ASCO Genitourinary Cancers Symposium

Ultra-Sensitive Whole-Genome Sequencing-Based Molecular Residual Disease Detection in Resectable Renal Cell Carcinoma: Preliminary Results from the MONSTAR-SCREEN-3 Study

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Key Takeaway Points/Conclusions

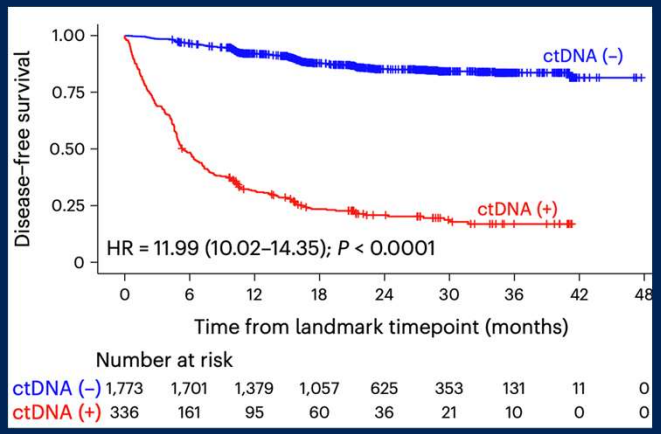
MONSTAR-SCREEN-3 successfully implemented tumor informed WGS-based ctDNA assay for MRD detection across a diverse spectrum of tumor types, including traditionally low ctDNA-shedding tumors; renal cell carcinoma.

- We achieved 100% baseline sensitivity and 11.1% MRD positivity at 1-month post-surgery with 50.0% detected at ultra-sensitive levels (<100 ppm).
- Patients with recurrence had persistently ctDNA-positive after the radical surgery.
- Tumor fraction (ctDNA levels) was associated with stage, size, and nodal status.

Background

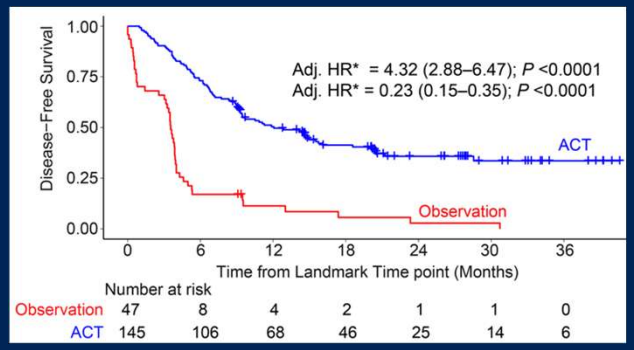
- ctDNA has emerged as a promising biomarker for post-surgical MRD detection.
- The CIRCULATE-Japan GALAXY study demonstrated that ctDNA-based MRD detection significantly correlates with recurrence risk and predicts benefit of adjuvant chemotherapy in patients with resectable colorectal cancer.

