JULY 25, 2025

Advancing multi-modal biomarker development in GU cancers with RNA, digital pathology AI, and ctDNA

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Myriad Genetics

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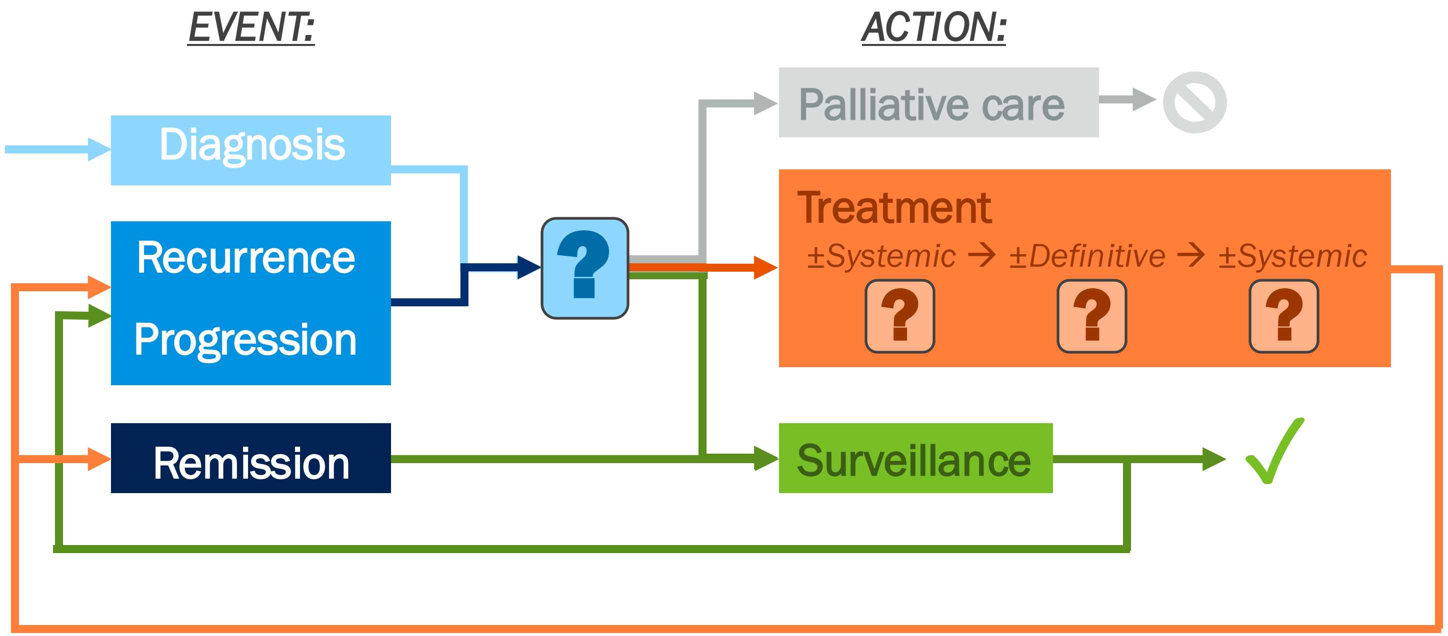
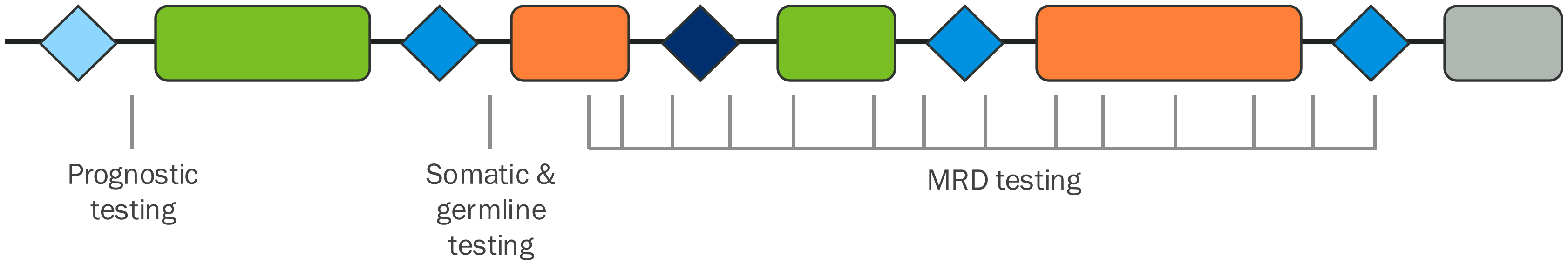
Disclosure

I am an officer and stockholder of Myriad Genetics, Inc.

Navigating the cancer journey: guiding choices, monitoring progress



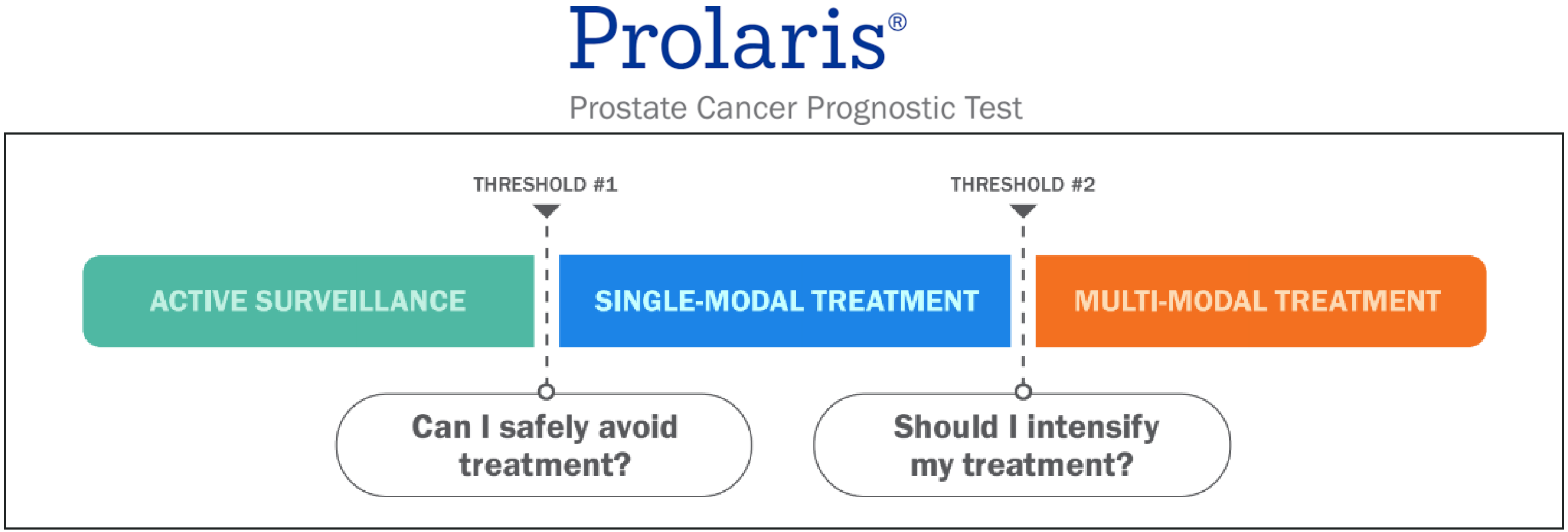


Outline

- **RNA**
    - Application of Prolaris in prostate cancer
- **AI**
    - Application of digital pathology in prostate cancer
- **ctDNA**
    - Ultrasensitive MRD testing pan-cancer, in renal cancer, & in prostate cancer

Introduction to Prolaris

- Launched in 2010
- 32 publications in >10,000 patients



Anatomy of the Prolaris CCR score

Coefficients trained on four cohorts (N=1059) with range of treatments and outcomes (BCR, DSM & Mets). Validated across all risk groups.

$$\mathbf{CCR} = 0.57 \cdot \mathbf{CCP} + 0.39 \cdot \mathbf{CAPRA}$$

Cell-Cycle Risk score

Prolaris®

Prostate Cancer Prognostic Test

Cell-Cycle Progression score

- Average qPCR level of 31 cell-cycle-correlated genes, measured as ΔC_t enrichment over C_t of 15 housekeeping genes
- Clinical range from 1.8 - 8.7

Cancer of the Prostate Risk Assessment

- Based on age, PSA, Gleason, clinical (T) stage, and % positive cores at diagnosis
- Score from 0-10

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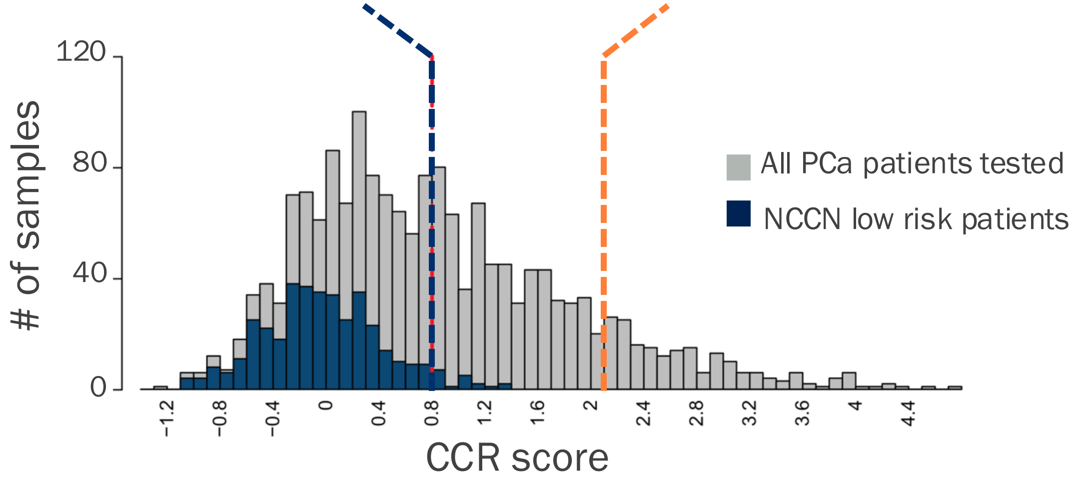
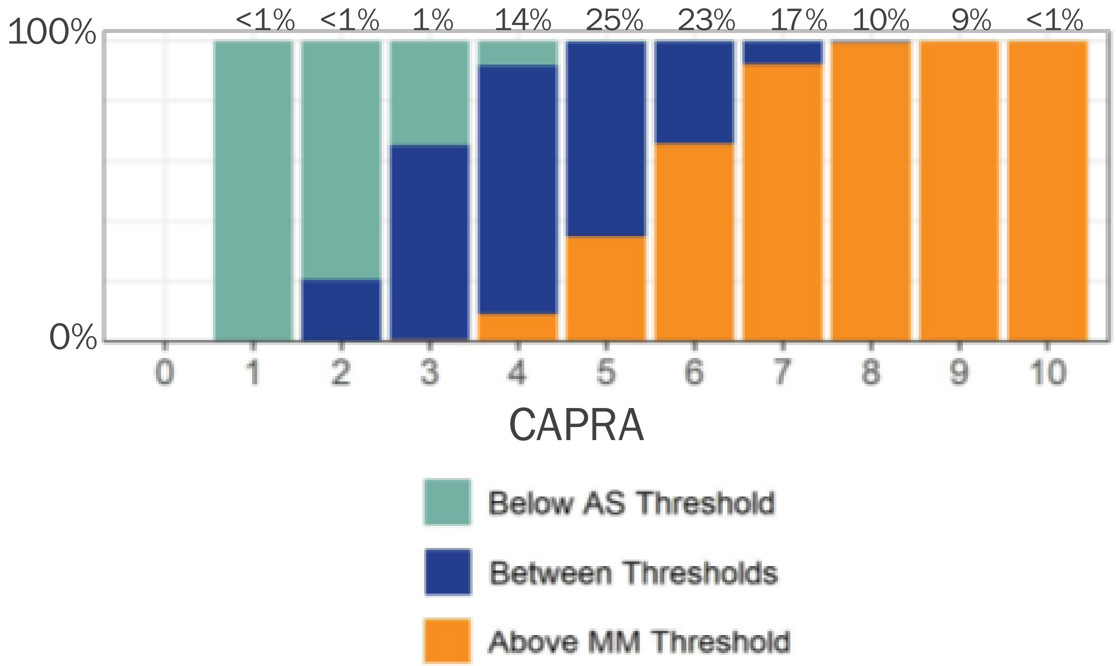
Development of the two Prolaris score cutoffs and risk stratification

ACTIVE SURVEILLANCE THRESHOLD:
90th percentile score among NCCN low-risk patients

MULTIMODAL THRESHOLD:
13% of PCa patients above threshold (64% High, 22% Unfavorable Int)

