/Int Decipher	→	Observation / early SRT
	High Decipher	→	Discuss adjuvant RT
PSA < 0.5 ng/mL High risk features	Low/Int Decipher	→	SRT +/- STADT
	High Decipher	→	SRT + PNRT + STADT
PSA >= 0.5 ng/mL High risk features	PSMA PET (-)	Low/Int Decipher →	SRT + PNRT + STADT
		High Decipher →	SRT + PNRT + LTADT?
	PSMA PET (+)	N+ →	SRT + PNRT + LTADT + Abi

*Life expectancy > 10 yrs

Conclusions

- Genomic classifiers have shown to be prognostic markers and may help individualize treatment decisions in the postoperative setting
- Decipher has the strongest level of evidence for genomic classifiers, particularly after surgery
  - salvage RT +/- ADT and postoperative RT timing
- Additional evidence is needed to support other treatment decisions
  - How to combine molecular imaging and genomic classifiers?
  - Can we use molecular imaging and genomic classifiers to select patients for Tx de-escalation/observation?
- Predictive biomarkers are urgently needed to guide treatment selection not only for intensification but to minimize the use of unnecessary treatments.