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Ultrasensitive MRD improves detection in resectable stage I NSCLC

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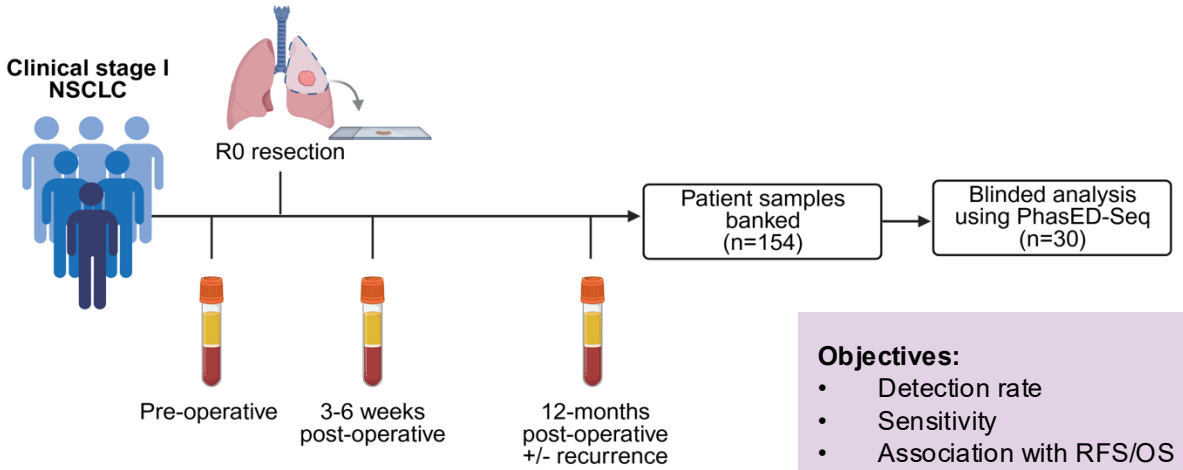
Suboptimal detection rates in stage I NSCLC using first-generation MRD assay

- Plasma ctDNA is a valuable tool for recurrence risk stratification in resected NSCLC
- First generation tumour-informed ctDNA MRD assays have suboptimal clinical sensitivity, particularly in stage I lung adenocarcinoma (LUAD) patients
- Our experience with a first generation MRD assay in clinical stage I NSCLC demonstrated a pre-op detection rate of 22.7% and a post-op detection rate of 2%[1]
- These findings highlight the need for **ultrasensitive ctDNA-MRD assays** to improve early detection and guide treatment decisions in stage I NSCLC



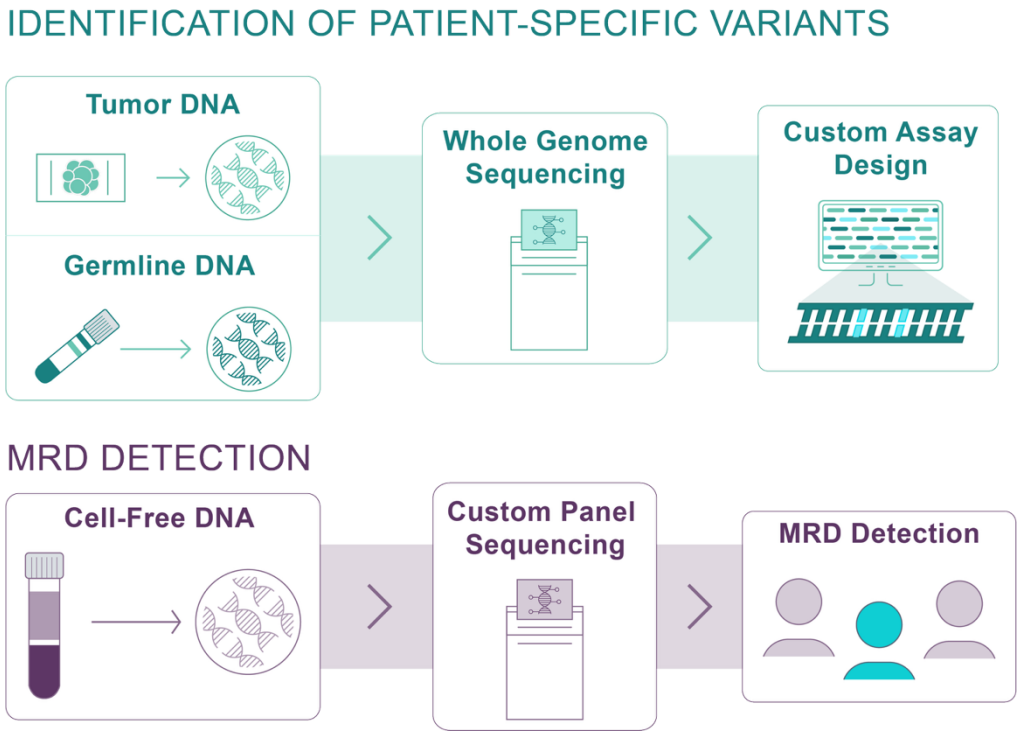
Objectives:
- Detection rate
- Sensitivity
- Association with RFS/OS

