Biopsia liquida: stato dell'arte e nuove frontiere

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DISCLOSURES

- **Personal financial interests (speaker's fee and/or advisory boards):** Astrazeneca, Biocartis, Daiichi Sankyo, GSK, Incyte, MERCK, MSD, Roche, Servier, Sophia Genetics, Thermofisher

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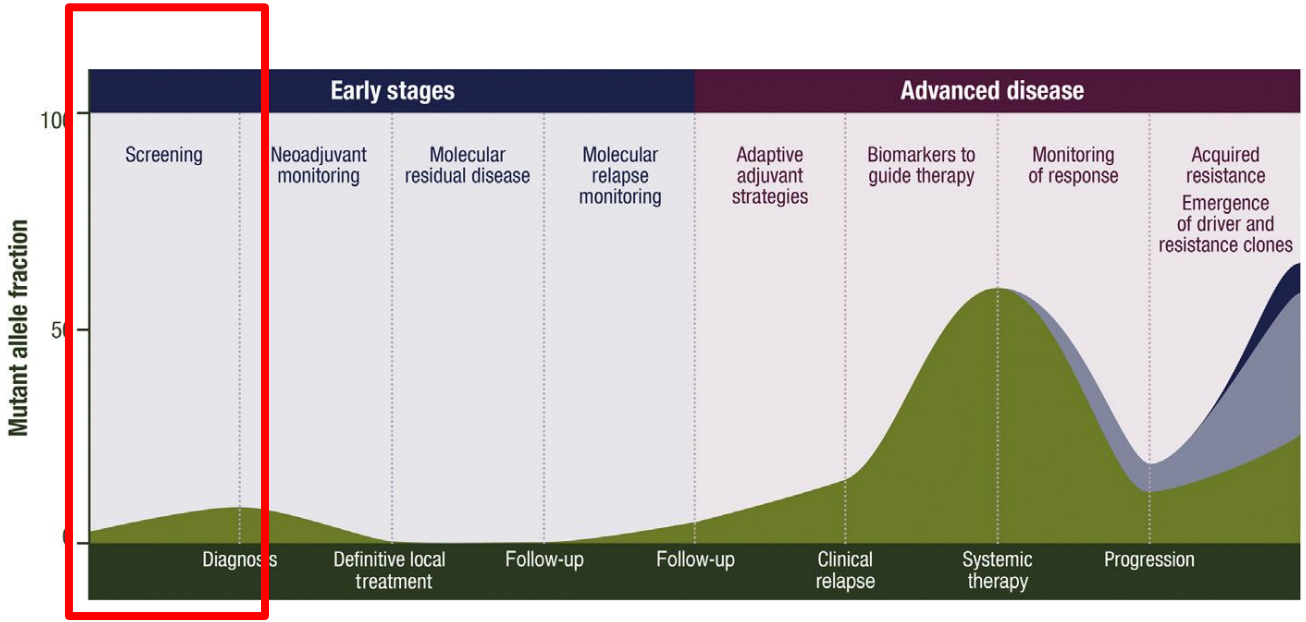
Clinical applications of ctDNA assays for patients with cancer and expected DNA levels in different phases of the disease



Pascual et al Ann Oncol 2022

Prenatal cfDNA Sequencing and Incidental Detection of Maternal Cancer

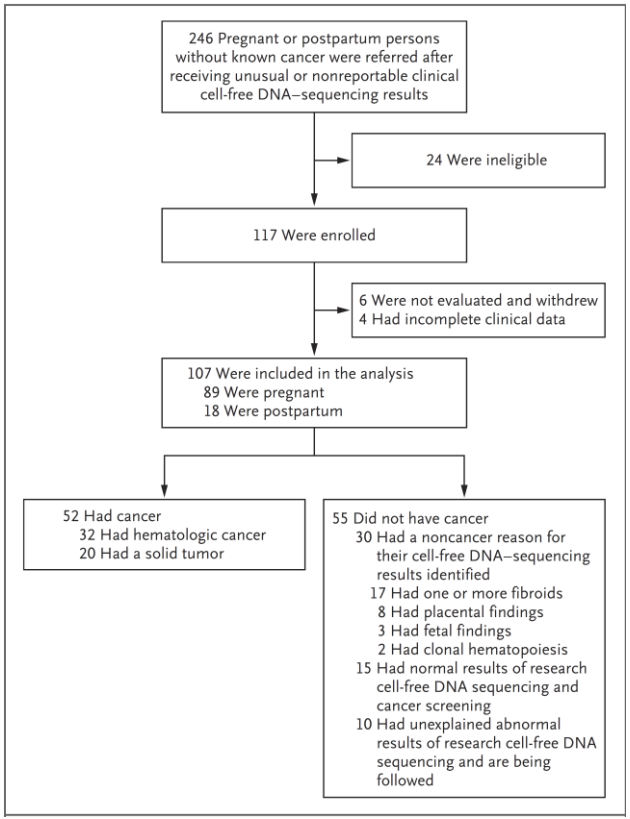
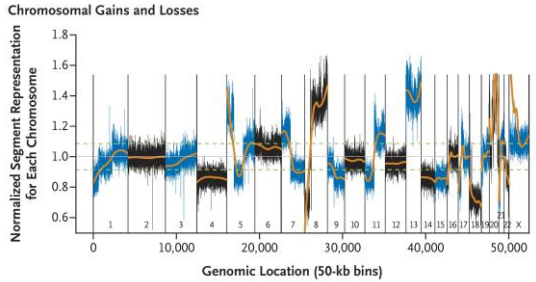


Table 2. Test Performance.*

Clinical Test	Whole-Body MRI (N=101)†	Serum Tumor Markers (N=103)‡	CEA, CA 15-3, CA 19-9 (N=103)§	Fecal Occult Blood (N=80)¶	Physical Examination (N=107)
True positive — no.	48	34	24	4	9
True negative — no.	46	39	48	71	55
False positive — no.	6	14	5	1	0
False negative — no.	1	16	26	4	43
Area under the ROC curve — % (95% CI)	93.2 (88.4–98.0)	70.8 (61.9–79.7)	69.3 (61.2–77.3)	74.3 (55.7–92.9)	58.7 (53.5–63.8)
Sensitivity — % (95% CI)	98.0 (89.1–99.9)	68.0 (53.3–80.5)	48.0 (33.7–62.6)	50.0 (15.7–84.3)	17.3 (8.2–30.3)
Specificity — % (95% CI)	88.5 (76.6–95.6)	73.6 (59.7–84.7)	90.6 (79.3–96.9)	98.6 (92.5–100.0)	100.0 (93.5–100.0)
Positive predictive value — % (95% CI)	88.9 (77.4–95.8)	70.8 (55.9–83.0)	82.8 (64.2–94.6)	80.0 (28.4–99.5)	100.0 (66.4–100.0)
Negative predictive value — % (95% CI)	97.9 (88.7–99.9)	70.9 (57.1–82.4)	64.9 (52.9–75.6)	94.7 (86.9–98.5)	56.1 (45.7–66.1)



Turriff NEJM 2024

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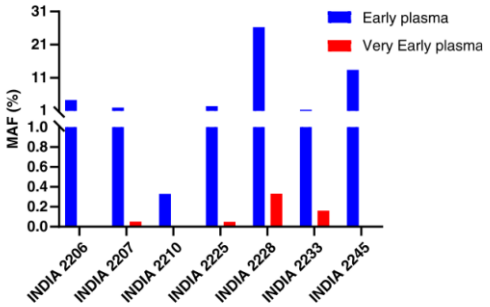
Detection of cancer three years prior to diagnosis using cfDNA

Table 1. Summary of participants in whom Early Plasma sample scored positively.