Impact of post-4w MRD status

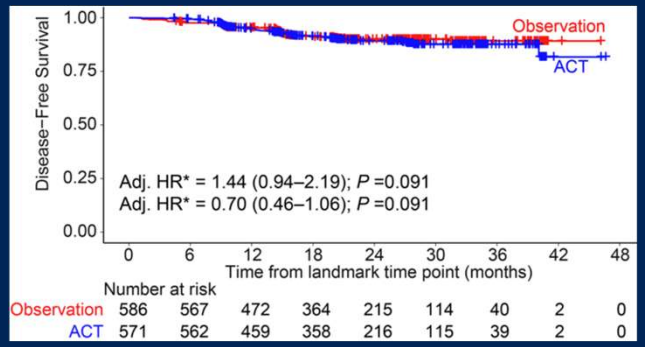


Benefit from adjuvant chemotherapy

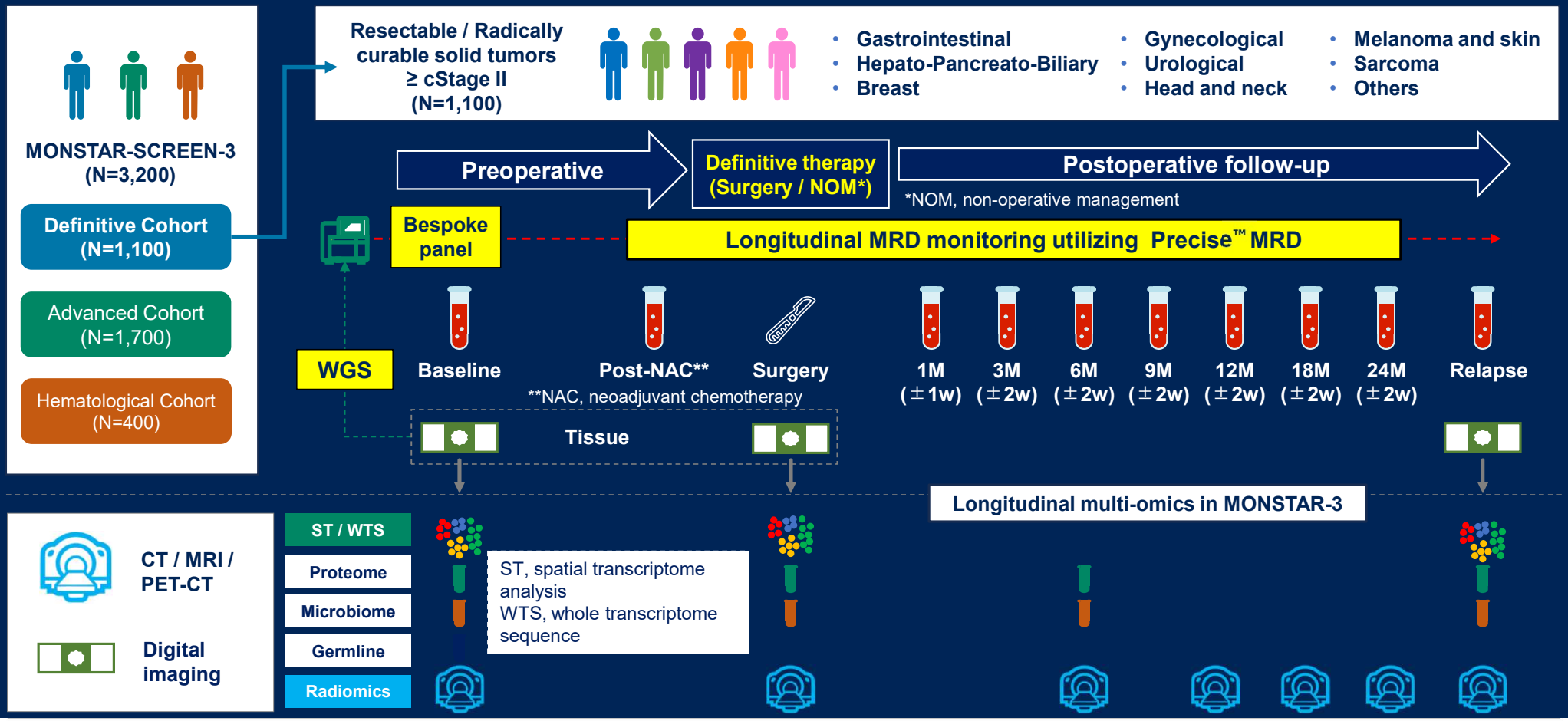
MRD positive



MRD negative



Study Schema of MONSTAR-SCREEN-3



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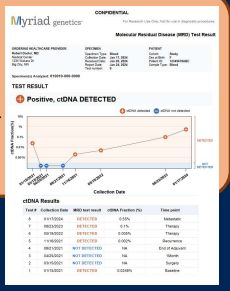
WGS-based ctDNA detection with Precise™ MRD