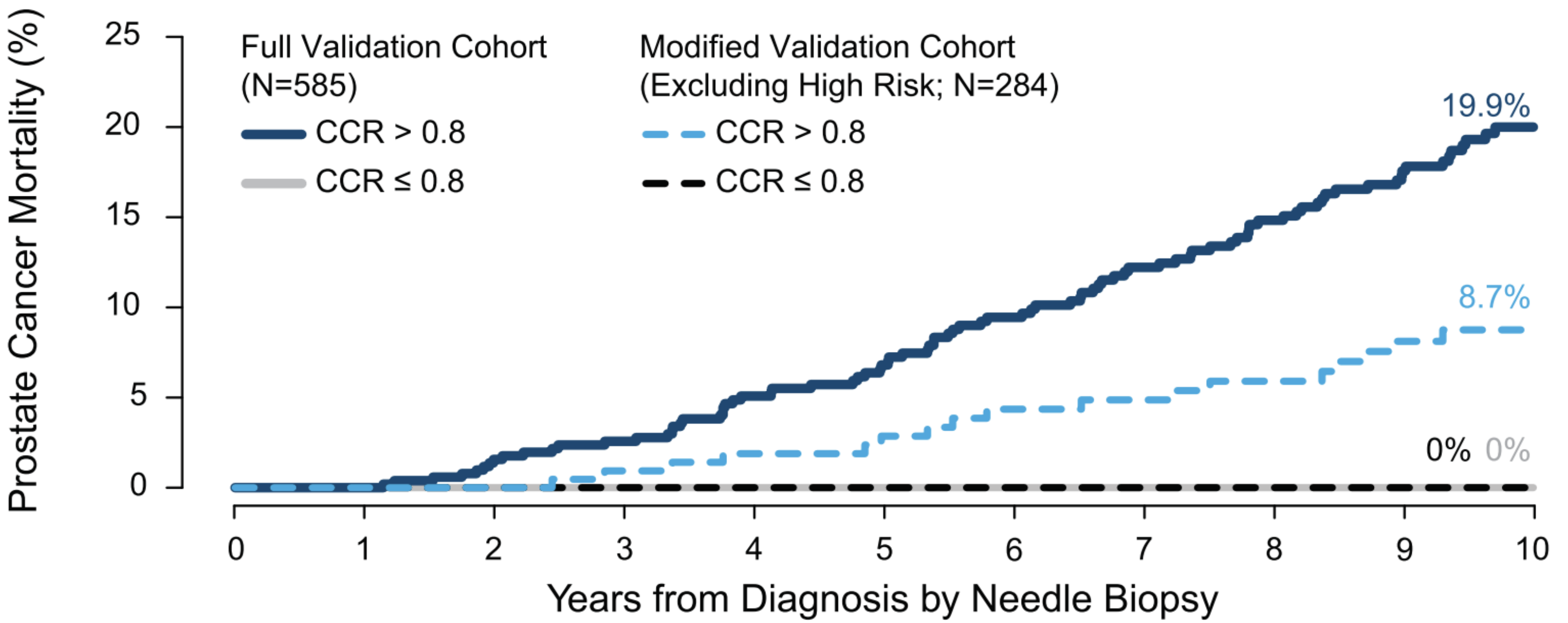


NCCN HIGH/VERY HIGH



Lin, DW et al (2018), Urologic Oncology

Validation of active-surveillance threshold



Full Validation Cohort (N=585)

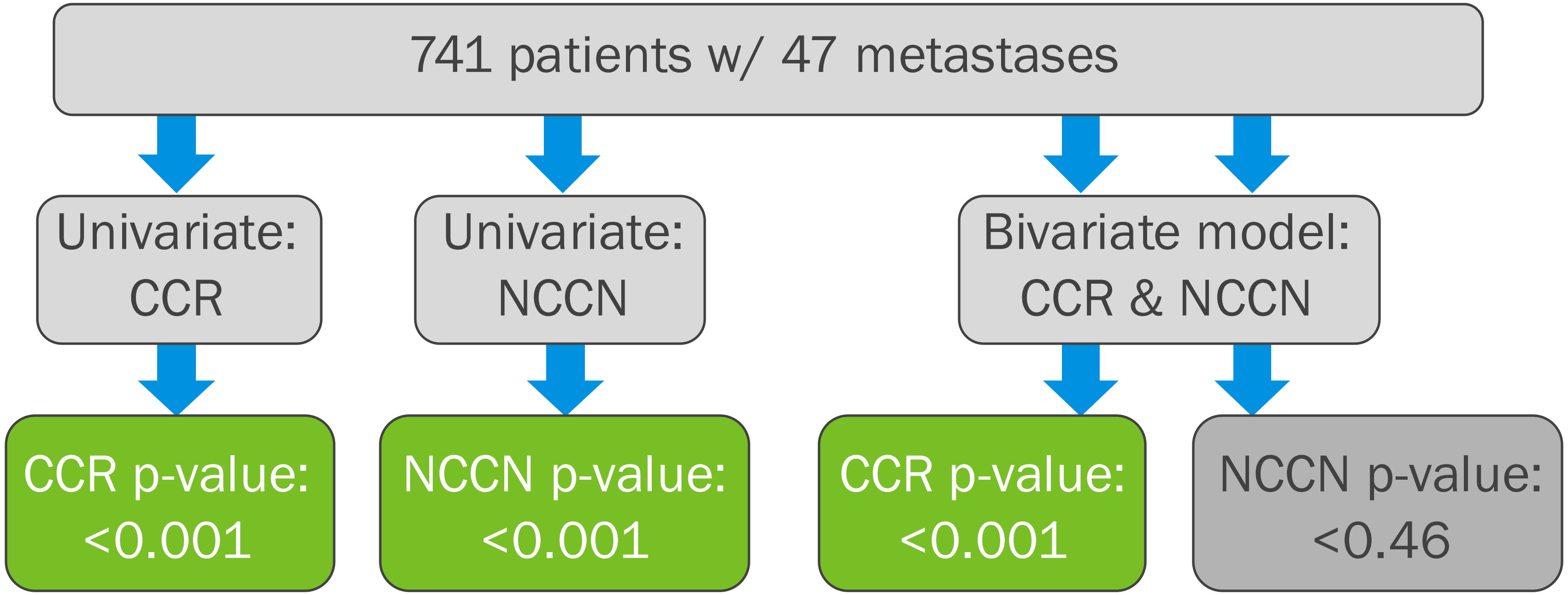
CCR > 0.8	525	520	503	479	451	431	404	378	356	328	189
CCR ≤ 0.8	60	59	58	56	54	52	52	51	51	50	27

Modified Validation Cohort (Excluding High Risk; N=284)

CCR > 0.8	225	224	222	213	207	201	190	186	178	165	96
CCR ≤ 0.8	59	58	57	55	53	52	52	51	51	50	27

Lin, DW et al (2018), Urologic Oncology

Prolaris CCR score prognosticates metastasis better than NCCN category



Tward et al., 2022, Int J Radiat Oncol Biol Phys

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Evaluating CCR efficacy in meta-analysis with >8,500pts & >330 events

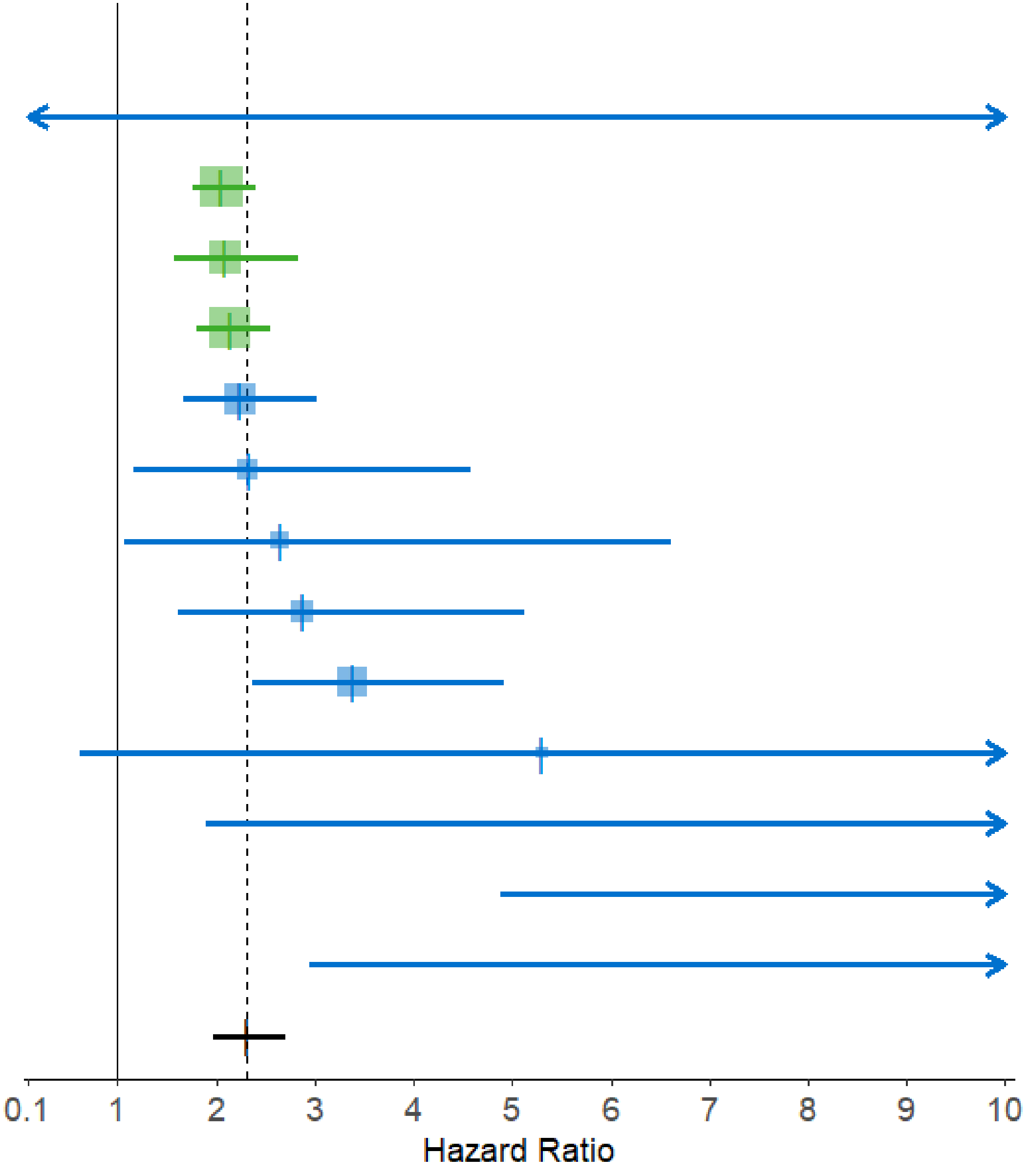
	TAPG1	TAPG2	TURP1B	Durham VA	Martini Clinic	Ochsner	Uni. Of Utah	URO-004	URO-005	URO-008	URO-009	PR04
Publication of cohort in full or in part	Cuzick 2012, 2022	Cuzick 2015, 2022; Lin 2018	Cuzick 2022	Tward 2021; Canter 2020; Bishoff 2014	Tward 2021; Canter 2020; Bishoff 2014	Tward 2021; Canter 2020	Tward 2021	Tward 2022	Not previously published	Not previously published	Kaul 2019	Not previously published
N	175	583	292	128	154	683	114	703	1020	219	639	3228
Recorded PCSM events	40	98	87	-	-	8	-	-	-	-	-	-
Recorded Metastasis events	-	-	-	2	1	23	3	48	7	1	5	21
Median follow-up in non-events (years)	10.6	9.7	11.2	8.6	5.1	5.5	1.9	6.0	2.2	1.5	3.8	3.0

- Hutten 2024 published results: N = 554

PROLARIS META-ANALYSIS

Effect of CCR after accounting for received treatment modality

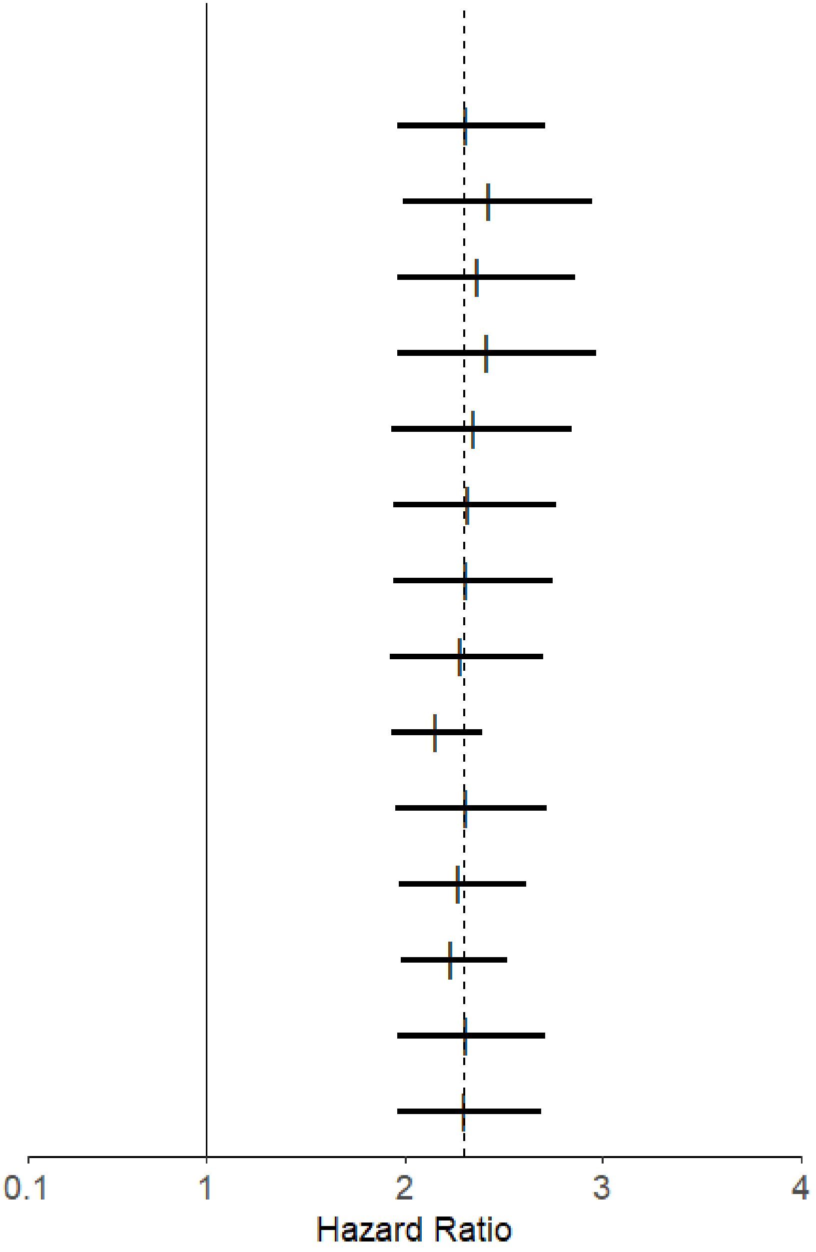
Cohort	N (events)	Endpoint	HR [95% CI]	P-value	Weight
URO-008	219 (1)	Metastasis	0.01 [7.05e-10, 10.10]	0.21	0.01%
TURP1B	292 (87)	PCSM	2.05 [1.76, 2.40]	8e-20	26.5%
TAPG1	175 (40)	PCSM	2.09 [1.57, 2.83]	1.8e-07	13.8%
TAPG2	583 (98)	PCSM	2.14 [1.81, 2.54]	4.3e-20	24.7%
URO-004	703 (48)	Metastasis	2.24 [1.67, 3.03]	2e-06	13.7%
Hutten	554 (?)	Metastasis	2.32 [1.17, 4.59]	0.02	3.5%
URO-005	1020 (7)	Metastasis	2.65 [1.07, 6.61]	0.041	2.1%
PR04	3238 (21)	Metastasis	2.87 [1.61, 5.13]	0.0011	4.8%
Ochsner	683 (23)	Metastasis	3.38 [2.36, 4.93]	3.2e-10	10.1%
Martini Clinic	154 (1)	Metastasis	5.30 [0.62, 88.45]	0.12	0.3%
URO-009	639 (5)	Metastasis	23.84 [1.90, 769.41]	0.013	0.2%
U of U	114 (3)	Metastasis	28.51 [4.88, 793.34]	0.00025	0.3%
Durham VA	128 (2)	Metastasis	84.21 [2.94, 2.91e+07]	0.0012	0.03%
Overall effect			**2.30 [1.97, 2.69]**	**7.1e-08**	