Participant	Cancer	Stage	Days to cancer diagnosis, Early plasma	MAF, Early plasma	Days to cancer diagnosis, Very Early plasma	MAF, Very Early plasma	Ratio of MAF in Early plasma to Very Early plasma
INDIA 2206	Rectal	III	96	4.31%	1,208	Mutation not detectable	Not applicable
INDIA 2207	Liver	Unknown	84	2.04%	1,230	0.05%	39.7
INDIA 2210	Colon	II	104	0.33%	1,270	Mutation not detectable	Not applicable
INDIA 2215	Pancreatic	Unknown	20	3.37%	Sample not available	Sample not available	Sample not available
INDIA 2225	Colon	Unknown	30	2.50%	1,117	0.05%	50.0
INDIA 2228	Lung	Unknown	112	26.26%	1,197	0.33%	79.2
INDIA 2233	Colon	I	12	1.39%	1,117	0.16%	8.6
INDIA 2245	Breast	Unknown	47	13.40%	1,139	Mutation not detectable	Not applicable



Wang Cancer Discov 2025

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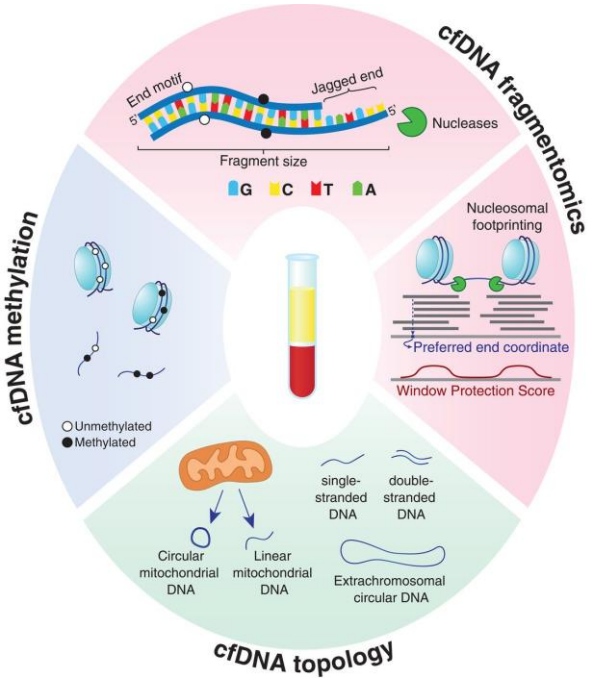
Spectrum of non-genetic signatures identified among circulating DNA molecules

- Tissue and cancer specific differentially methylated regions (DMRs) are potential biomarkers for ctDNA detection
- DNA methylation profiles differ between cells of differing tissues of origin, thus providing information on the organ site of the cancer



- The ctDNA has a shorter median length as compared with DNA from non-transformed cells (150 bp vs 166 bp), reflecting chromosomal, genomic and epigenetic alterations of cancer cells
- DNA fragmentation is a non-random process: specific sequences are found at the end of plasma DNA fragments (preferred ends)

Dennis Lo Science 2021

A Cell-free DNA Blood-Based Test for CRC Screening

Table 1. Demographic Characteristics of the Participants.*

Characteristic	Enrolled Cohort (N=22,877)	Clinical Validation Cohort (N=10,258)	Evaluable Participants (N=7861)
Age			
Mean — yr	60.8±8.2	60.6±9.1	60.3±9.1
Median (range) — yr	62 (22–90)	60 (45–90)	60 (45–84)
Age group — no. (%)			
45–49 yr	1,881 (8.2)	776 (7.6)	640 (8.1)
50–59 yr	6,414 (28.0)	3877 (37.8)	3055 (38.9)
60–69 yr	11,179 (48.9)	3284 (32.0)	2440 (31.0)
70–79 yr	3,237 (14.1)	2226 (21.7)	1670 (21.2)
≥80 yr	144 (0.6)	95 (0.9)	56 (0.7)
Missing data or other†	22 (0.1)	0	0
Sex — no. (%)			
Female	12,284 (53.7)	5493 (53.5)	4218 (53.7)
Male	10,580 (46.2)	4765 (46.5)	3643 (46.3)
Missing data	13 (0.1)	0	0
Race or ethnic group — no. (%)‡			
American Indian or Alaska Native	53 (0.2)	19 (0.2)	14 (0.2)
Asian	1,867 (8.2)	685 (6.7)	560 (7.1)
Black or African American	2,915 (12.7)	1353 (13.2)	931 (11.8)
Native Hawaiian or other Pacific Islander	50 (0.2)	24 (0.2)	19 (0.2)
White	17,424 (76.2)	7939 (77.4)	6167 (78.5)
Other	441 (1.9)	189 (1.8)	137 (1.7)
Multiple	65 (0.3)	32 (0.3)	23 (0.3)
Missing data	62 (0.3)	17 (0.2)	10 (0.1)
Hispanic or Latino ethnic group — no. (%)‡			
Yes	3,301 (14.4)	1561 (15.2)	1044 (13.3)
No	19,447 (85.0)	8643 (84.3)	6779 (86.2)
Missing data	129 (0.6)	54 (0.5)	38 (0.5)

Table 2. Sensitivity and Specificity of the Cell-free DNA (cfDNA) Blood-Based Test for the Most Advanced Findings on Colonoscopy.*

Variable	Most Advanced Finding on Colonoscopy	cfDNA Blood-Based Test	
		Positive Test	Sensitivity (95% CI)
	no.	*no.*	%
Colorectal cancer			
Any	65	54	83.1 (72.2–90.3)
Stage I, II, or III*	48	42	87.5 (75.3–94.1)
Advanced precancerous lesions†	1116	147	13.2 (11.3–15.3)
			Specificity (95% CI)
Nonadvanced adenomas, nonneoplastic findings, and negative colonoscopy	6680	698	89.6 (88.8–90.3)
Nonneoplastic findings and negative colonoscopy	4514	457	89.9 (89.0–90.7)

The test under assessment is a cfDNA blood based assay that interrogates:

- ✓ **cfDNA genomic alterations**
- ✓ **aberrant methylation status**
- ✓ **fragmentomic patterns**

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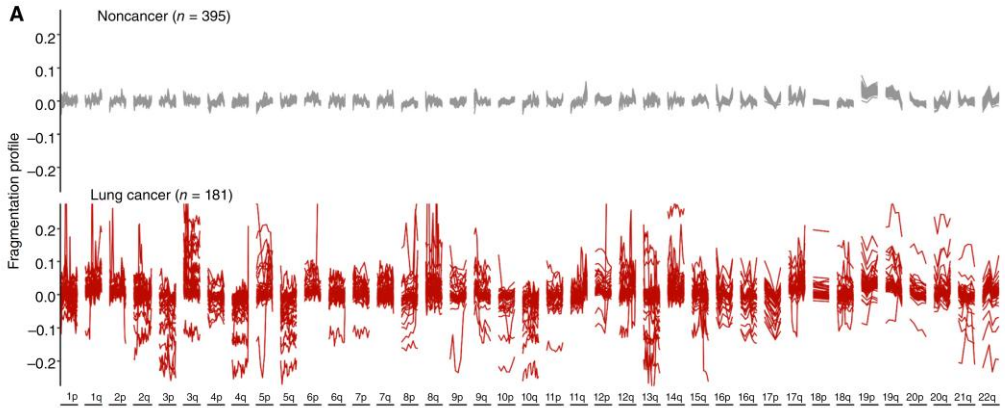
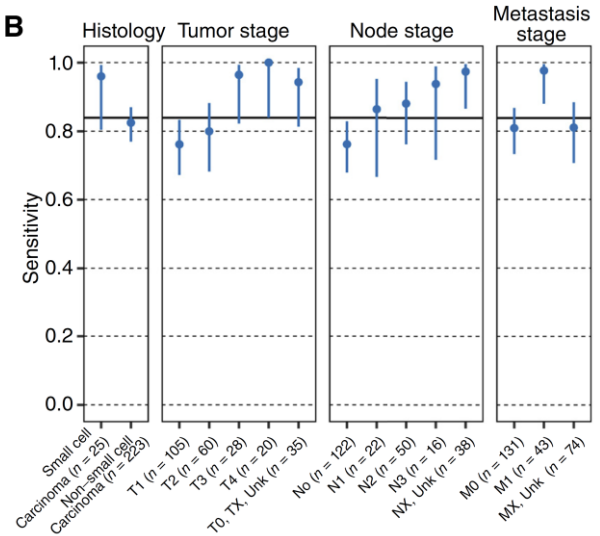
Chung NEJM 2024