Tumor-Normal WGS: ≥30X

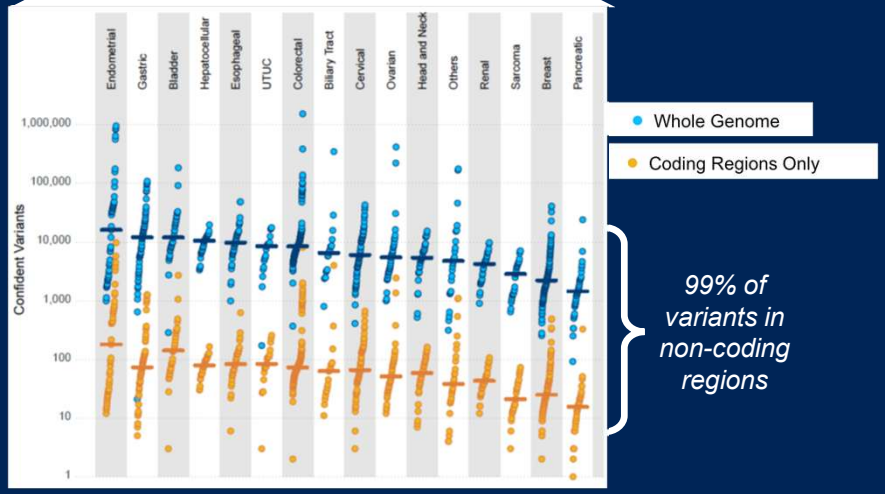
Tumor + Normal → **Somatic Pipeline**: SNVs, indels, CNAs via custom ensemble-based pipeline → ~1,000 somatic sites selected for bespoke panel

Plasma Monitoring

$T_1, T_{2...} T_N$ cfDNA → Bespoke capture panel → **Detection Pipeline**: Ultra-deep NGS with UMI error correction, tumor fraction estimate