NCT05254782

[1]Khan et al. *ASCO* 2024

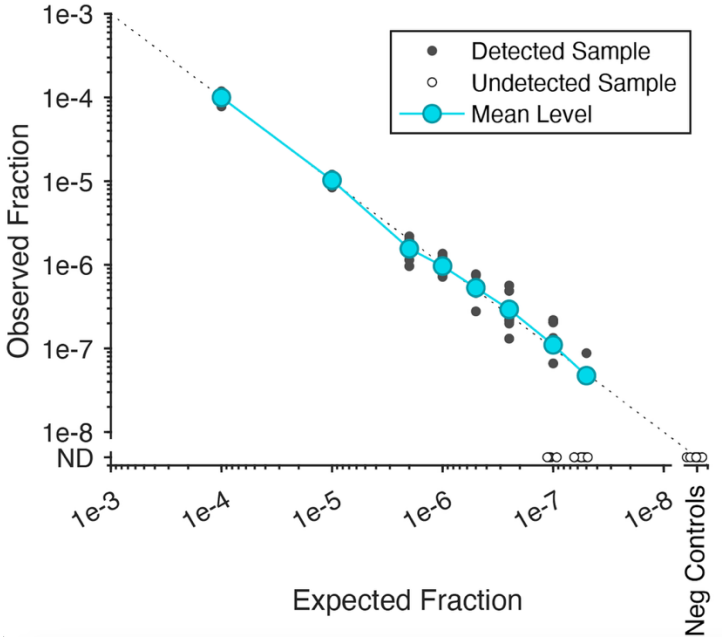
Analysis of banked samples from resected clinical stage I NSCLC with an ultrasensitive assay built on PhasED-Seq

ctDNA-MRD Test Workflow



Analytical LOD95* = **0.3 parts per million** (3×10^{-7})

- This ctDNA-MRD test includes up to 5,000 patient-specific loci:
  - Phased variants (e.g., PhasED-Seq)
  - Additional alterations with low error profiles (e.g., selected SNVs) to maximize sensitivity