Cell-Free DNA Fragmentome Assay for of Lung Cancer Early Detection





Mazzone Cancer Discov 2026

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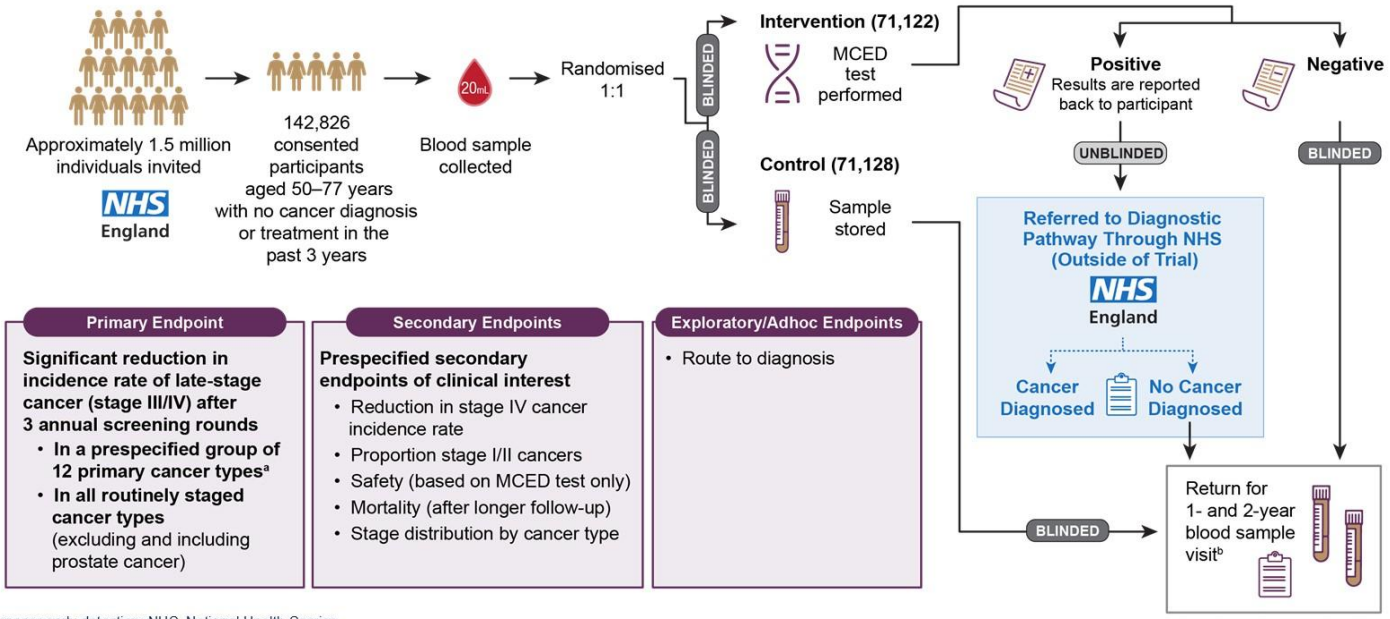
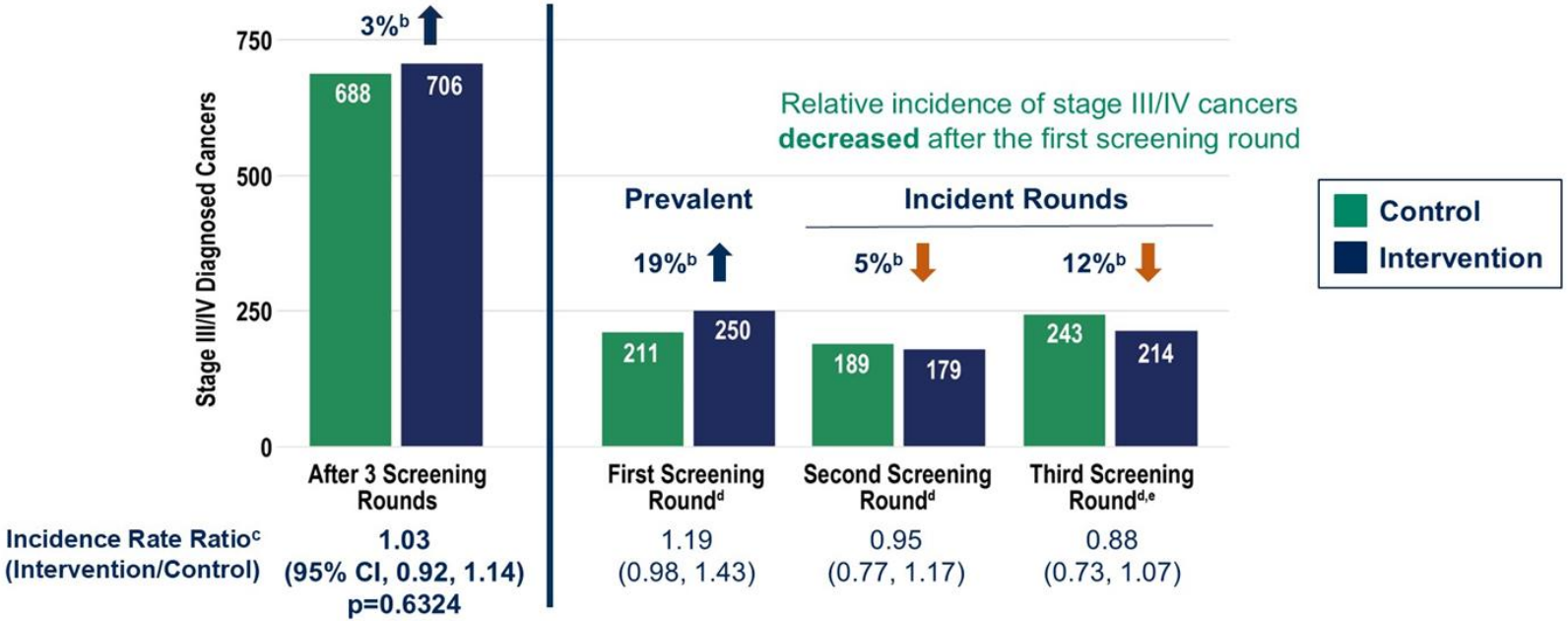
NHS-Galleri Is the Largest, First, and Only Randomised Controlled Clinical Utility Trial of an MCED Test to Date



MCED, multi-cancer early detection; NHS, National Health Service.
[a]Lung, head & neck, colorectal, pancreas, myeloma/plasma cell neoplasm, liver/bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder. [b]Participants who were diagnosed with cancer were not required to return for blood samples.
Sasieni P, et al. *Cancers (Basel)*. 2022;14(19):4818.