WGS identifies 100x more variants than exome



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)

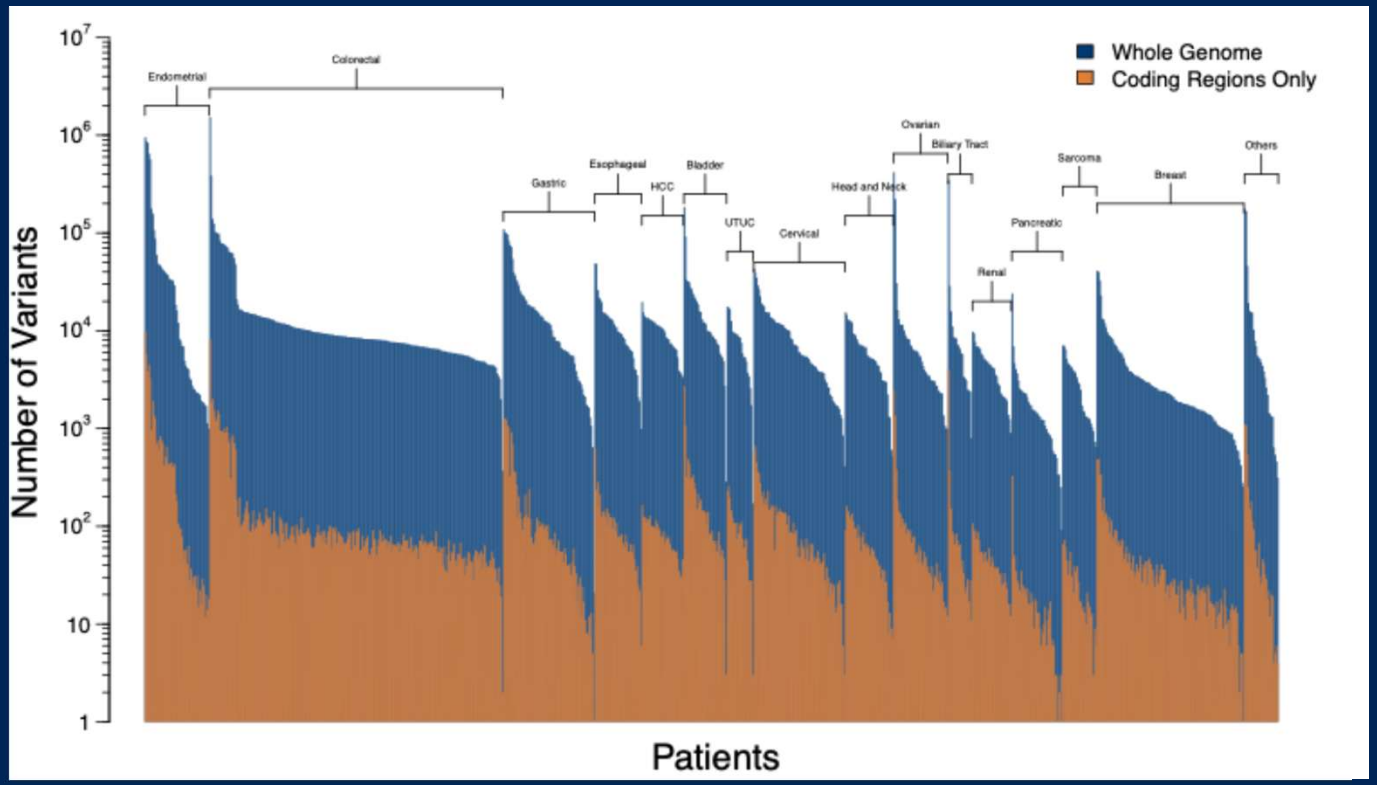
[1]Northcott et al. 2024. Oncotarget 15:200-218
[2]Company web site
[3]Zhao et al. 2024. Mol Diag & Ther. 27:753-768
[4]Kandasamy et al. 2022. J. Clin.Oncol. 40:e13582
[5]Artieri et al. 2020. J. Clin. Oncol. 38:e15549
image adapted from Alexandrov et al., *Nature*, 2013