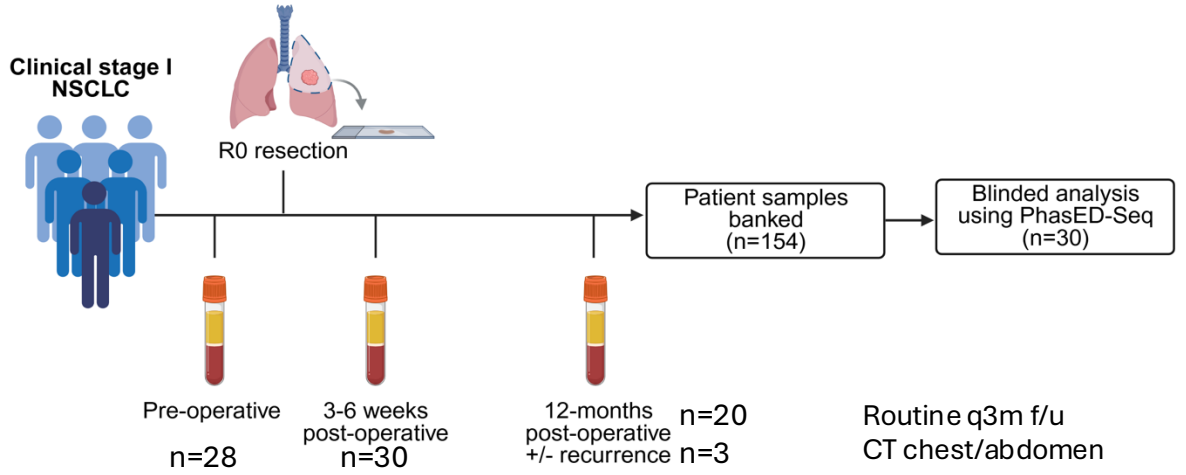


*The LOD95 was determined in an analytical study using contrived cfDNA-into-cfDNA samples in a limited dilution series and modeled by Probit regression

Cabel et al. *ESMO* 2024

Cohort demographics & methods

Characteristic		N=30 (%)
Clinical Stage	I	30 (100%)
Pathological Stage	IA	9 (30)
	IB	7 (23.3)
	II	8 (26.7)
	III	5 (16.7)
	IV	1 (3.3)
Histology	Adenocarcinoma	25 (83.3)
	Squamous	3 (10)
	Other	2 (6.7)
Smoking status	Never	12 (40)
	Former	15 (50)
	Current	3 (10)
Sex	Female	23 (76.7)
Median age (range)		67 (38-85)
Adjuvant therapy		17 (57.0)



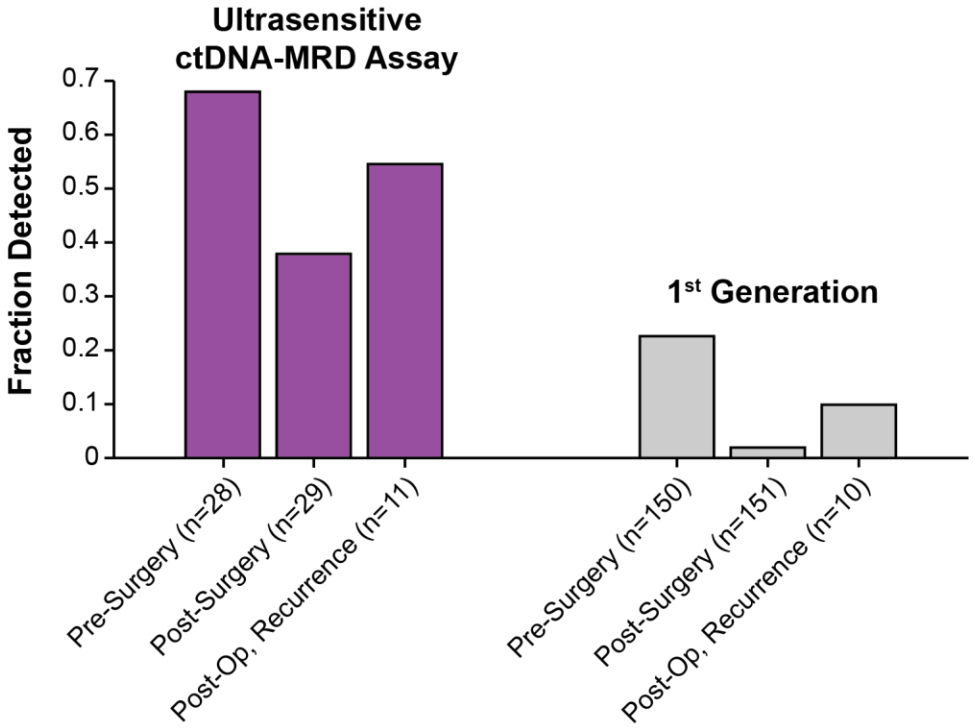
- Panels designed starting from WGS and selecting up to 5000 targets, focused on phased variants
  - 100% success in panel design (30/30)
  - Median 4055 variants tracked
- cfDNA input for library preparation: median 18.5ng (8.5 - 48.0)
  - Plasma volume: median 4.9mL (3.8 – 6.0)