Primary Endpoint | 12 Prespecified Cancer Types[a]

No Significant Reduction in Stage III/IV Cancers Observed in the Intervention Arm With the Current Follow-Up Window

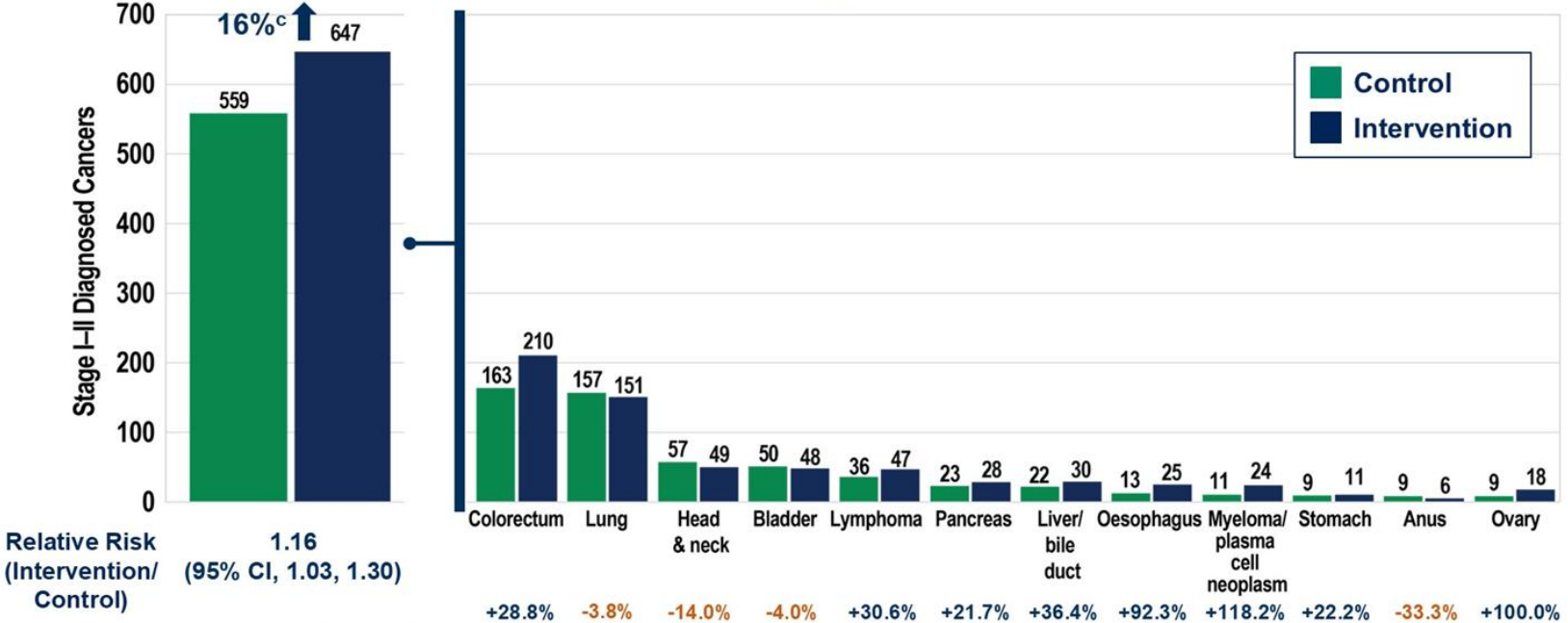


[a]12 prespecified cancer types were lung, head & neck, colorectal, pancreas, myeloma/plasma cell neoplasm, liver/bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder. [b]Percent difference was calculated with incidence rate ratios as part of the prespecified analysis, not raw cancer counts (graphed in bar charts for illustrative purposes). [c]Incidence rate ratio compares the frequency of cancer diagnoses between the intervention and control arm and accounts for different lengths of follow-up time. [d]Not all participants attended every screening round; thus, some cancers were not assigned a screening round. [e]Follow-up time was variable in the third screening round and ranged from 12 to 22 months.

PRESENTED BY: Charles Swanton, MBPhD

Descriptive Summary | 12 Prespecified Cancer Types[a]

Shift to Stage I-II Cancer[b] Detection With MCED Screening Added to SOC After 3 Screening Rounds



MCED, multi-cancer early detection; SOC, standard-of-care. [a]12 prespecified cancer types were lung, head & neck, colorectal, pancreas, myeloma/plasma cell neoplasm, liver/bile duct, stomach, esophagus, anus, lymphoma, ovary, and bladder. [b]Per highest stage. [c]Percent difference was calculated with relative risk as part of the prespecified analysis, not raw cancer counts (graphed in bar charts for illustrative purposes).

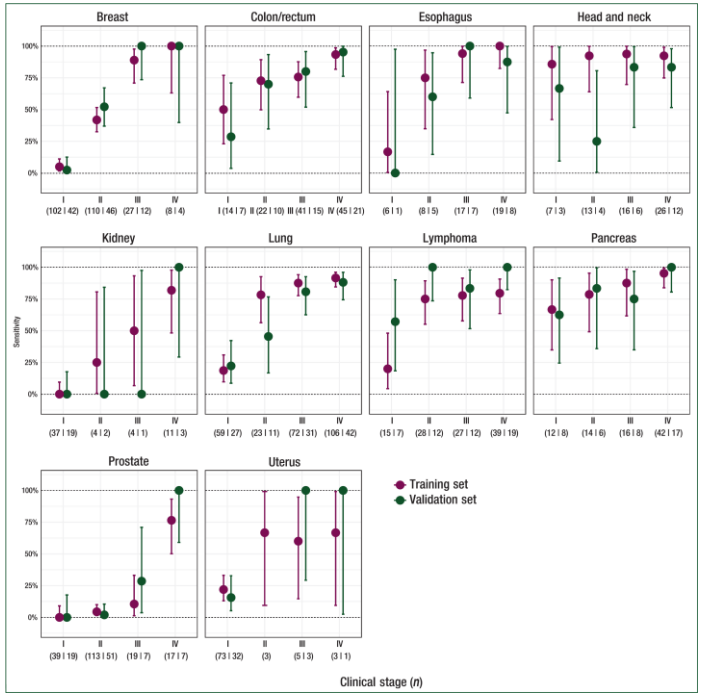
PRESENTED BY: Charles Swanton, MBPhD

Distribution of Stage I/II Cancers Detected After 3 Years (12 prespecified cancer types)

Cancer Type	Control	Intervention
Colorectum	163	210
Lung	157	151
Head & neck	57	49
Bladder	50	48
Lymphoma	36	47
Pancreas	23	28
Liver/bile duct	22	30
Oesophagus	13	25
Myeloma/plasma cell neoplasm	11	24
Stomach	9	11
Anus	9	6
Ovary	9	18
TOTAL	**559**	**647**

Swanton et al, presentation at ASCO Annual Meeting 2026, Chicago, IL

Multi-cancer detection and localization using methylation signatures in cfDNA



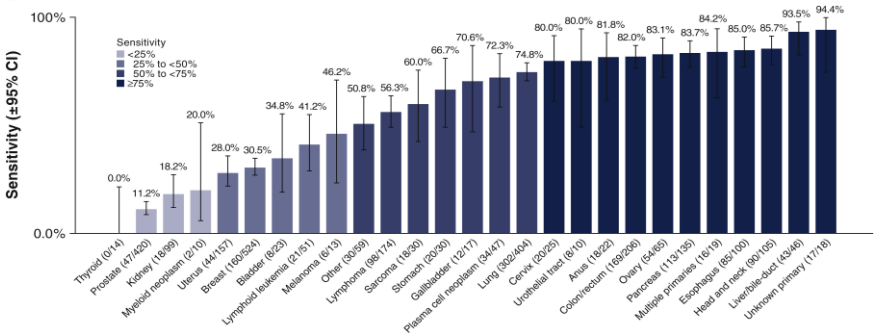
Liu Ann Oncol 2020

A

	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

Two-sided 95% Wilson confidence intervals were calculated.