Patient Characteristics

Baseline characteristics		n=29, n (%)
Age, median (range), years		72 (41-87)
Sex, Male/Female		22 (75.9)/7 (24.1)
Histology	Clear cell	24 (82.8)
	Papillary	2 (6.9)
	Others	3 (10.3)
Surgery performed		29 (100)
Post-surgery characteristics		**n=29, n (%)**
Pathological stage (UICC TNM)	0	0 (0)
	I	3 (10.3)
	II	4 (13.8)
	III	20 (69.0)
	IV	2 (6.9)
T stage	T1	3 (10.3)
	T2	3 (10.3)
	T3	22 (75.9)
	T4	1 (0.3)
N stage	N0	27 (93.1)
	N1	2 (6.9)
Adjuvant therapy		11 (38.0)

Results

- 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

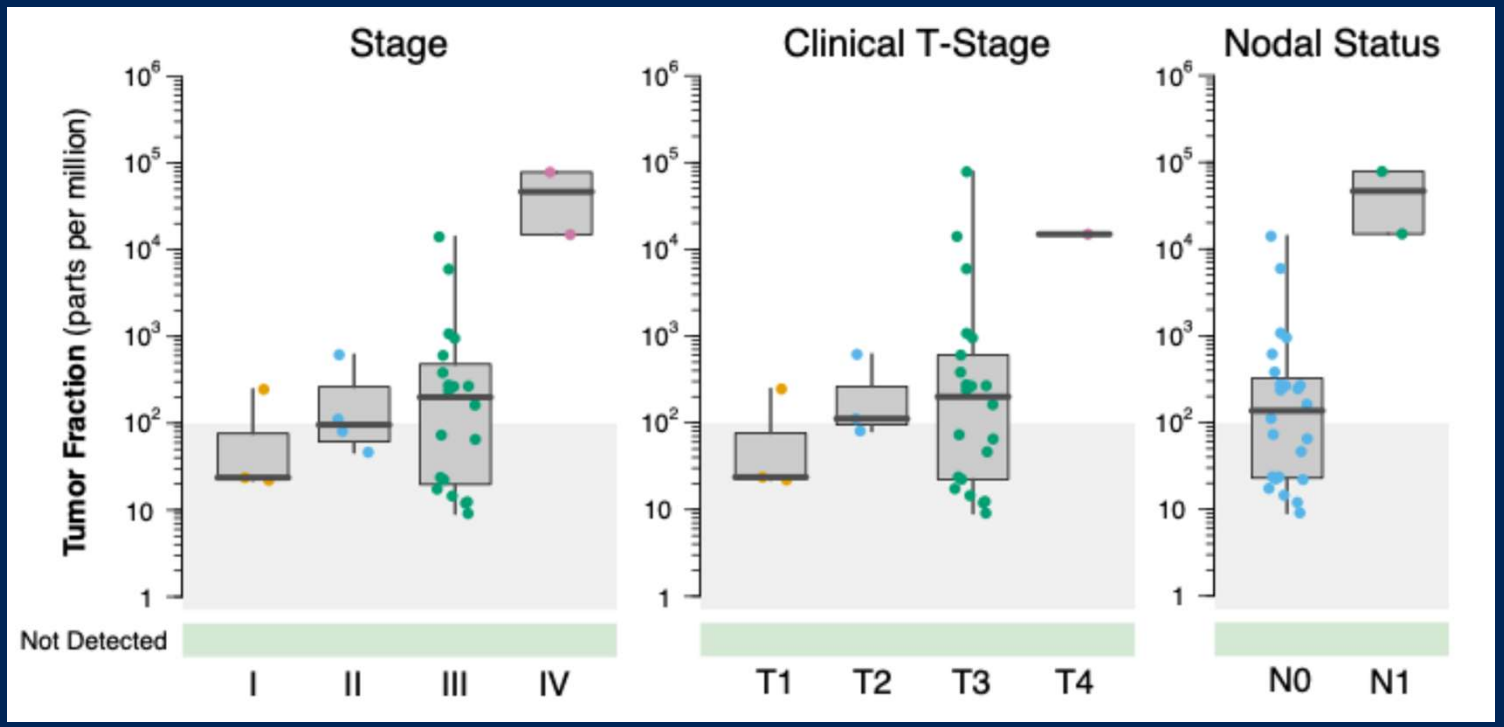
Indication	Panel Size		
	<500*	500-999	1000
Colorectal	1	0	226
Gynecologic	2	3	156
Gastric/Esophageal	2	2	104
Breast	4	10	97
Head & Neck	1	2	36
Bladder	1	0	33
Liver	0	0	31
Renal	1	0	29
Pancreatic	6	8	26
Sarcoma	0	4	23
UTUC	1	0	20
Biliary Tract	0	1	17
Other	4	1	26

*Insufficient variants for ctDNA analysis

WGS panel-creation success rate = 97.3%

Baseline ctDNA tumor fraction

- 100% baseline detection (range 9.1- 78,177 PPM), 13/29 in the ultra-sensitive range <100 PPM
- ctDNA levels was associated with stage, size, and nodal status