Detection of post-surgical ctDNA MRD in NSCLC patients with relapse using ultrasensitive assay

- This cohort (n=30) was derived from the ctDNA-Lung-DETECT study which used a 1st generation MRD assay in patients with Stage I NSCLC reported at ASCO 2024[1]

- **In this selected subgroup (n=30), the PhasED-Seq-based assay demonstrated ctDNA detection in Stage I NSCLC*:**
  - **Pre-operative detection 68% (n=28)**
  - **Post-operative detection 38% (n=29)**
  - **Post-operative MRD detected in 55% of relapsed cases (n=11)**

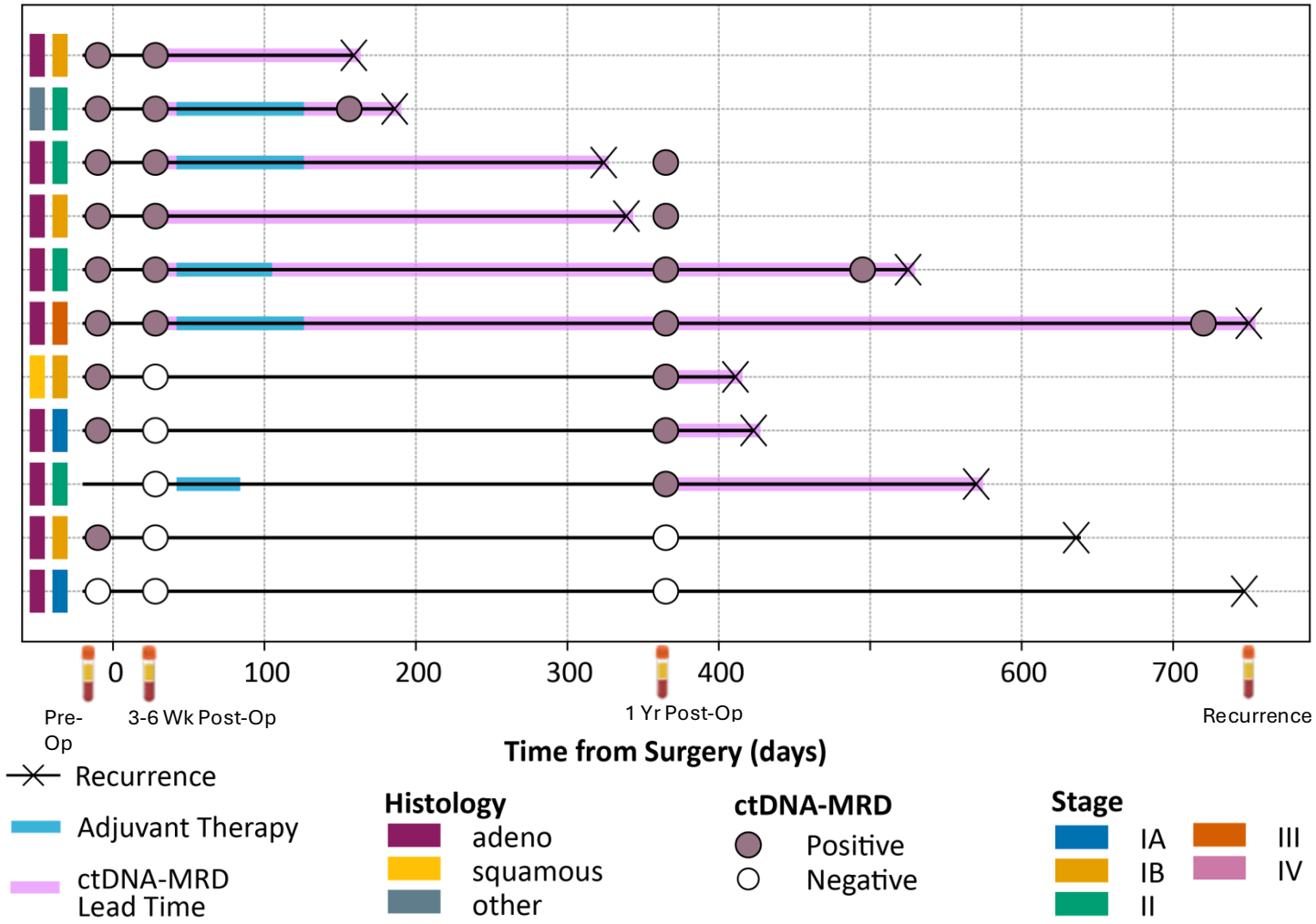
- **Detectable MRD post-operatively was associated with adverse RFS**
  - **Post-operative landmark: HR = 3.14, P = 0.0425**
  - **1-year post-op landmark: HR = 8.20, P = 0.0001**