B



Klein Ann Oncol 2021

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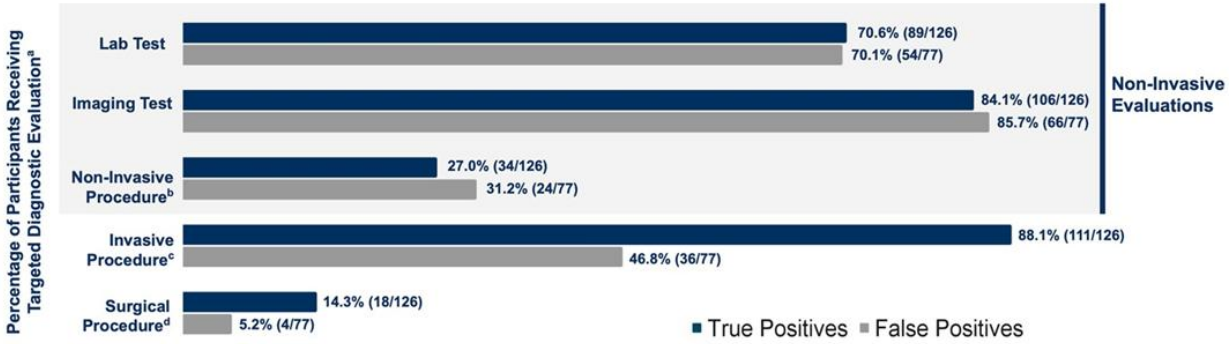
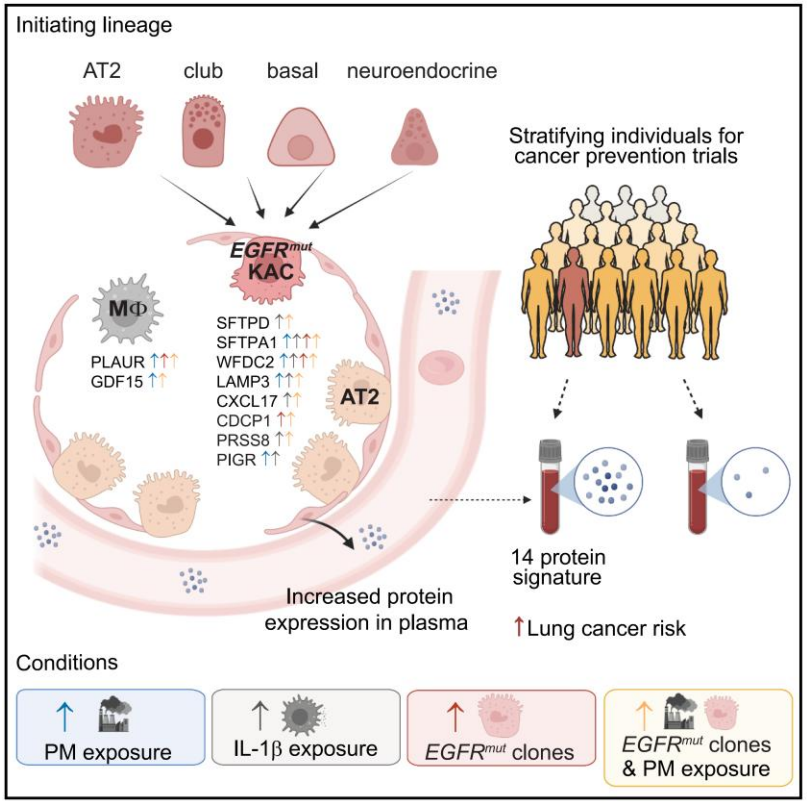


Nabavizadeh N, et al. Presentation at European Society for Medical Oncology Congress. October 17-21. 2025; Berlin Germany.

The Human Cost

Estimated N Procedures in False Positive Participants in NHS-Galleri (n=864)	
Labs	605
Imaging	740
Non-Invasive procedure	269
Invasive Procedure	404
Surgical Procedure	45

Plasma signals of lung tumor promotion for molecular cancer prevention



Highlights

- A 14-protein plasma signature predicts lung cancer more than 5 years before diagnosis
- Diverse epithelial lineages converge on a transitional state in *EGFR*-driven LUAD
- Particulate matter, oncogenic mutations, and IL-1β elevate the plasma signature
- The signature stratifies benefit from anti-IL-1β lung cancer prevention

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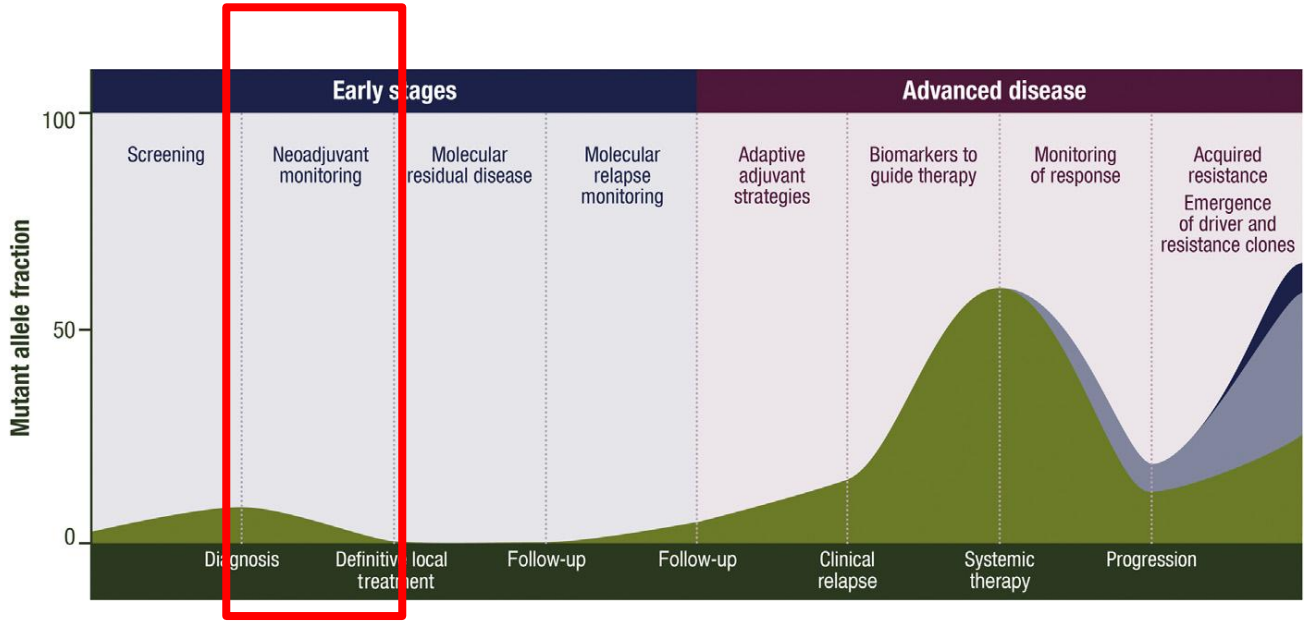
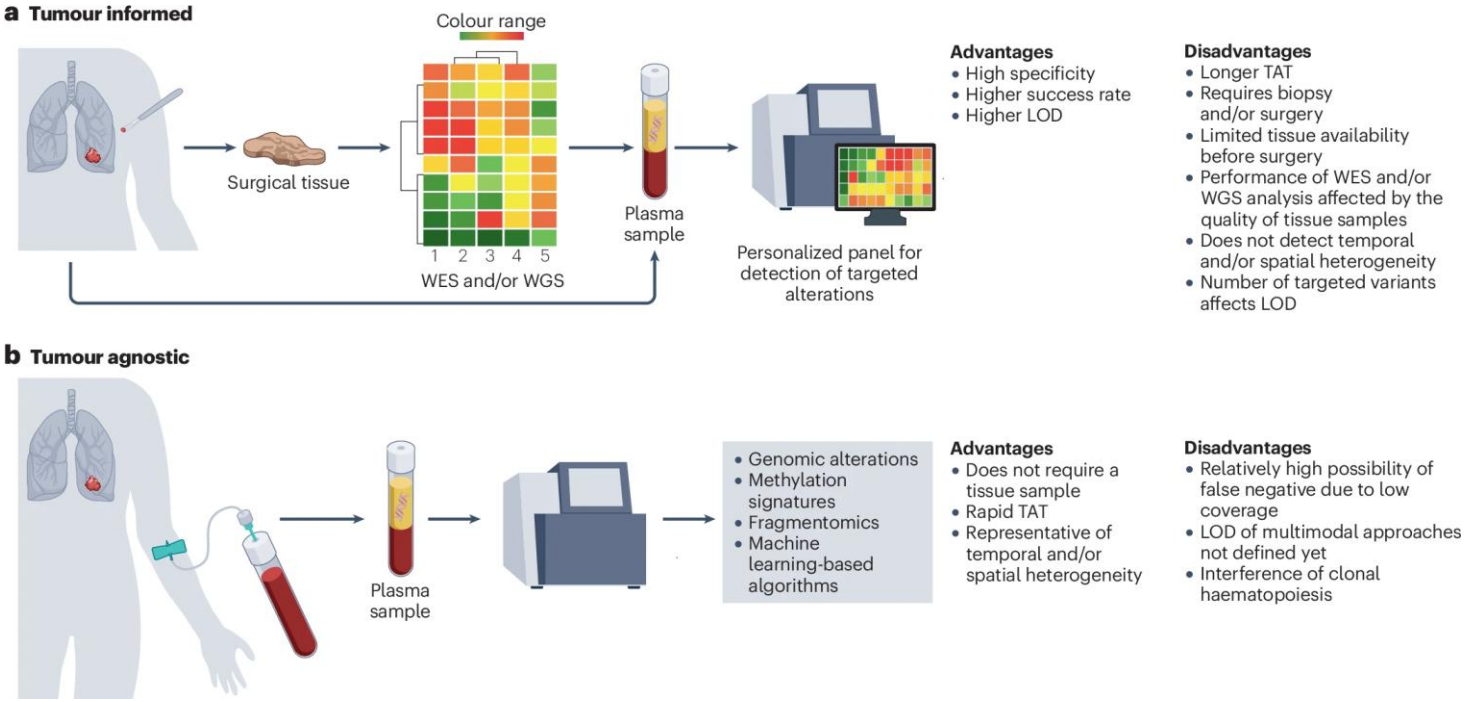
Pandya Cell 2026