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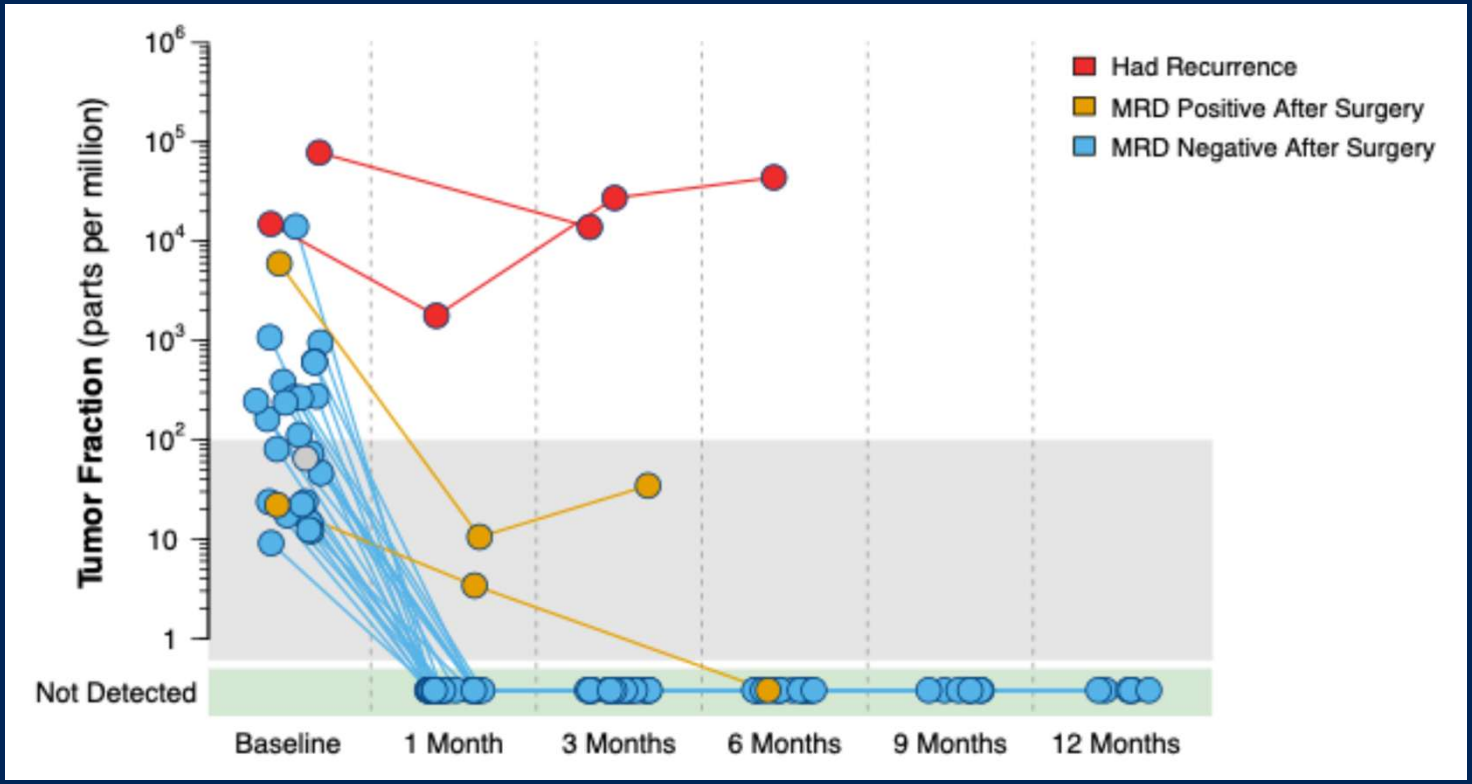
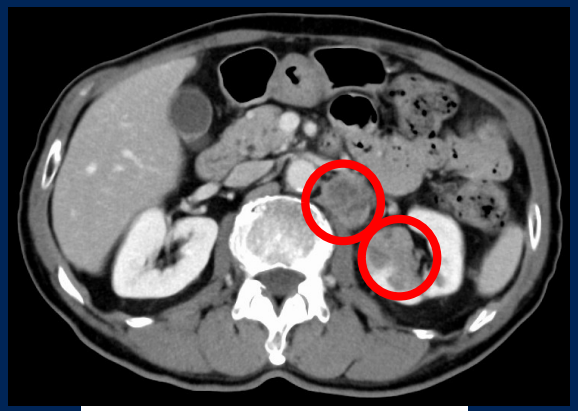
ctDNA stratifies patients at risk of recurrence