* This is not a direct patient level comparison.

[1]Khan et al. *ASCO* 2024

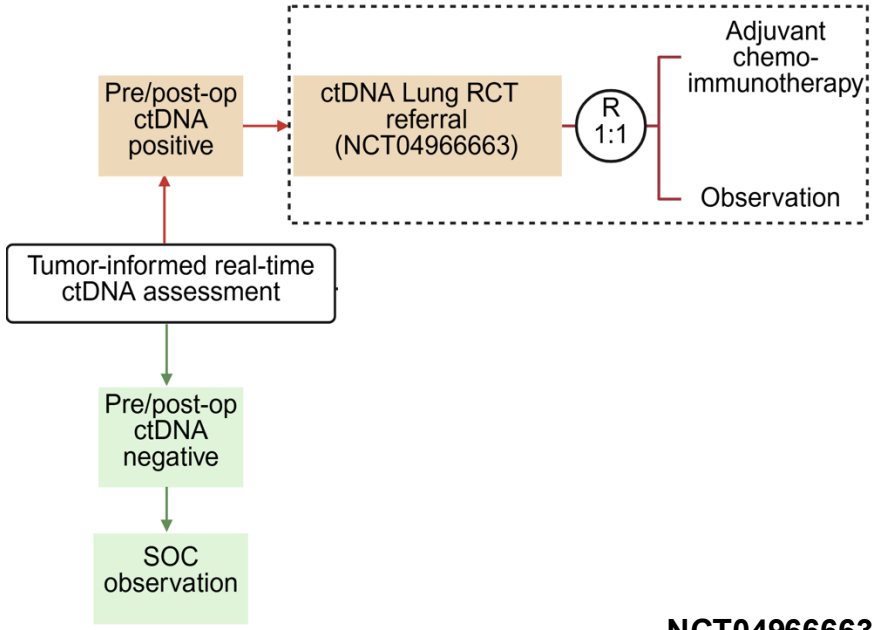
Post-operative ctDNA MRD detection in cases with relapse



- 11 cases with recurrence assessed
- In patients with MRD detected at the post-operative landmark, the median lead-time to recurrence was 10 months
- 11/12 (92%) of samples collected within 12 months preceding relapse had MRD detected

Concluding remarks

- Ultrasensitive ctDNA-MRD detection using a WGS tumour-informed assay demonstrated high rates of MRD detection in patients with clinical stage I NSCLC
- In the absence of a direct comparison, this is higher than a previous report for a larger cohort using a first-generation WES-based assay[1]
- ctDNA-MRD detection was associated with RFS and provided clinically meaningful lead-times
- These results support exploring an ultrasensitive MRD-guided approach in stage I NSCLC to escalate adjuvant therapy



NCT04966663

[1]Khan et al. *ASCO* 2024

Thank You

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