Heterogeneity: $I^2 = 23\%$, $\tau^2 = 0.0114$, $p = 0.21$

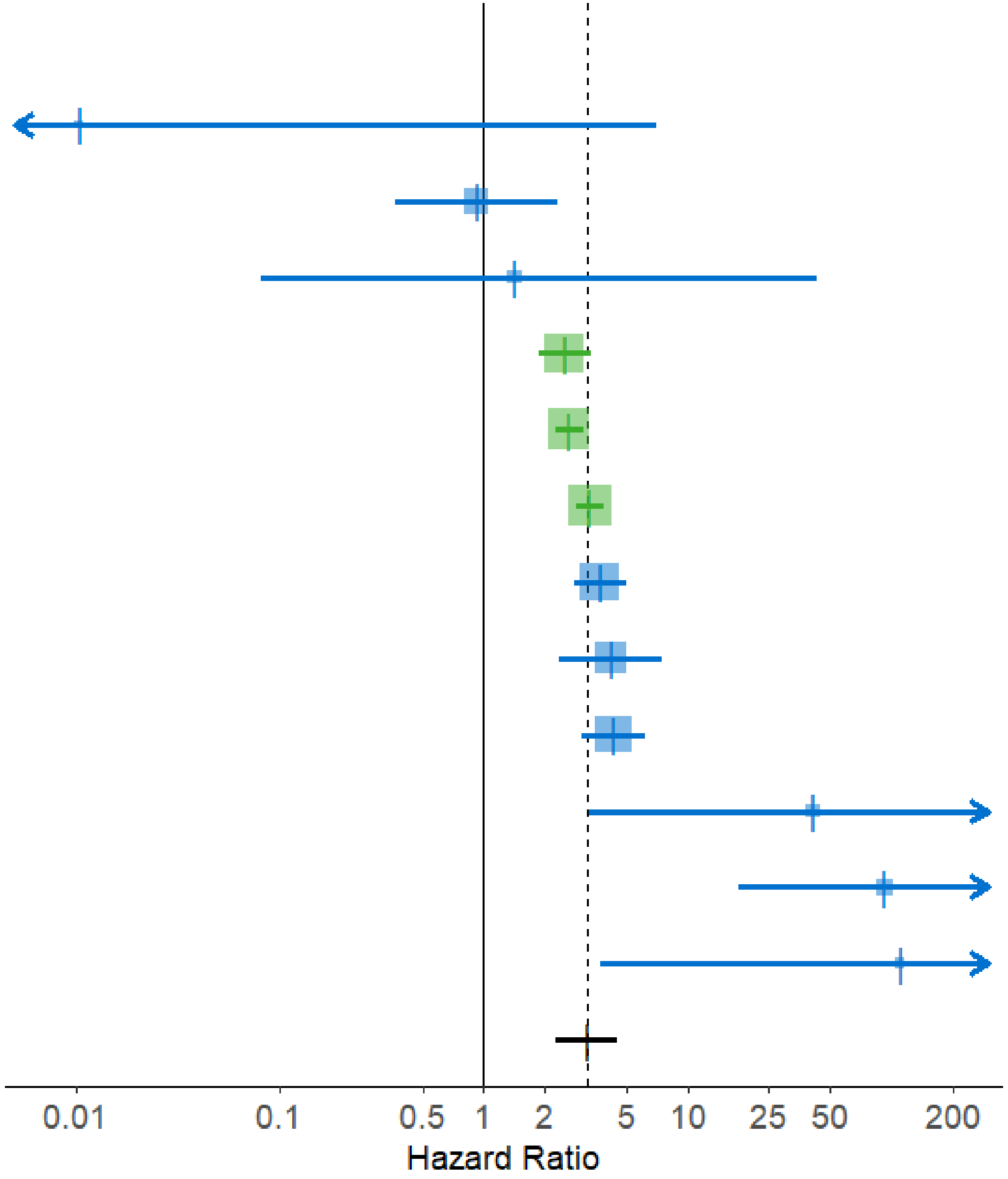
Leave-one-out analysis demonstrates robustness of results

Cohort	HR [95% CI]	P-value	tau²
Omitting URO-008	2.31 [1.97, 2.71]	1.8e-07	0.012
Omitting TURP1B	2.42 [1.99, 2.95]	7.6e-07	0.017
Omitting TAPG1	2.37 [1.96, 2.86]	6.6e-07	0.017
Omitting TAPG2	2.41 [1.96, 2.97]	1.4e-06	0.022
Omitting URO-004	2.35 [1.94, 2.84]	9.0e-07	0.017
Omitting Hutten	2.32 [1.95, 2.77]	4.6e-07	0.015
Omitting URO-005	2.31 [1.94, 2.75]	4.0e-07	0.014
Omitting PR04	2.28 [1.93, 2.71]	3.6e-07	0.013
Omitting Ochsner	2.15 [1.94, 2.39]	6.1e-09	0.000
Omitting Martini Clinic	2.31 [1.95, 2.72]	2.7e-07	0.013
Omitting URO-009	2.27 [1.97, 2.61]	5.9e-08	0.007
Omitting U of U	2.23 [1.98, 2.52]	1.3e-08	0.002
Omitting Durham VA	2.30 [1.96, 2.71]	2.1e-07	0.012
Pooled estimate	**2.30 [1.97, 2.69]**	**7.1e-08**	0.011



Effect of CCR after accounting for received treatment modality and CAPRA

Cohort	N (events)	Endpoint	HR [95% CI]	P-value	Weight
URO-008	219 (1)	Metastasis	0.01 [3.99e-09, 6.99]	0.18	0.05%
URO-005	1020 (7)	Metastasis	0.92 [0.37, 2.32]	0.93	4.8%
Martini Clinic	154 (1)	Metastasis	1.42 [0.08, 43.08]	0.86	0.5%
TAPG1	175 (40)	PCSM	2.49 [1.88, 3.36]	0.0027	15.8%
TAPG2	583 (98)	PCSM	2.62 [2.23, 3.11]	1.1e-06	19.2%
TURP1B	292 (87)	PCSM	3.31 [2.86, 3.85]	1.6e-07	19.6%
URO-004	703 (48)	Metastasis	3.71 [2.77, 5.00]	1e-04	15.7%
PR04	3238 (21)	Metastasis	4.19 [2.34, 7.50]	0.0054	8.9%
Ochsner	683 (23)	Metastasis	4.29 [3.01, 6.24]	0.00024	13.8%
URO-009	639 (5)	Metastasis	41.09 [3.26, 1421.71]	0.007	0.5%
U of U	114 (3)	Metastasis	92.19 [17.61, 2103.74]	0.0019	0.9%
Durham VA	128 (2)	Metastasis	109.73 [3.71, 8.92e+07]	0.013	0.07%
Overall effect			**3.19 [2.25, 4.51]**	**1.5e-05**	



Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.0629$, $p = 0.00089$

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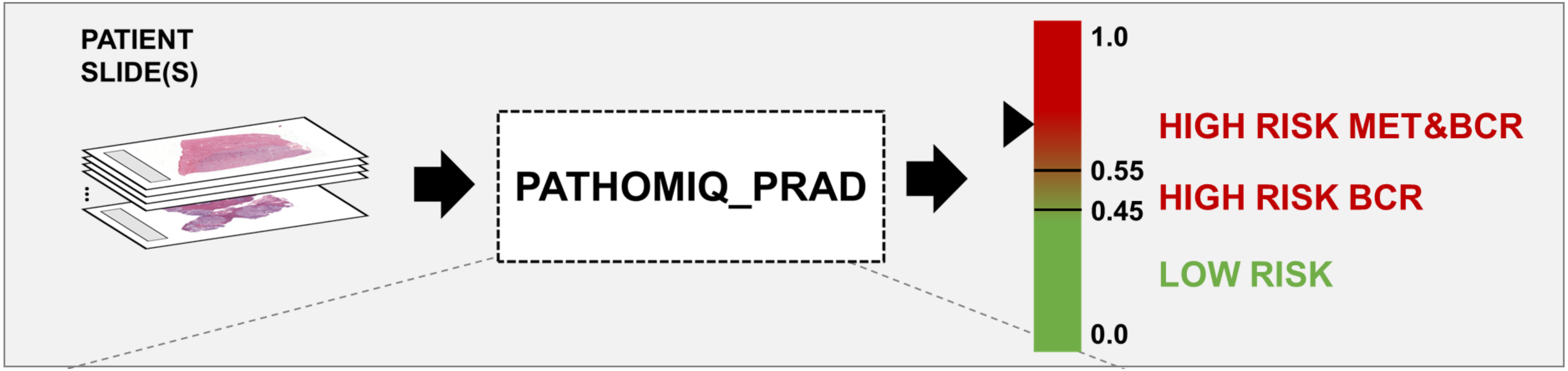
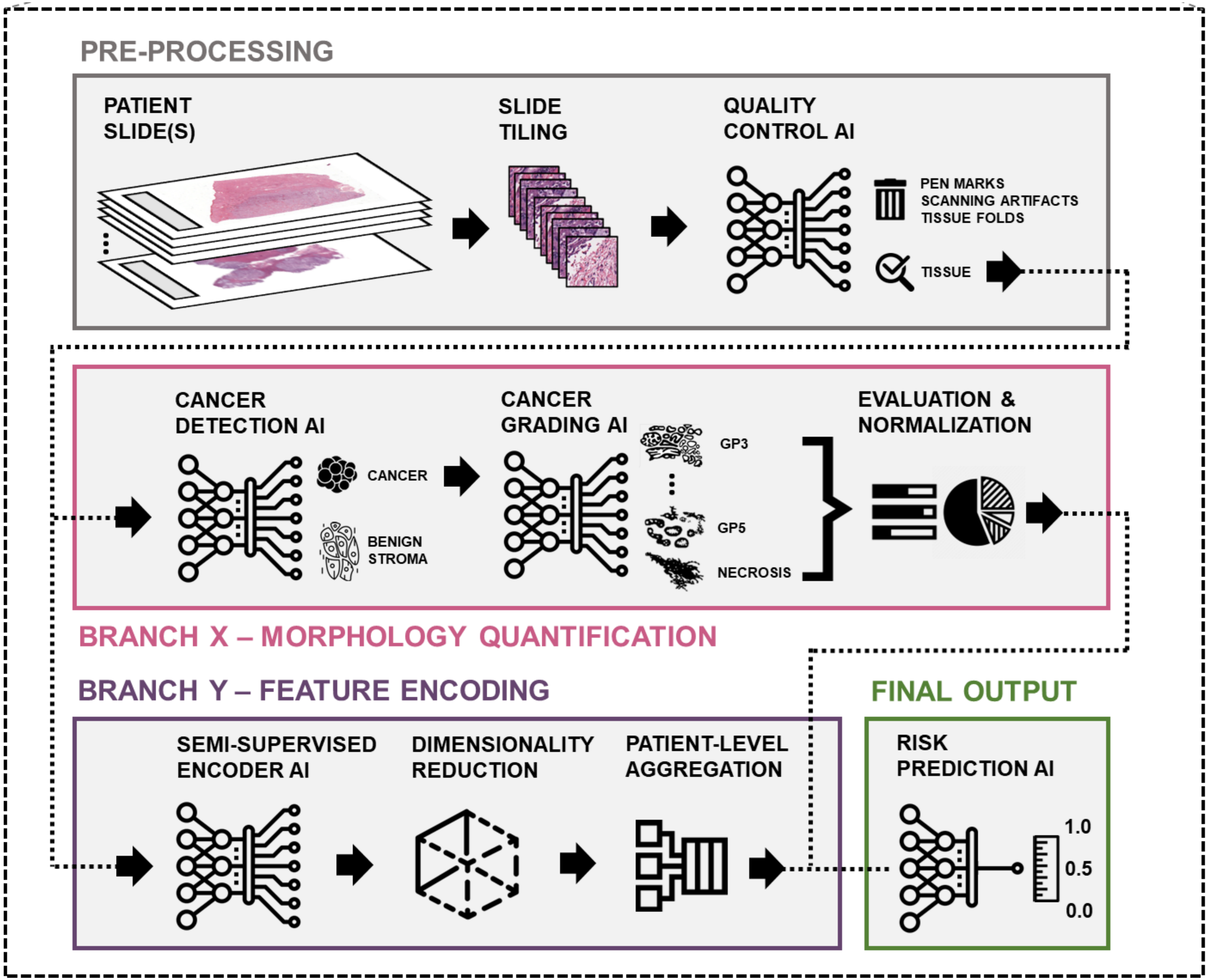
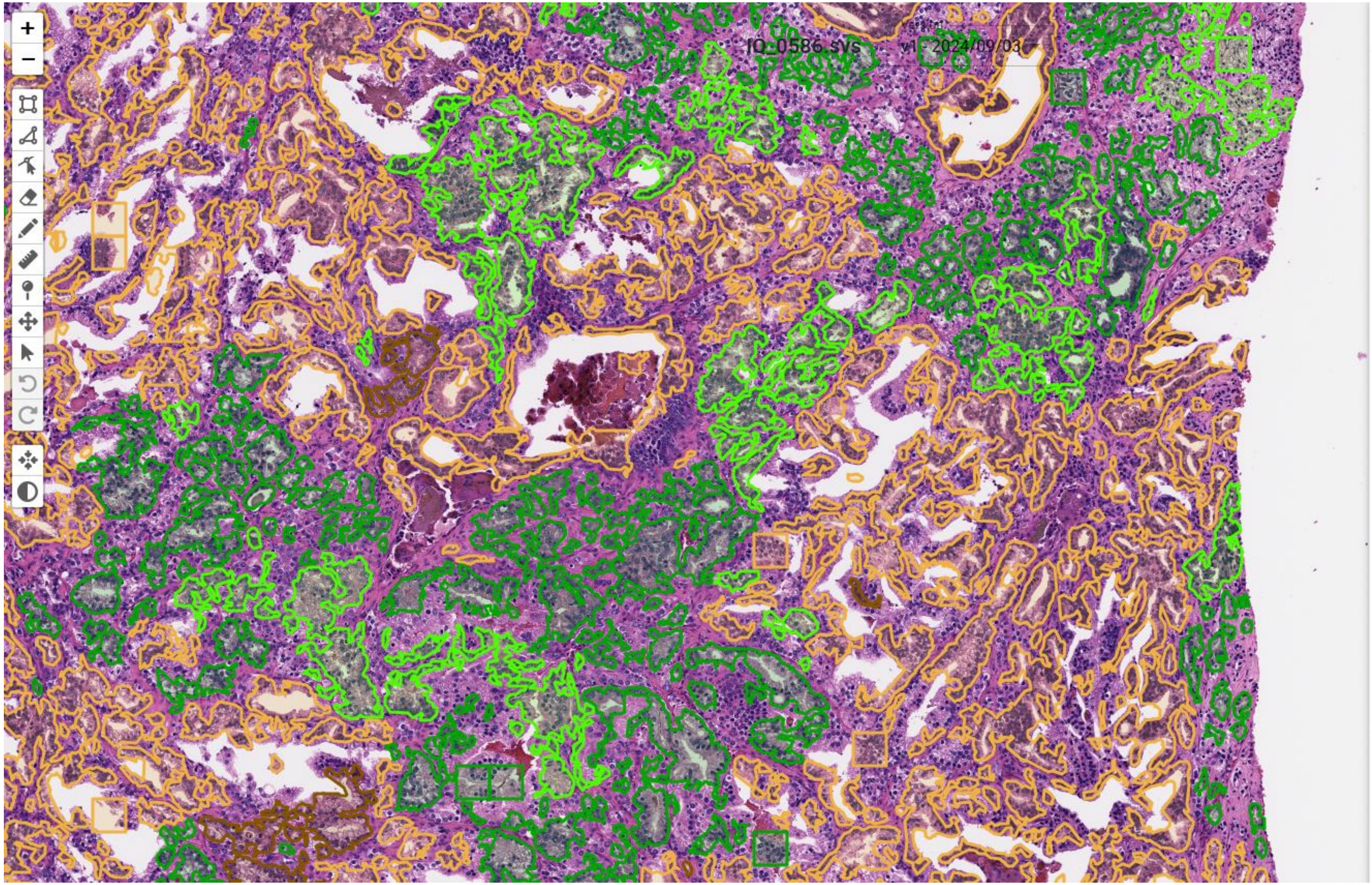
PATHOMIQ PRAD