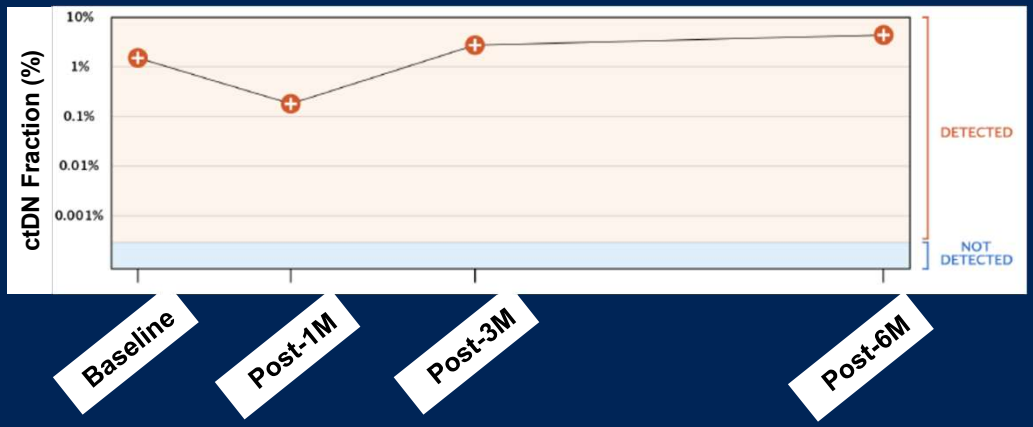
- 25 patients became MRD negative after surgery and have remained negative
- 4 patients were MRD positive after surgery and 2 have recurred clinically



Case study of RCC patient with recurrence



[Massive primary tumor]

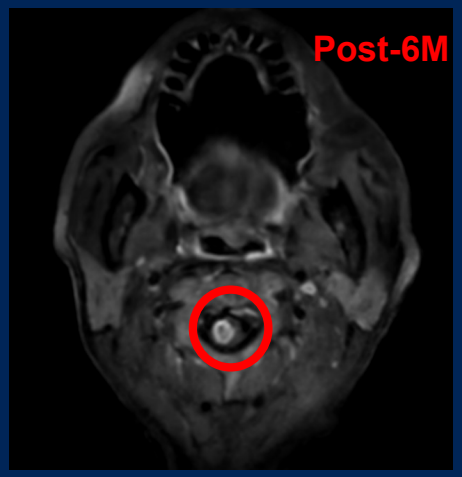


Clinical stage: cT3N1M0

↓

Treated with up-front radical surgery with curative intent (pT4N1M0)

- **Adjuvant pembrolizumab**
- **ctDNA testing was persistently positive**
- **Post-6M, the patient developed brain metastasis**



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Conclusions

- MONSTAR-SCREEN-3 successfully implemented tumor informed WGS-based ctDNA assay for MRD detection across a diverse spectrum of tumor types, including renal cell carcinoma.
- We demonstrated robust detection capabilities with 100% baseline sensitivity and 11.1% MRD positivity at 1-month post-surgery, with 50.0% of positive cases detected at ultra-sensitive levels.
- Patients with recurrence had persistently ctDNA-positive after the radical surgery. We will carefully follow up patients with ctDNA-positive at ultra-sensitive levels.
- ctDNA levels were associated with stage, size, and nodal status.
- Additional validation with extended follow-up and an expanded cohort is necessary to confirm these promising initial findings.

Acknowledgements

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Participating institutions

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Myriad Genetics. Inc.

Jeff Jasper, Dale Muzzey, Katie Johansen Taber, Greg Hogan, Matt LaBella, Ravi Patel, Siming Zhang, Myriad R&D and Tech Teams

Lay summary

What We Did and What We Found

We developed a highly sensitive blood test that can detect tiny amounts of cancer DNA in the blood after surgery across many different types of cancer, including renal cell carcinoma.

The results of this ongoing trial show that the test successfully detected cancer DNA in all patients with known to have cancer before treatment. After surgery, about 14% patients still had detectable cancer DNA in their blood, often at extremely low levels that would be missed by standard tests.

Patients who had cancer DNA in their blood one month after surgery were much more likely to have a cancer recurrence later.

In the future, this approach may allow doctors to personalize cancer care by determining which patients truly need additional therapy after surgery and which specific treatments might work best for each individual patient, advancing precision medicine in cancer care.