Clinical applications of ctDNA assays for patients with cancer and expected DNA levels in different phases of the disease



Pascual et al Ann Oncol 2022

Workflow for detection of ctDNA in patients with early stage cancer



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Normanno Nat Rev Clin Oncol 2025

Clinical studies testing ctDNA in patients with NSCLC receiving neoadjuvant treatment

Study	Patients (*n*); disease stage	Time point	Neoadjuvant therapy	ctDNA assay (*n* of genes)	LOD	ctDNA detection rate	ctDNA clearance before surgery
Studies using tumour-informed strategies							
Forde et al. (2022)[67], Deutsch et al. (2024)[68]	358;IB–II(35%) and IIIA (64%)	Before cycles 1 and 3	Platinum-based chemotherapy ±nivolumab	ArcherDX Personalized Cancer Monitoring	NR	Before cycle 1: 93% and 95% with and without nivolumab, respectively; before cycle 3: 42% and 62%	56% and 35% with and without nivolumab
Reck et al. (2024)[69]	283; II (31%), IIIA (45%) and IIIB (24%)	Before each one of 4 neoadjuvant cycles, and before and after surgery	Platinum-based chemotherapy+ durvalumab or placebo	Invitae Personalized Cancer Monitoring (16–50 variants)	Up to 0.008%	90% at baseline	65% and 42% with or without durvalumab, respectively
Studies using tumour-agnostic strategies							
Kris et al. (2021)[66]	104; IB–IIIB[a]	Before and after neoadjuvant treatment, and after surgery	Atezolizumab	AVENIO Surveillance (197)	NR	72%, 56% and 12% before and after neoadjuvant treatment, and after surgery, respectively	32% of ctDNA-positive patients at baseline
Provencio et al. (2022, 2024)[64,65]	46; IIIA (100%)	Before and after neoadjuvant treatment	Paclitaxel+ carboplatin+ nivolumab	Oncomine Pan-Cancer Cell-Free Assay (52)	0.1%	70% both before and after therapy	68%

Normanno Nat Rev Clin Oncol 2025

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Clinical studies testing ctDNA in patients with BC receiving neoadjuvant treatment

Reference (author and year)	Number of patients (*N*) and subtypes of BC	Technique for ctDNA analysis	Median follow-up	*N* (%) of ctDNA-positivity at baseline	Relevant outcomes associated with ctDNA during NAT
Cavallone et al.[54]	*N* = 26 TNBC	Tumor-informed Pre-amplification and ddPCR	55 months	25 (96)	cDNA Pre-surgery timepoint • The average tumor VAF was lower in pCR patients, and ctDNA-positivity was a predictor of decreased RFS and OS
Li S. et al.[44]	*N* = 44 All subtypes	Tumor-agnostic Hybridization-based NGS 1021 genes	46 months	21 (48)	ctDNA during NAT • Decrease in tumor VAF: associated with the response at surgery
Rothé et al.[62]	*N* = 69 HER2+	Tumor-informed ddPCR *PIK3CA* or *TP53* mutation	Not given	28 (41)	ctDNA-positivity at baseline • Lower pCR
Lin P.H. et al.[110]	*N* = 95 All subtypes	Tumor-agnostic Amplicon-based NGS	61 months	60 (63)	ctDNA-positivity after NAT • Decreased RFS
Riva et al.[111]	*N* = 38 TNBC	Tumor-informed ddPCR for *TP53*	24 months	27 (75)	ctDNA-positivity after 1 C NAT • Lower RFS and OS
McDonald et al.[12]	*N* = 33 All subtypes	Tumor-informed TARDIS	Not given	32 (100)	Timepoint pre-surgery • Tumoral VAF 5.7 fold lower in pCR patients compared to RD
Takahashi et al.[39]	*N* = 87 All subtypes	Tumor-informed OS-MSP of *RASSF1A*	23 months	20 (23)	Timepoint pre-surgery • Tumoral VAF decreased in patients with lower RCB scores at surgery
Ortolan et al.[112]	*N* = 26 TNBC	Tumor-informed ddPCR	24 months	10/13 (77)	ctDNA-positivity pre-surgery • Worse 2-year EFS
Zhou Q. et al.[61]	*N* = 145 HR+ and TNBC	Tumor-informed Personalized amplicon-based NGS via SiMSen-Seq	Not given	63 (43)	ctDNA-positivity mid-NAT • Higher RCB score
Magbanua et al.[14]	*N* = 283 HR+ and TNBC	Tumor-informed Signatera™	50 months	224 (80)	ctDNA-positivity pre-surgery • Lower DRFS for patients with RD at the surgery
Ciriaco et al.[63]	*N* = 20 HER2+ and TNBC	Tumor-informed Personalized amplicon-based NGS via Sysmex SafeSEQ	Not given	19 (95)	Timepoint pre-surgery • ctDNA-negative 93.3% accurate to predict pCR
Moss et al.[34]	*N* = 34 All subtypes	Tumor-agnostic Amplification of breast-specific methylation loci and targeted methylation analysis	Not given	22/30 (73)	Level of breast cfDNA pre-surgery • Predict the presence of RD at surgery
Cailleux et al.[113]	*N* = 44 All subtypes	Tumor-informed Signatera™	36 months	22/38 (58)	ctDNA-positivity pre-surgery • Lower EFS
Parsons et al.[64]	*N* = 38 TNBC and ER low (≤ 5%)	Tumor-informed MAESTRO	Not given	38/38 (100)	Baseline to 2nd cycle of NAT • Mean decrease in tumoral VAF higher in responder