PATHOMIQ PRAD



PATHOMIQ – Deep Insights Of Interpretable Features



System Annotations

User Annotations

Diagnostic Predictions

Total tissue area : 48.07 mm²

Total cancer area : 1.5 mm²

Cancer Volume (System) : 3.12% (0% Threshold)

Cancer Volume (User) : 0%

GP3 : 9.08% (5% Threshold)

GP4 : 90.67% (5% Threshold)

GP4-CRIB : 44.76%

GP5 : 0% (5% Threshold)

PNI : Present

Diagnosis/Gleason Score : 4+3

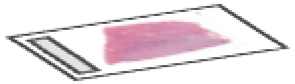
Show Report

Prognostic Outcome Predictions

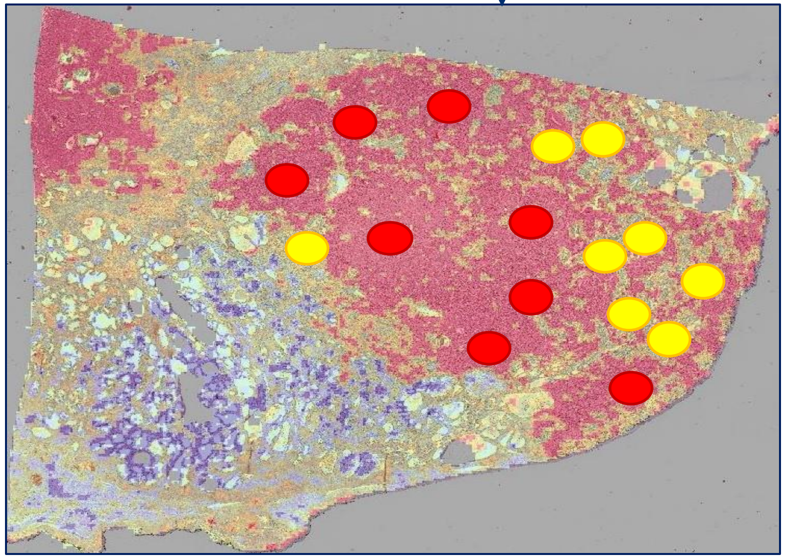
PathomIQ Score: 0.82

Patient is at high risk of metastasis

Phenotype-guided ROIs Capture Molecular Changes and Enables Novel Biomarker Discovery



PATHOMIQ_PRAD



High probability of disease progression

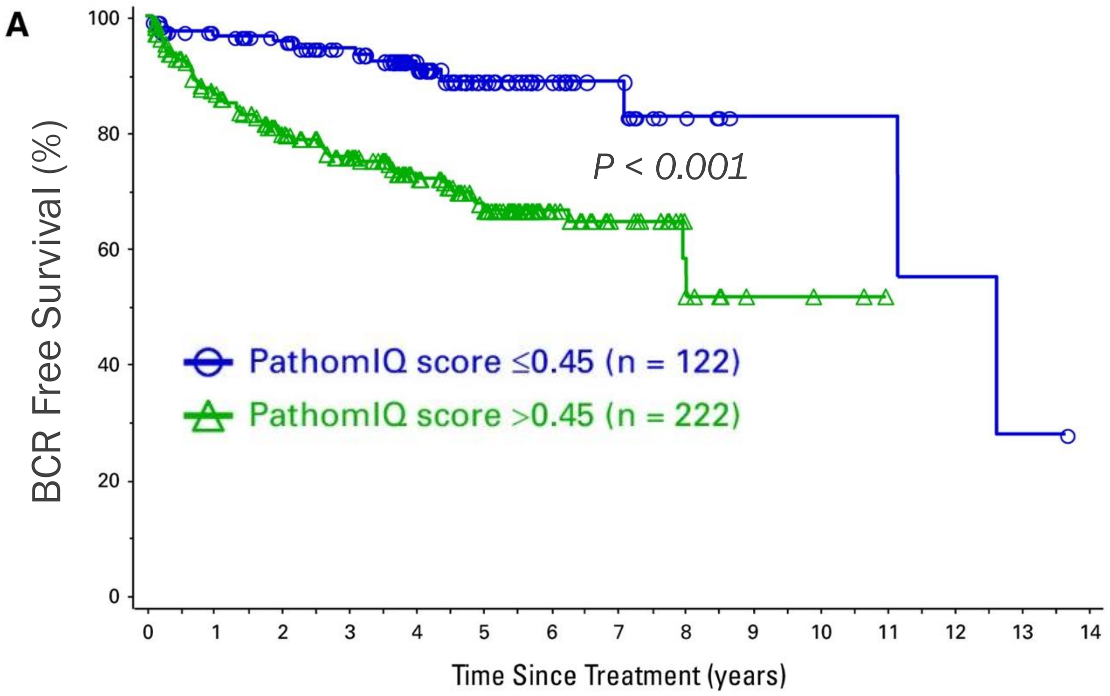
Low probability of disease progression

	↑ % Ki67	↓ % CC3	↑ % TMEM173*	↑ CD8 Density*	↑ CD163 Density
	ROIs / non-ROIs	ROIs / non-ROIs	ROIs / non-ROIs	ROIs / non-ROIs	ROIs / non-ROIs
Mean	2.4	9.8	14	2.75	4.7
p-value	0.00370	0.04760	0.00980	0.05200	0.01330

* Previously never reported to be significant in prostate cancer progression

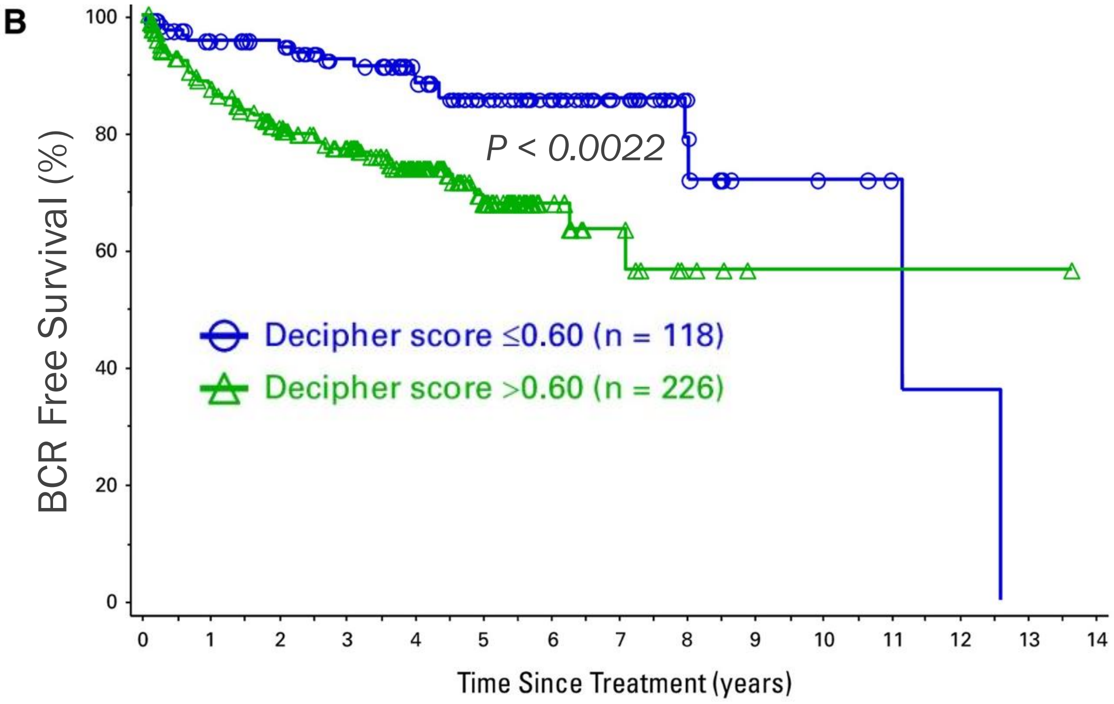
Huang et al., JCO Clinical Cancer Informatics Feb 2022

Post-RP retrospective performance of AI and genomic classifier: BCRFS



No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
PathomIQ BioRec score <0.45	122 (12)	107 (7)	85 (20)	36 (13)	15 (7)	3 (0)	3 (0)	1 (1)
PathomIQ BioRec score >0.45	222 (22)	173 (15)	120 (23)	69 (34)	21 (11)	3 (1)	0 (0)	0 (0)

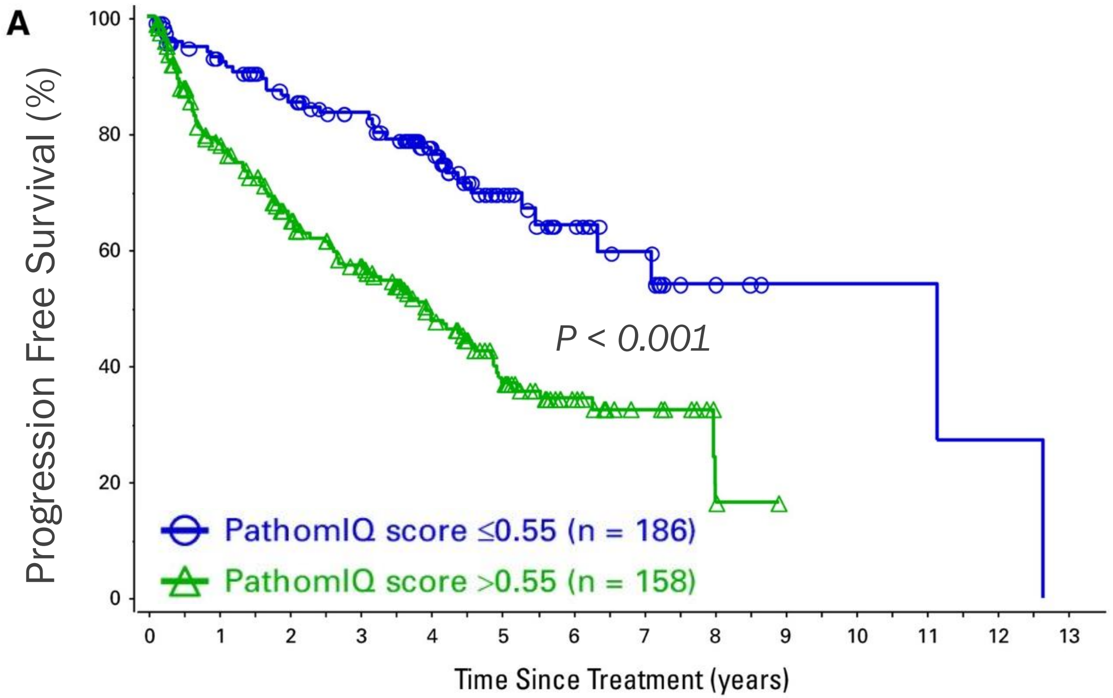


No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
Decipher score <0.6	118 (12)	101 (6)	79 (10)	51 (13)	26 (13)	5 (1)	2 (0)	0 (0)
Decipher score >0.6	226 (22)	179 (16)	126 (33)	54 (34)	10 (5)	1 (0)	1 (0)	1 (1)

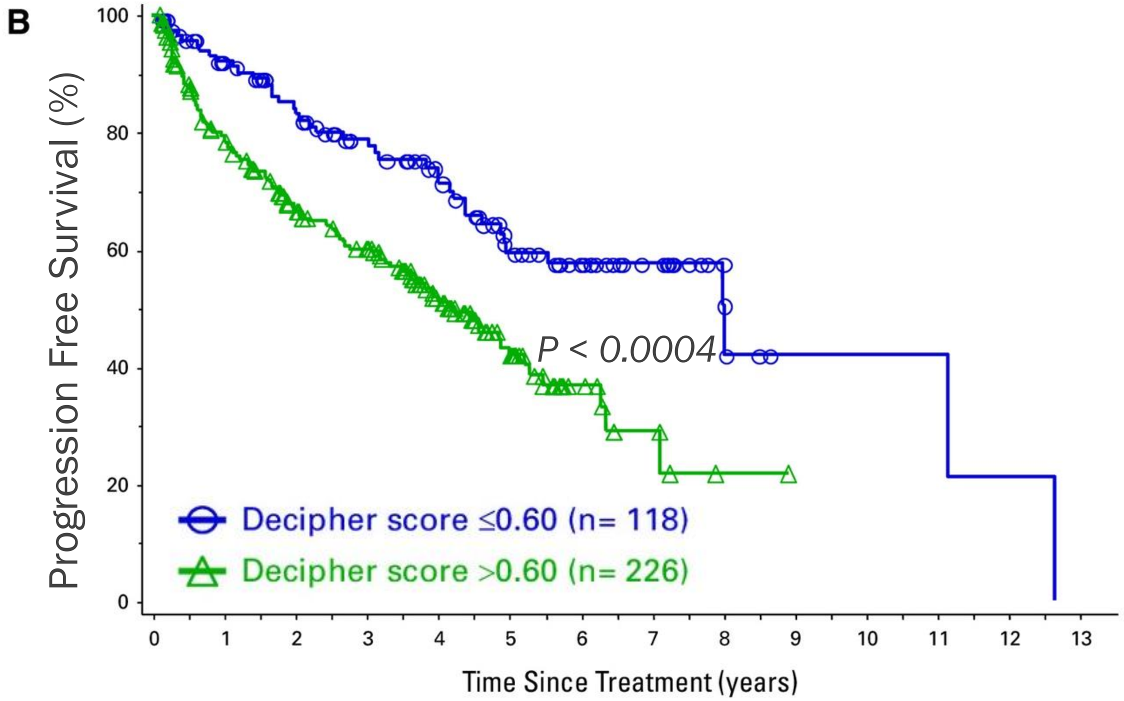
Fay et al., JCO Clin Cancer Inform., 2025

Post-RP retrospective performance of AI and genomic classifier: PFS



No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
PathomIQ BioRec score <0.45	122 (12)	102 (7)	77 (18)	30 (9)	12 (6)	2 (0)	2 (0)	0 (0)
PathomIQ BioRec score >0.45	222 (21)	156 (14)	91 (17)	39 (17)	10 (6)	0 (0)	0 (0)	0 (0)

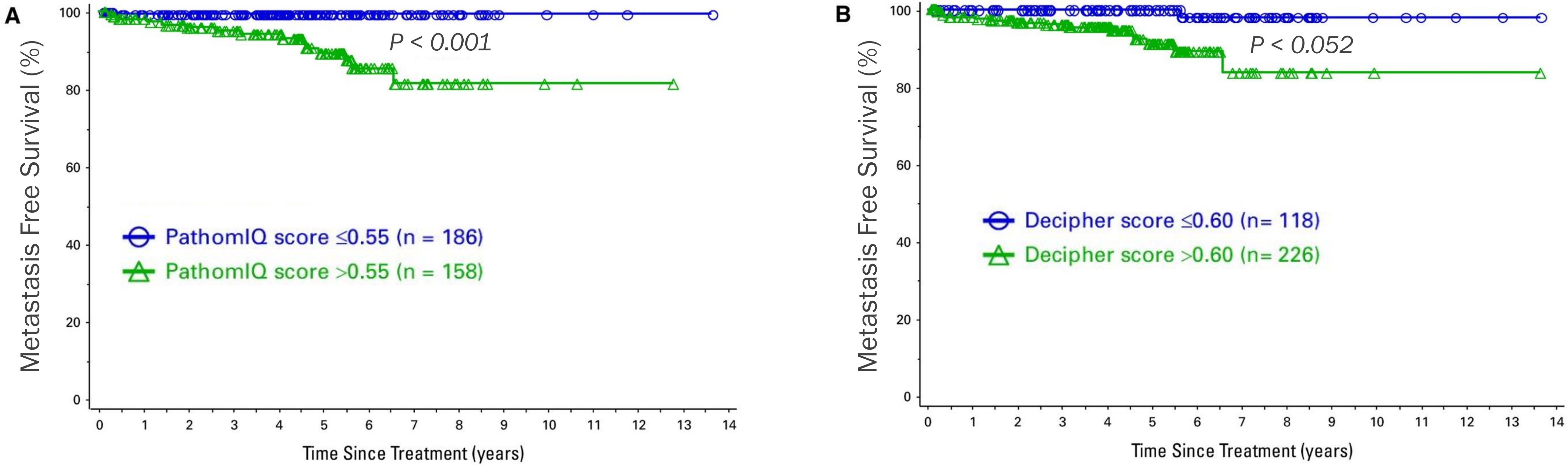


No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
Decipher score <0.6	118 (12)	97 (6)	67 (8)	36 (9)	17 (9)	2 (0)	2 (0)	0 (0)
Decipher score >0.6	226 (21)	161 (15)	101 (27)	33 (17)	5 (3)	0 (0)	0 (0)	0 (0)

Fay et al., JCO Clin Cancer Inform., 2025

Post-RP retrospective performance of AI and genomic classifier: MFS



No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
PathomIQ Mets score <0.55	186 (21)	164 (14)	130 (35)	66 (24)	26 (10)	5 (1)	3 (1)	2 (2)
PathomIQ Mets score >0.55	158 (14)	141 (12)	109 (17)	66 (34)	17 (9)	3 (1)	1 (0)	0 (0)

No. at risk (No. censored)

Time (years)	Baseline	1	3	5	7	9	11	13
Decipher score <0.6	118 (13)	105 (6)	83 (11)	59 (14)	30 (13)	6 (1)	3 (1)	1 (1)
Decipher score >0.6	226 (22)	200 (20)	156 (41)	73 (44)	13 (6)	2 (1)	1 (0)	1 (0)

Fay et al., JCO Clin Cancer Inform., 2025

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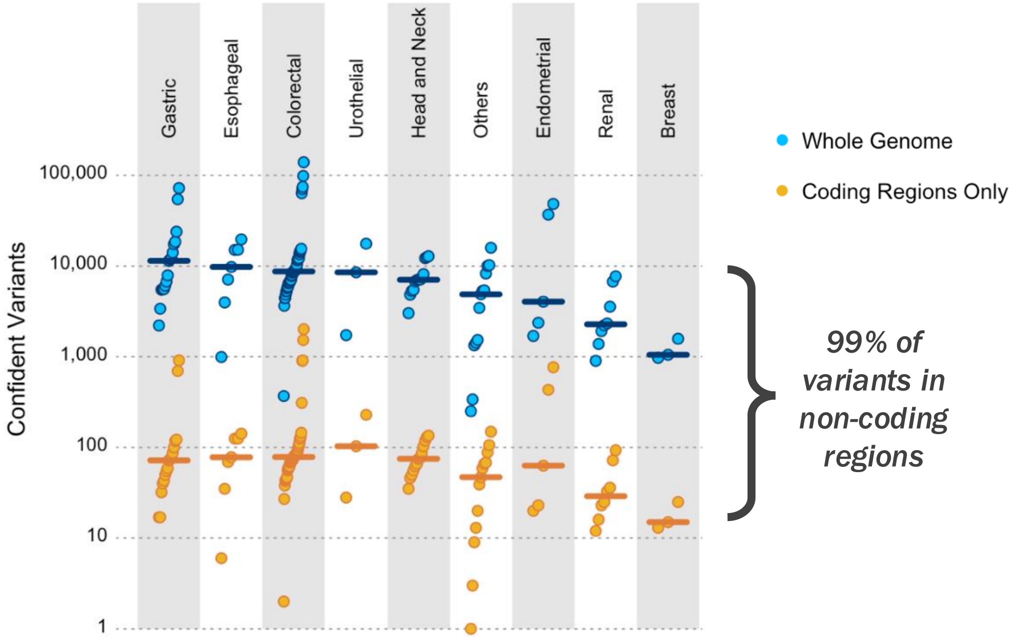
WGS-based ctDNA detection with Precise™ MRD

Tumor-Normal WGS: ≥30X

Tumor + Normal → **Somatic Pipeline**: SNVs, indels, CNAs via custom ensemble-based pipeline → ~1,000 somatic sites selected for bespoke panel

WGS identifies 100x more variants than exome



Plasma Monitoring

$T_1, T_2 \ldots T_N$ cfDNA → Bespoke capture panel → **Detection Pipeline**: Ultra-deep NGS with UMI error correction, tumor fraction estimate →

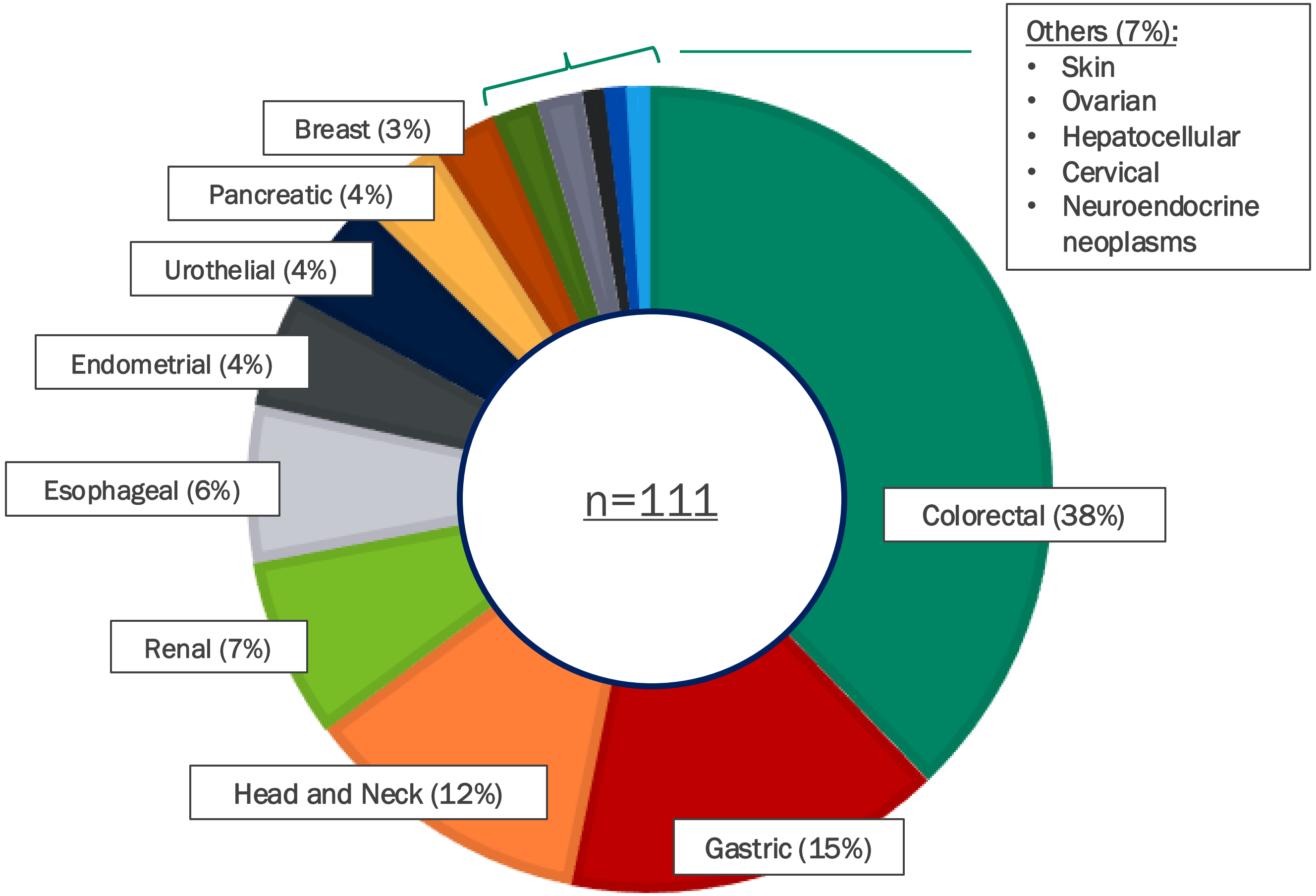
Analytical performance of Precise MRD

	Limit of Blank (ppm)	**Limit of Detection** (ppm)
Myriad Precise MRD	**0.3**	**<5**
Laboratory A[1]	0.719	3.45
Laboratory B[2]	—	100
Laboratory C[3]	—	80
Laboratory D[4]	—	100
Laboratory E[5]	—	3000