Decrease in ctDNA detection or tumor VAF is associated with improved pCR or RFS

Panet npj Breast Cancer 2025

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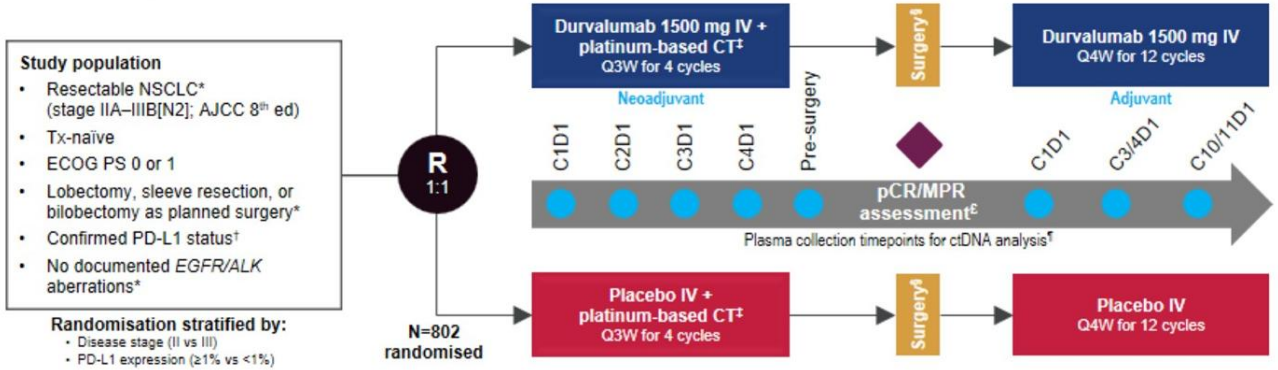
AEGEAN Study Design

Phase 3, global, randomised, double-blind, placebo-controlled study



Predictive Value of ctDNA Clearance at Different Timepoints for pCR‡

D arm	pCR	
	PPV	NPV
C2D1	49%	89%
C3D1	39%	94%
C4D1	40%	100%
Pre-surgery	40%	100%

PBO arm	pCR	
	PPV	NPV
C2D1	11%	98%
C3D1	12%	100%
C4D1	12%	100%
Pre-surgery	13%	100%

Second EFS interim analysis DCO = 10 May 2024. *ctDNA clearance was defined as a change from ctDNA detected at baseline (neoadjuvant C1D1) to undetected at the specified on-Tx timepoint. ctDNA non-clearance was defined as ctDNA-positive at the specified timepoint (where baseline could be either evaluable or non-evaluable). †In the BEP, pCR (23% vs 4%) and MPR (42% vs 14%) rates were higher in the D vs PBO arm. ‡Assessed in patients who were ctDNA-positive at baseline (neoadjuvant C1D1). In the D arm, the number of patients analysed at each timepoint (had ctDNA clearance, were pCR-positive) were as follows: C2D1 (41, 29), C3D1 (62, 27), C4D1 (63, 25) and Pre-surgery (65, 26). In the PBO arm, the number of patients analysed at each timepoint (had ctDNA clearance, were pCR-positive) were as follows: C2D1 (27, 5), C3D1 (50, 6), C4D1 (51, 6) and Pre-surgery (45, 6). NPV, negative predictive value; PPV, positive predictive value.

BARCELONA 2024 ESMO congress

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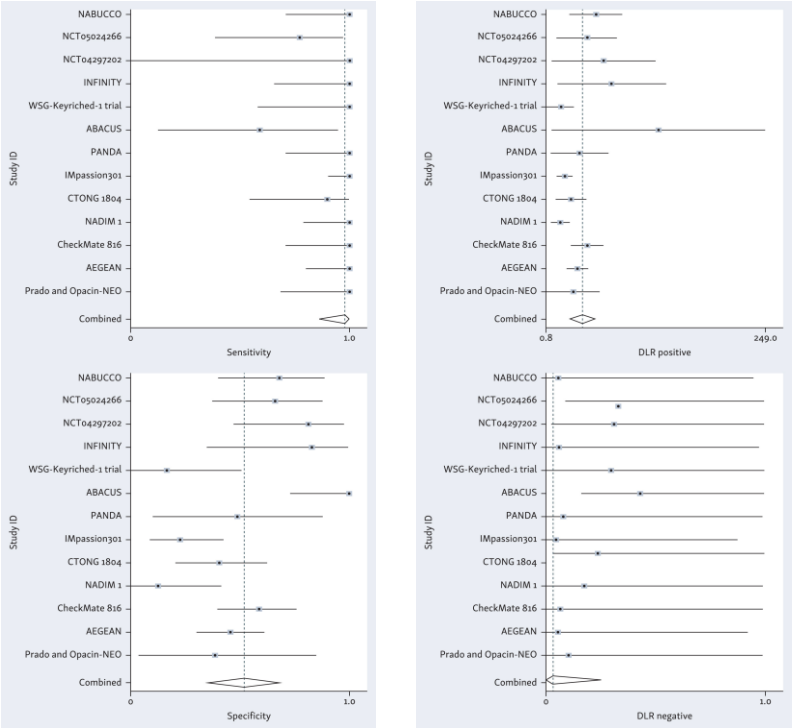
ctDNA clearance and prediction of pCR in Patients with Solid Tumors Treated with Neoadjuvant ICIs



- The lack of ctDNA clearance may identify patients unlikely to have a pCR
- The confirmatory power of ctDNA clearance is limited by low specificity and high heterogeneity due to the variability of the assays, and warrants further study

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Valenza Ann Oncol 2025

Heterogeneity of the ctDNA assays

Table 2. Characteristics of the ctDNA assays

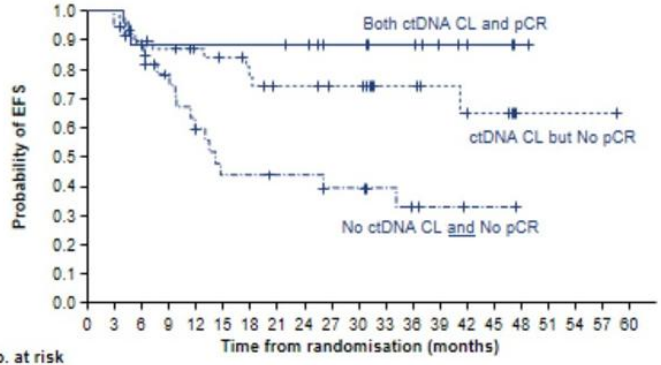
Study name	Assay	Approach	Sequencing	Coverage and/or limit of detection 95% (LOD95%)
NABUCCO[39]	RaDaR	Tumor-informed	WES	0.0006%
NCT05024266[40]	Mutation capsule	Tumor-informed	WES	0.001%
NCT04297202[41]	NA	Tumor-naive	Comprehensive genomic profile (Illumina NovaSeq6000 NGS)	30 000×
INFINITY[42]	ddPCR (in house)	Tumor-informed	Comprehensive genomic profile (Foundation)	0.001%
WSG-Keyriched-1[43]	NA (in house)	Tumor-informed	Comprehensive genomic profile	100 000×
ABACUS[44]	Signatera™	Tumor-informed	WES	100 000× 0.01%
PANDA[45]	Signatera™	Tumor-informed	WES	100 000× 0.01%
IMpassion031[46]	NA	Tumor-informed	WGS	NA
CTONG1804[47]	NA	Tumor-informed	Comprehensive genomic profile (Illumina NovaSeq6000 NGS)	>15 000×
NADIM 1[48]	Oncomine™ Pan-cancer cell-free assay	Tumor-naive	Comprehensive genomic profile	0.01%
CheckMate 816[49]	ArcherDX personalized cancer monitoring (PCM™)	Tumor-informed	WES	0.005%
AEGEAN[50]	Invitae personalized cancer monitoring (PCM™)	Tumor-informed	WES	0.005%
Prado and Opacin-NEO[51]	ddPCR (QX600)	Tumor-informed	WES	0.1%

ctDNA, circulating tumor DNA; ddPCR, digital droplet PCR; NA, not available; NGS, next-generation sequencing; WES, whole exome sequencing; WGS, whole genome sequencing.