(100% PPA and 100% NPA among 237 samples)

[1]Northcott et al. 2024. Oncotarget 15:200-218
[2]Company web site
[3]Zhao et al. 2024. Mol Diag & Ther. 27:753-768
[4]Kandasamy et al. 2022. J. Clin.Oncol. 40:e13582
[5]Artieri et al. 2020. J. Clin. Oncol. 38:e15549
image adapted from Alexandrov et al., *Nature*, 2013

Patient Characteristics

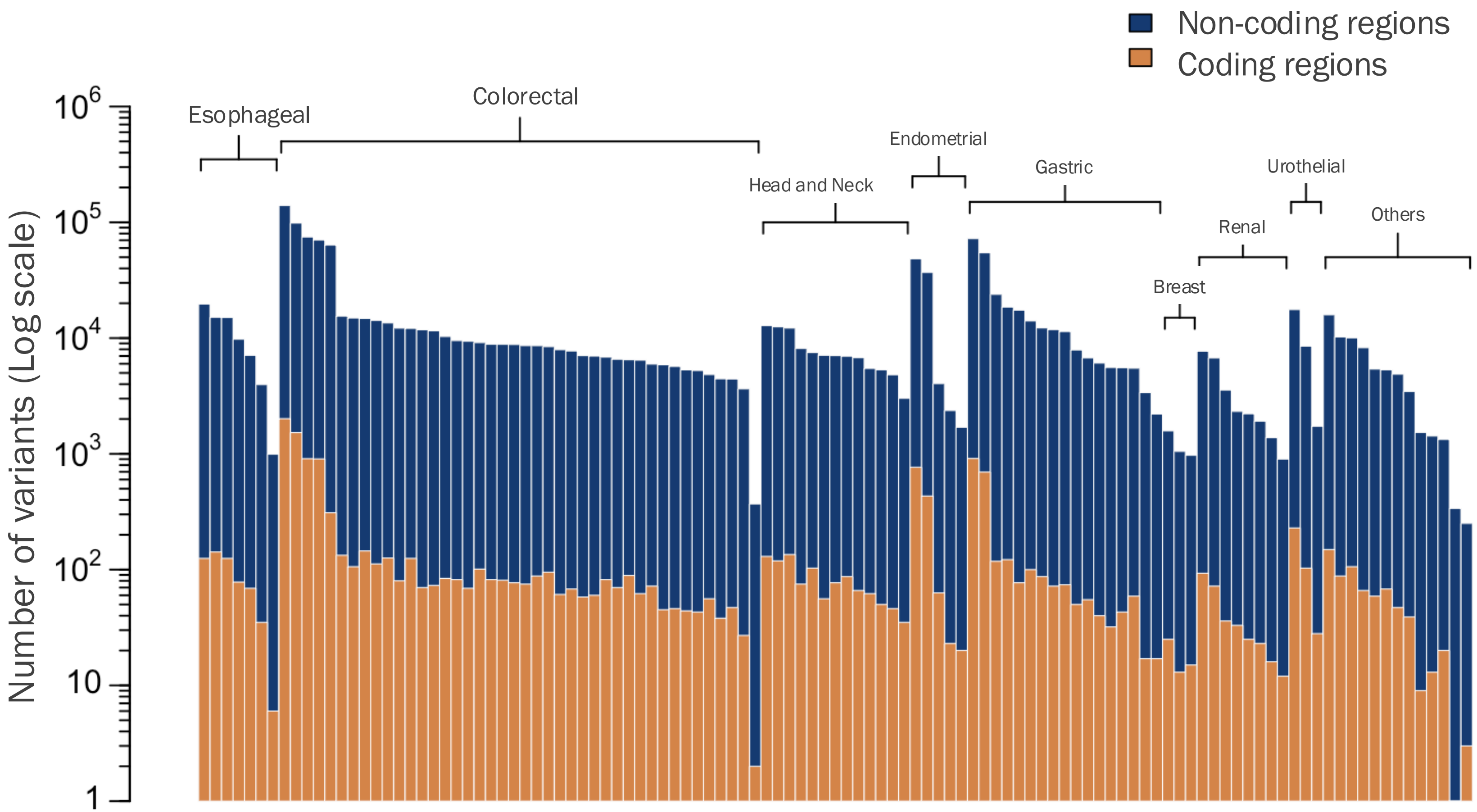


Baseline characteristics		n=111, n (%)
Age, median (range), years		69 (34—87)
Sex, Female		40 (36.0)
Histology	Adenocarcinoma	63 (56.8)
	SCC	23 (20.7)
	Others	25 (22.5)
NAC administered		31 (27.9)
Surgery performed		102 (91.9)
Post-surgery characteristics		**n=102, n (%)**
Pathological stage (UICC TNM)	0	6 (5.4)
	I	17 (15.3)
	II	28 (25.2)
	III	39 (35.1)
	IV	12 (10.8)
TRG (n=22*)	0	4 (18.2)
*In patients treated with both NAC and surgery	1	5 (22.7)
Assessed locally at participating institutions	2	7 (31.8)
	3	6 (27.3)
Adjuvant therapy		57 (55.9)

SCC, squamous cell carcinoma; TRG, Tumor regression grade (AJCC/CAP)

Variants identified through tumor tissue WGS

- Number of variants identified through WGS and selected for the bespoke panels demonstrated approximately 100-fold enrichment of non-coding regions compared to coding regions.



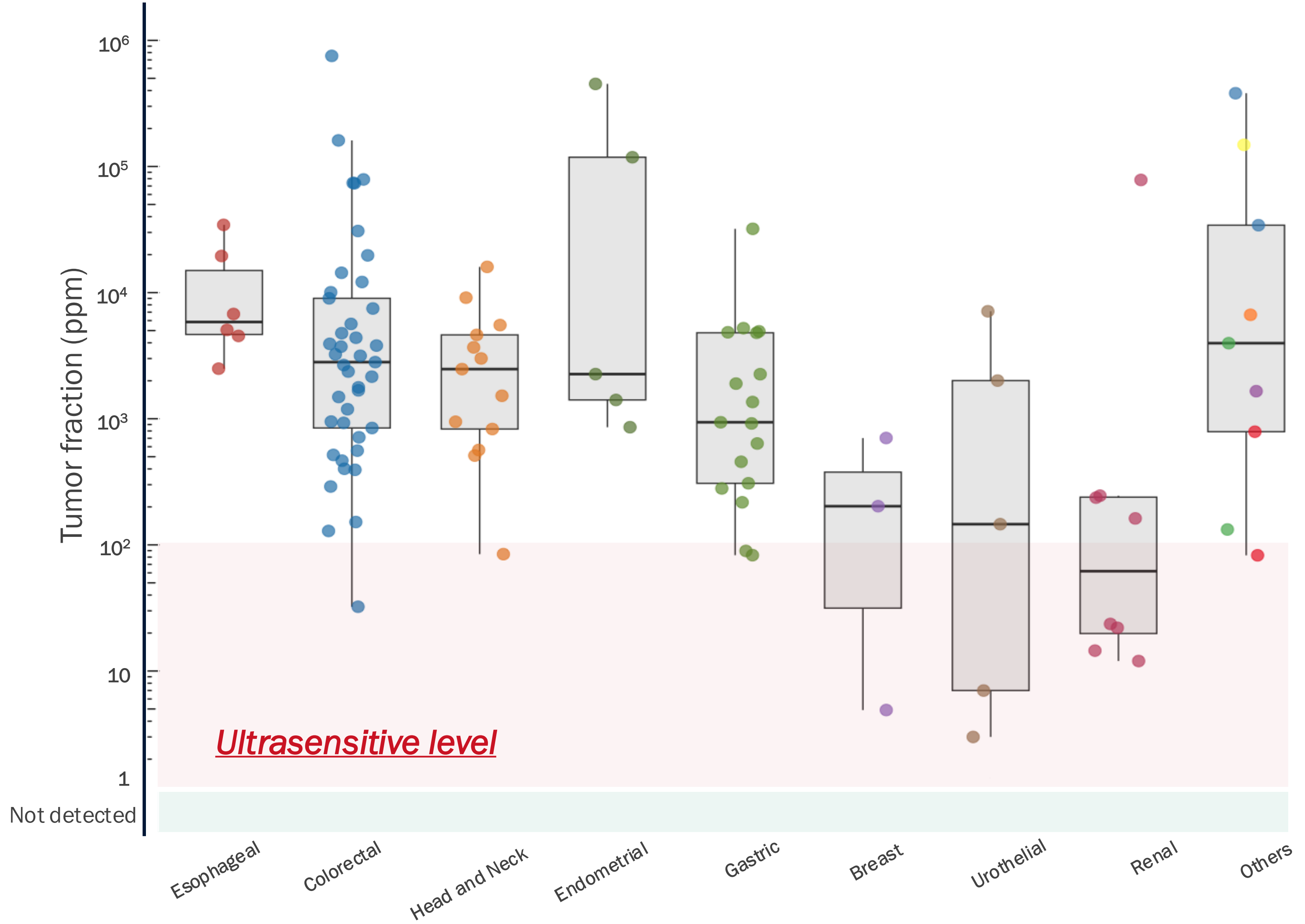
Select up to 1000 variants for bespoke panel

Indication	Panel Size		
	<500*	500-999	1000
Colorectal	1	0	41
Gastric	0	0	17
Head and Neck	0	0	13
Esophageal	0	2	5
Urothelial	0	2	3
Renal	0	4	4
Endometrial	0	3	2
Breast	0	3	0
Pancreatic	2	2	0
Others	0	2	5

*Insufficient variants for ctDNA analysis

WGS panel-creation success rate = 97.3%

Baseline ctDNA tumor fraction across cancer types



Cancer type	Median TF
Esophageal	5,910 (ppm)
Colorectal	2,810 (ppm)
Head and Neck	2,480 (ppm)
Endometrial	2,260 (ppm)
Gastric	938 (ppm)
Breast	202 (ppm)
Urothelial	146 (ppm)
Renal	92.8 (ppm)
Others	
Cervical	
Hepatocellular	
Neuroendocrine	
Ovarian	
Pancreatic	
Skin	

Spanning widely across cancer types

- Median ctDNA levels spanning three orders of magnitude across cancer types

- 100% Baseline sensitivity with 11.1% ultrasensitive levels

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Hashimoto et al., ASCO, 2025

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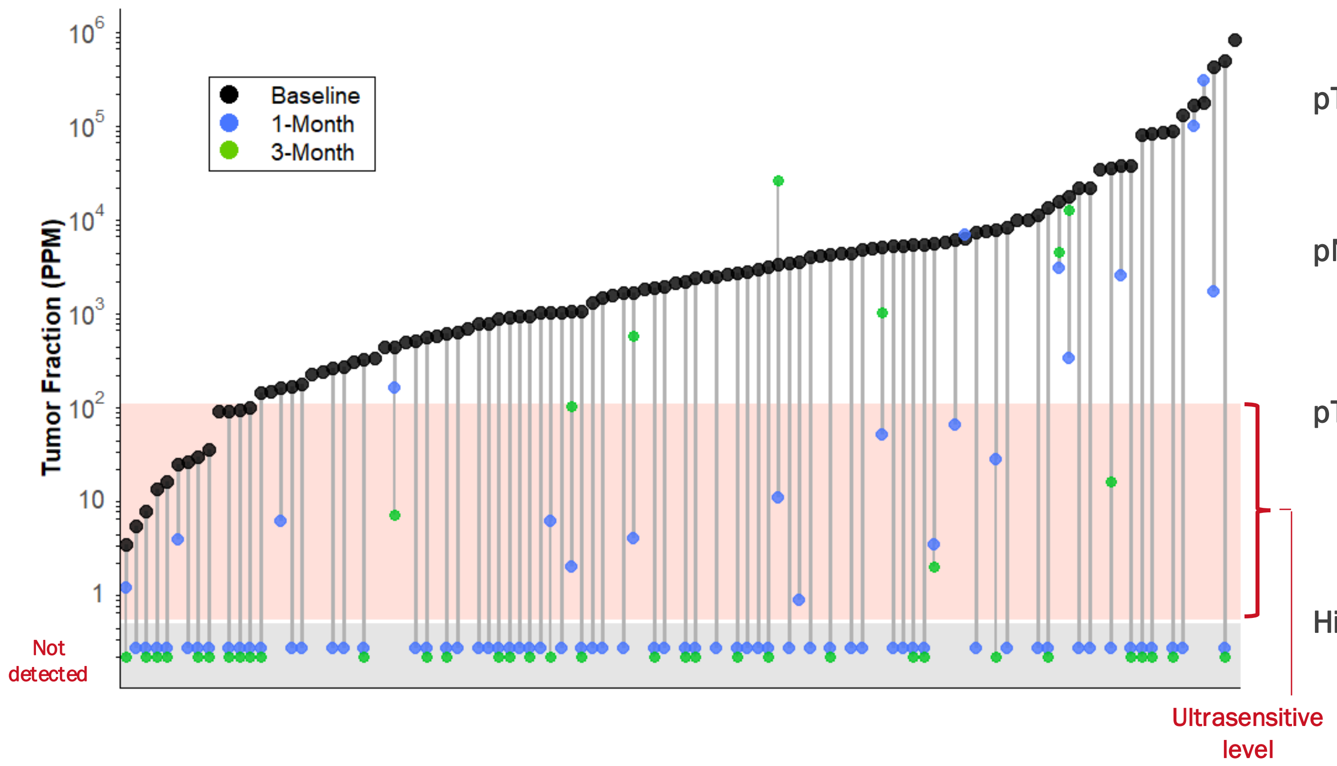
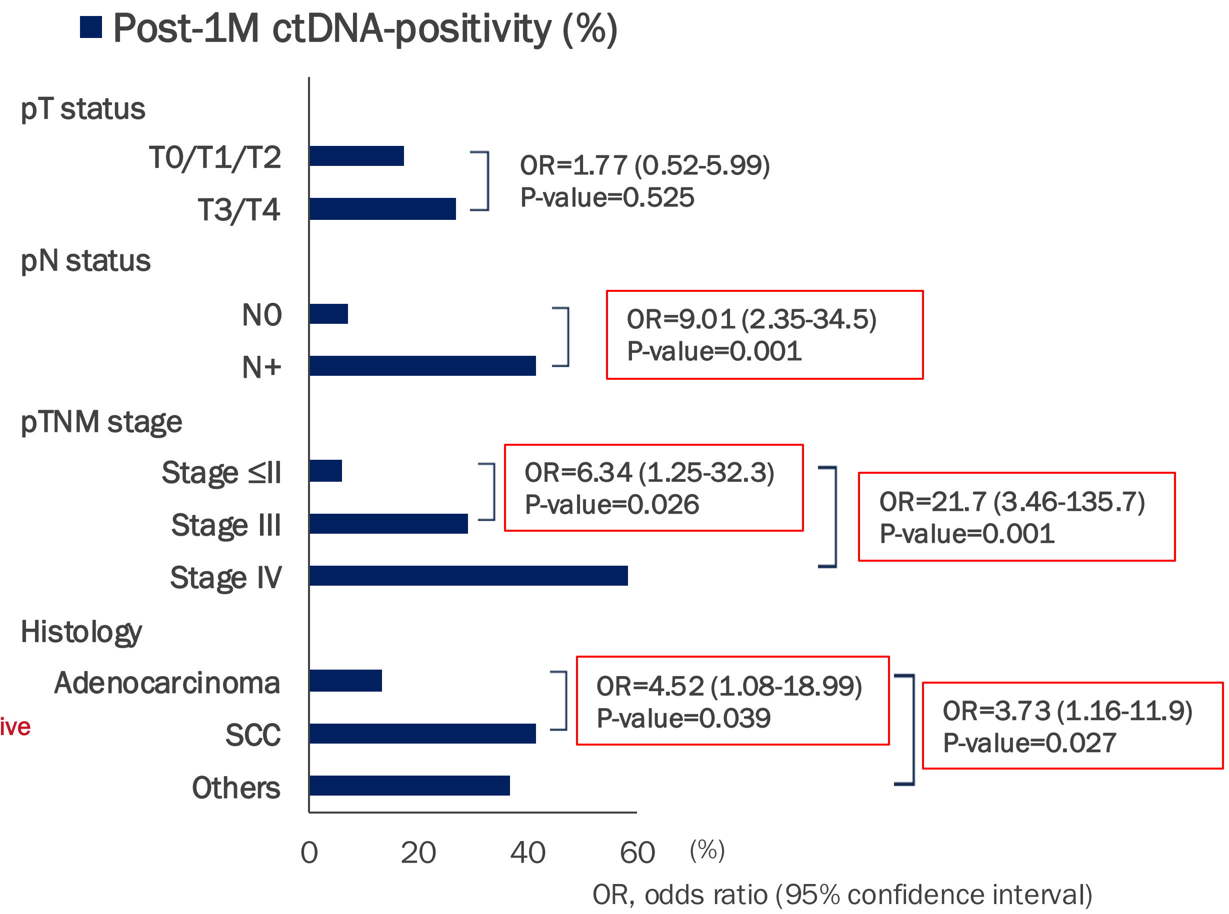
Post-surgery ctDNA positivity and tumor fraction



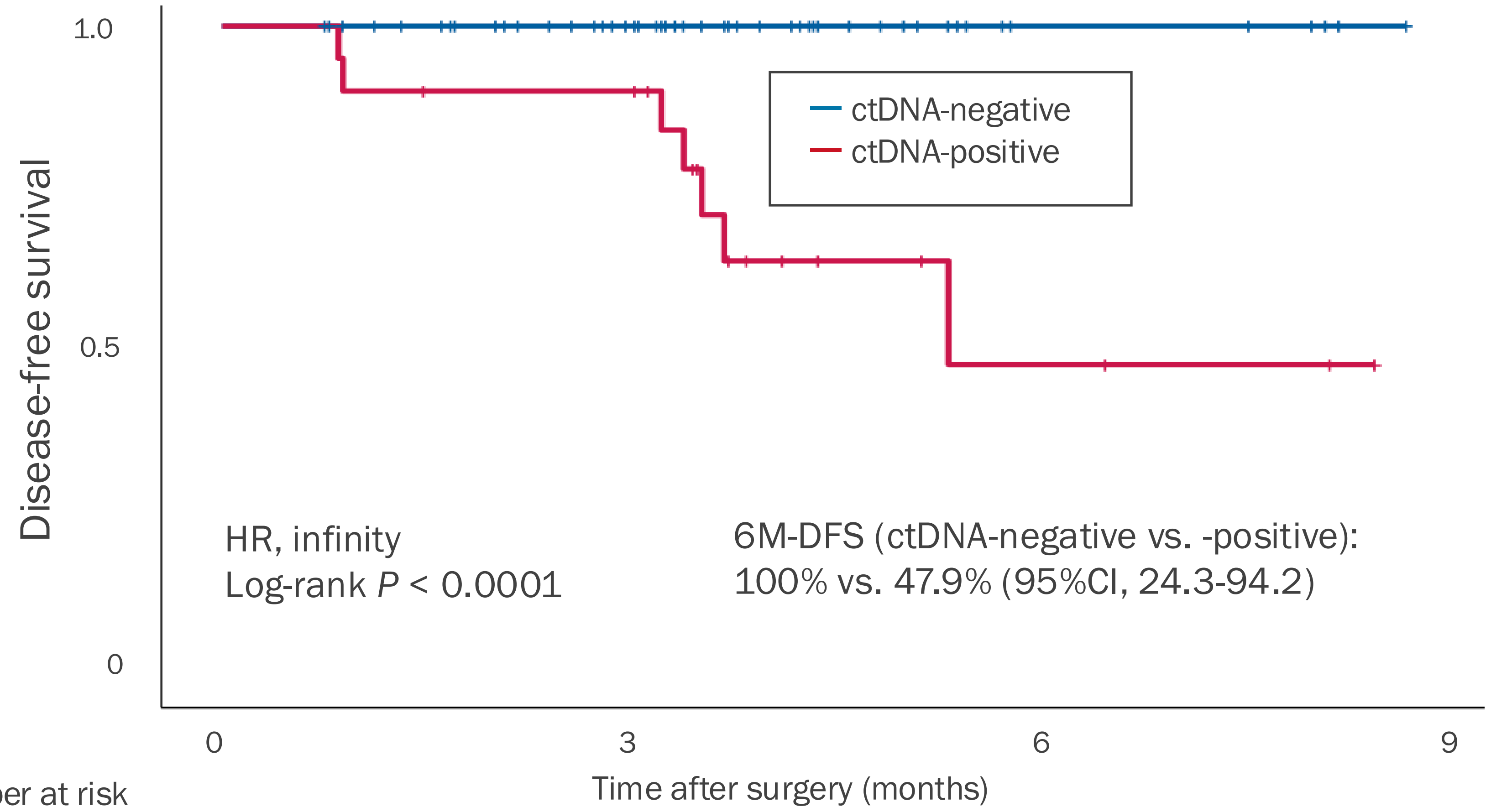
- 24.4% ctDNA positivity at 1M post-surgery, with 60% detected at ultrasensitive levels (min. 0.7 ppm).
- 22.0% ctDNA positivity at 3M post-surgery, with 44.4% detected at ultrasensitive levels.



- Significant associations between post-1M ctDNA positivity and pN, pStage, and histology

Disease-free survival by 1M post-surgery ctDNA positivity

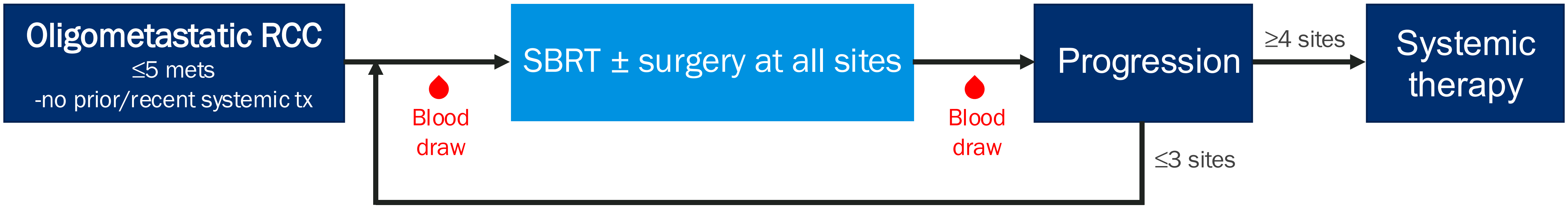
Median follow-up period: 3.4 months (range: 0.8–8.7 months)

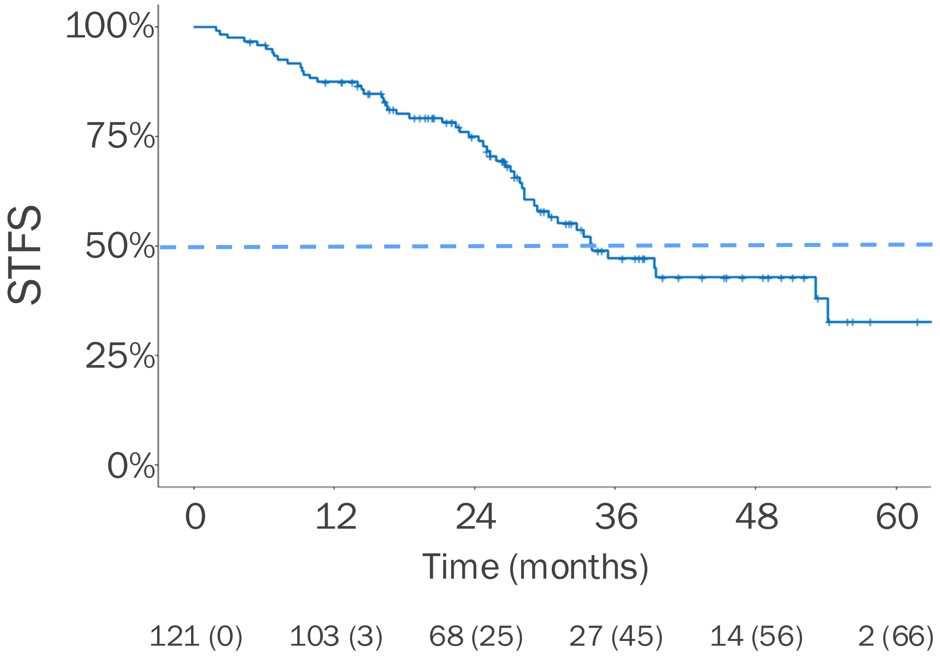


Number at risk	0	3	6	9
Negative	62	41	5	0
Positive	20	17	3	0

Hashimoto et al., ASCO, 2025

Oligometastatic renal cancer trial design





Primary endpoint:

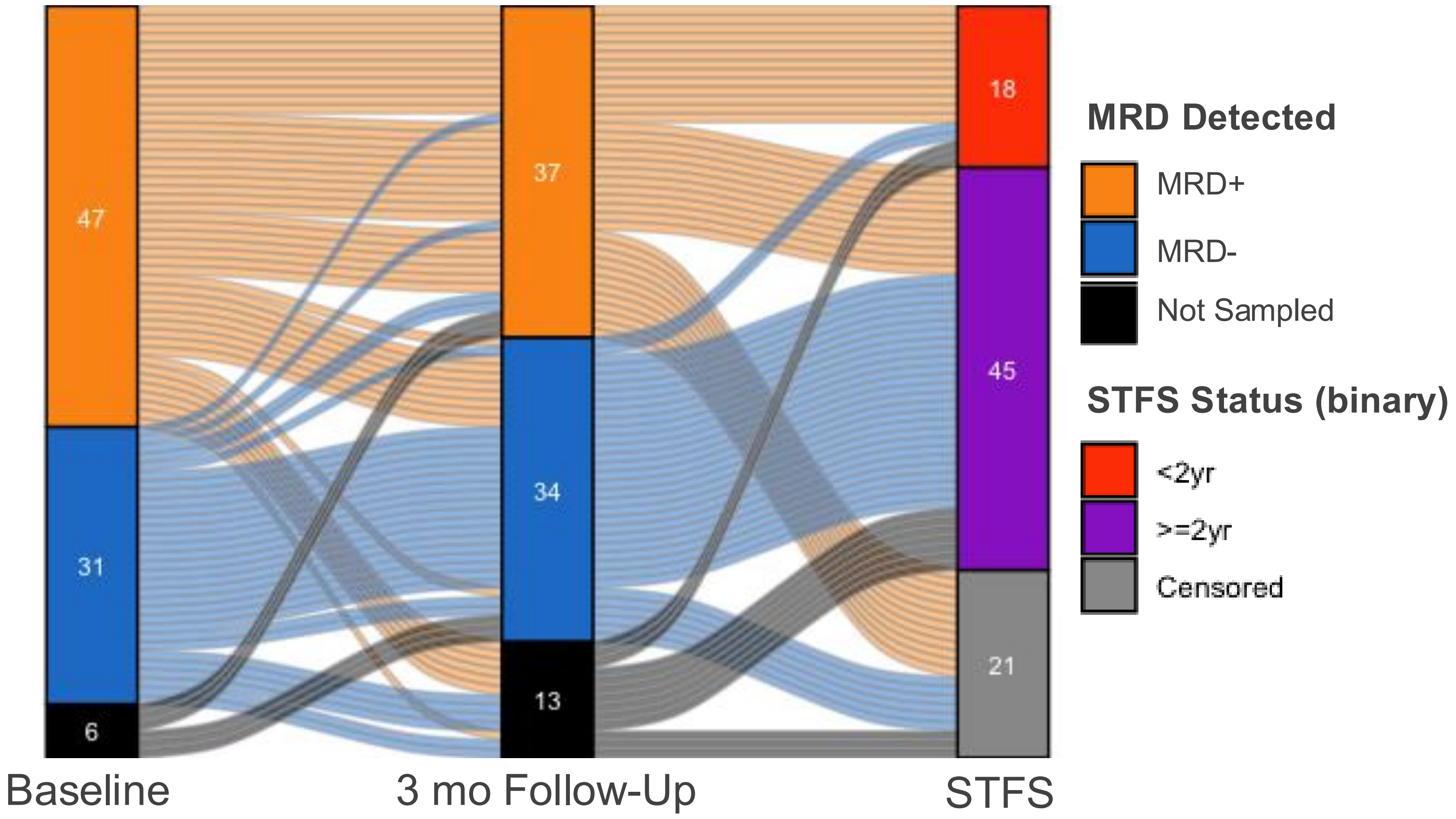
- STFS
  - Success if Median(STFS) > 24 months

Exploratory endpoint:

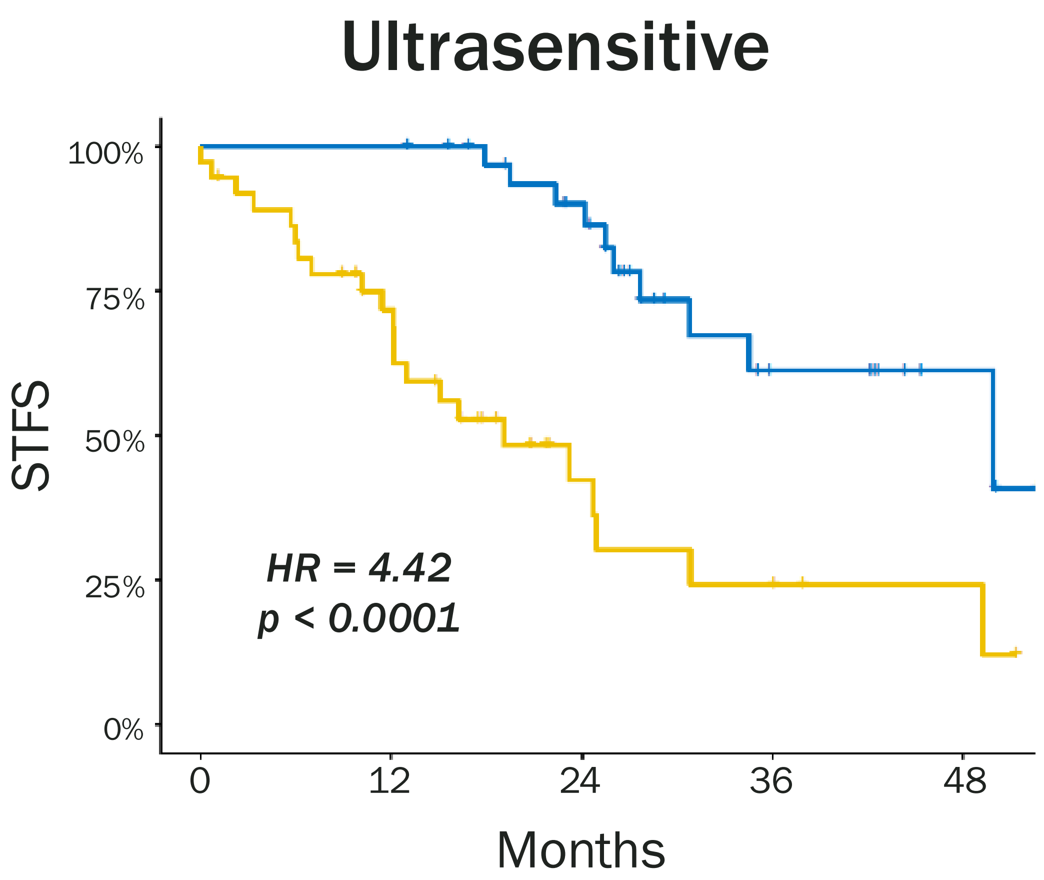
- Ultrasensitive ctDNA testing

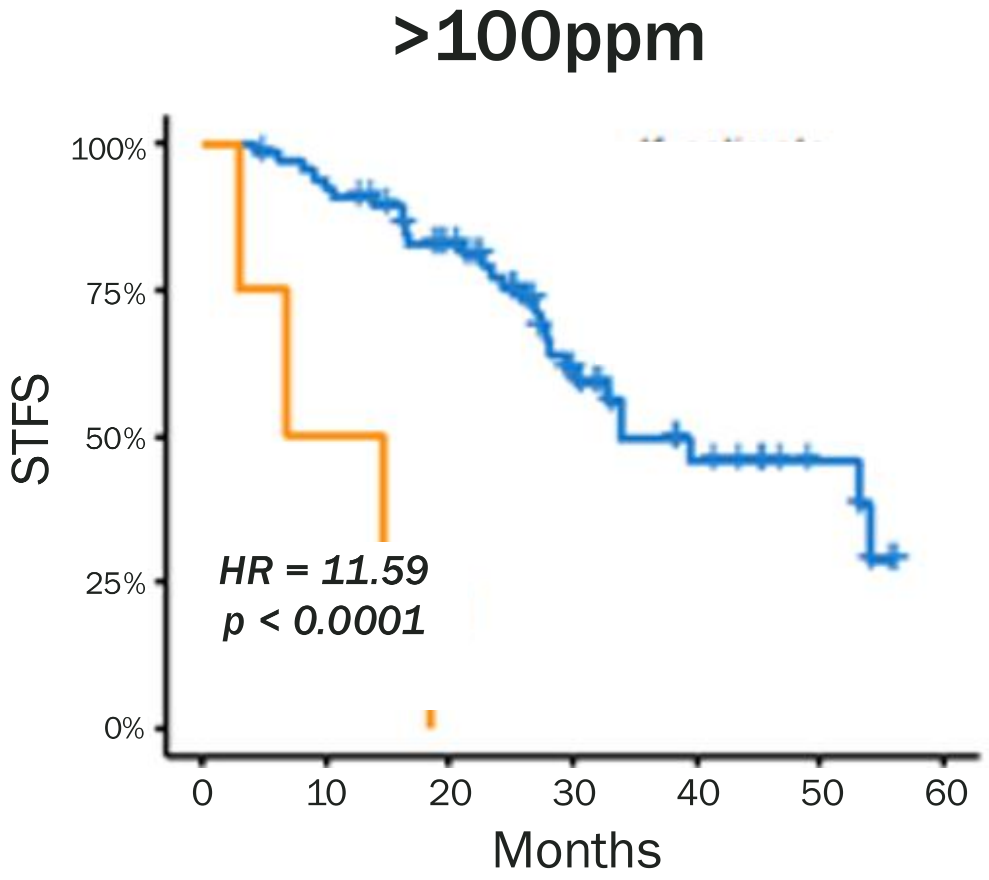
ctDNA Trends in RCC

- Baseline 47 of 78 (60%) patients were MRD+
- At 3 months FU, 37 out of 71 (52%) patients were MRD+
- At 3 months FU, 25% of patients baseline MRD+ converted to MRD–
- Median baseline tumor fraction among MRD+ patients was 22.5 ppm and at 3 months FU was 18.5 ppm



Ultrasensitive MRD finds more patients at elevated risk for progression

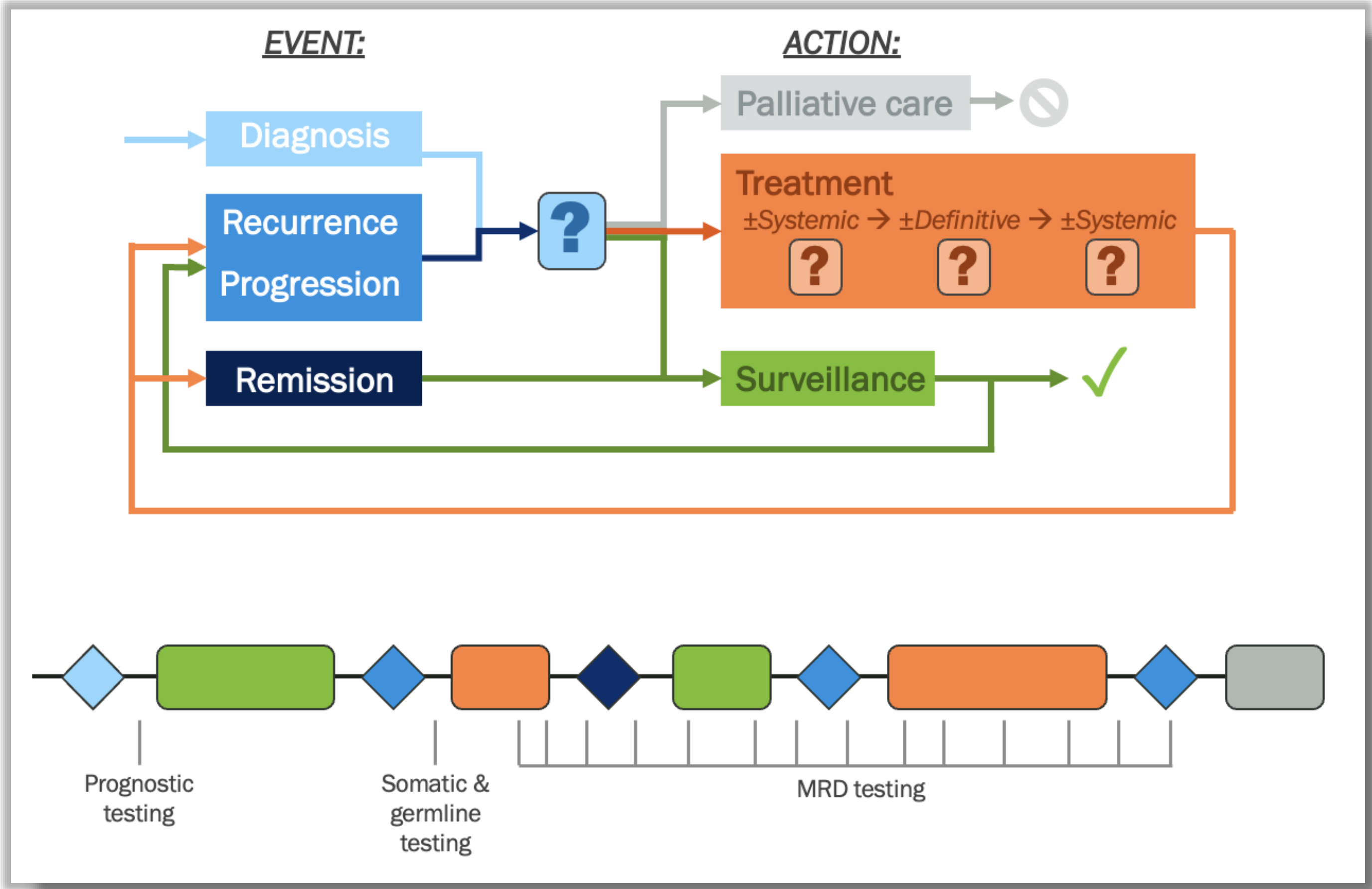




52% MRD+ at t=0

6% MRD+ at t=0

Summary



- Multi-modal diagnostics help to inform and monitor the cancer journey
- Digital pathology and molecular analysis bring independent and synergistic value to prognosis
  - Further validation needed
- GU cancers are amenable to ultrasensitive tumor-informed MRD
  - Tumor fractions are very low but could augment toolbox of biomarkers
  - Further clinical-validity assessment needed

Thank you

NRG/RTOG for the invitation

Myriad Genetics R&D team

PATHOMIQ team

MONSTAR-3 team at NCC Hospital East, Japan

Chad Tang lab at MD Anderson

Myriad genetics®