Associations of ctDNA Clearance at Pre-surgery and pCR with EFS

- In both Tx arms, patients with no ctDNA clearance at pre-Sx and no pCR had the poorest EFS outcomes
- Patients with ctDNA clearance, with or without pCR, had longer EFS than patients with no ctDNA clearance and no pCR*

D arm

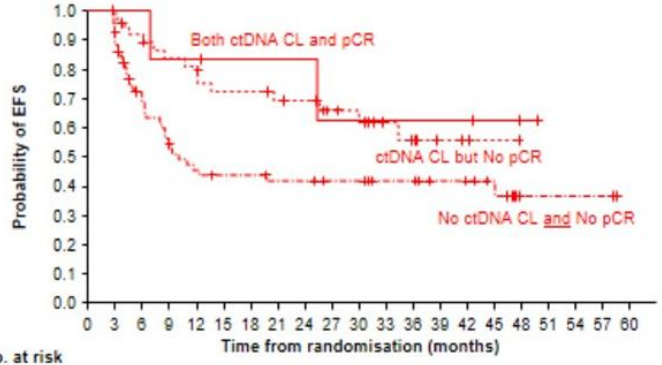


No. at risk

Both ctDNA CL and pCR	26	26	23	23	23	23	23	23	22	18	18	14	14	11	9	7	1	0	0	0	0
ctDNA CL but No pCR	39	39	34	32	29	27	24	21	21	17	17	10	10	8	5	5	1	1	1	1	0
No ctDNA CL and No pCR	35	33	29	21	15	11	11	10	10	8	8	6	4	3	1	1	0	0	0	0	0

	Both ctDNA CL and pCR	ctDNA CL but No pCR
HR vs No ctDNA CL and No pCR	0.14 (95% CI: 0.04–0.48)	0.35 (95% CI: 0.16–0.76)
HR vs ctDNA CL but No pCR	0.39 (95% CI: 0.11–1.41)	–

PBO arm



No. at risk

Both ctDNA CL and pCR	6	6	6	5	5	4	4	4	4	3	3	3	3	3	3	2	1	0	0	0	0
ctDNA CL but No pCR	39	38	34	30	29	25	25	23	22	17	16	10	7	3	2	1	0	0	0	0	0
No ctDNA CL and No pCR	63	60	41	31	25	23	23	21	21	17	17	14	14	11	10	7	2	2	2	2	0

	Both ctDNA CL and pCR	ctDNA CL but No pCR
HR vs No ctDNA CL and No pCR	0.40 (95% CI: 0.09–1.65)	0.48 (95% CI: 0.26–0.90)
HR vs ctDNA CL but No pCR	0.80 (95% CI: 0.18–3.55)	–

BARCELONA 2024 ESMO congress

Second EFS interim analysis DCO = 10 May 2024. HRs were calculated using an unstratified Cox proportional hazard model using the Efron method to adjust for ties and Wald confidence intervals. *Data are shown for the pre-Sx timepoint for comparison of pCR; similar data were observed at earlier cycles of neoadjuvant Tx.

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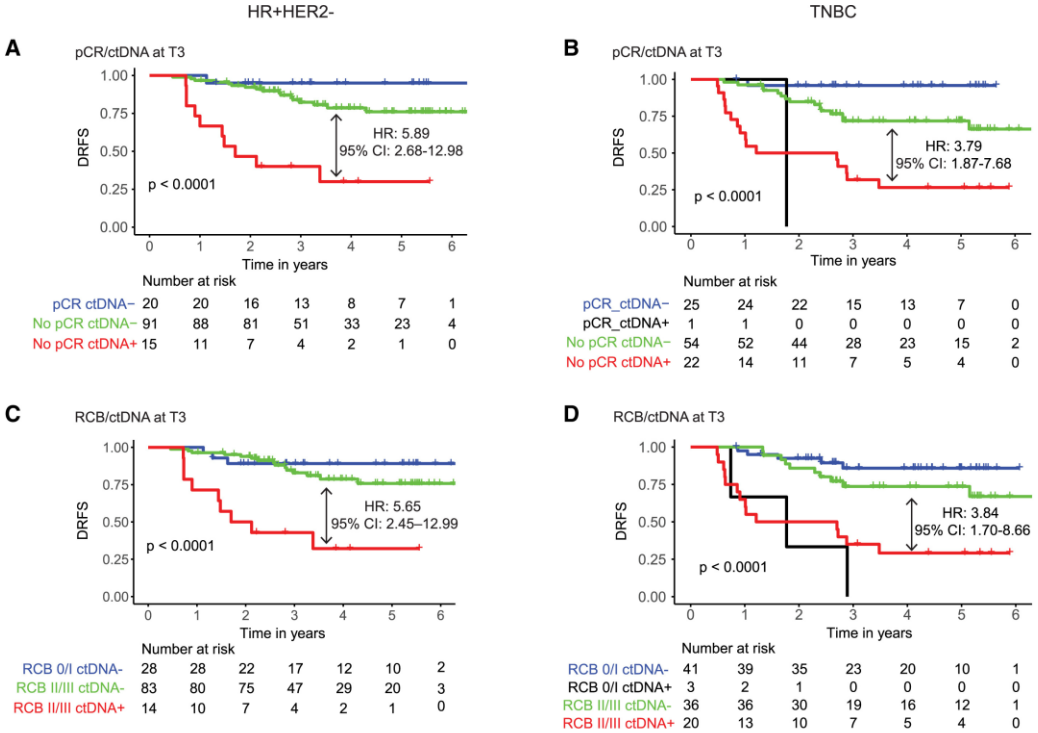
Prognostic significance of ctDNA status after NAT and pCR in patients with HER2- BC



Magbanua Cancer Cell 2023

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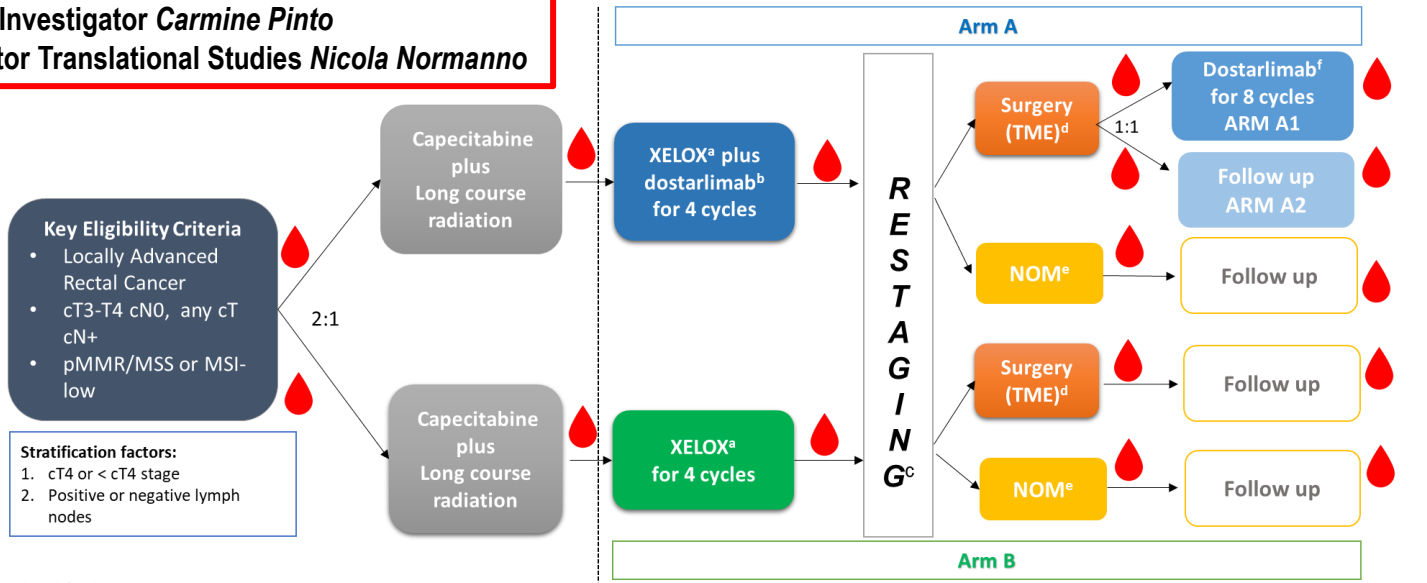
The IMMUNOSTAR Trial

Principal Investigator *Carmine Pinto*
Coordinator Translational Studies *Nicola Normanno*



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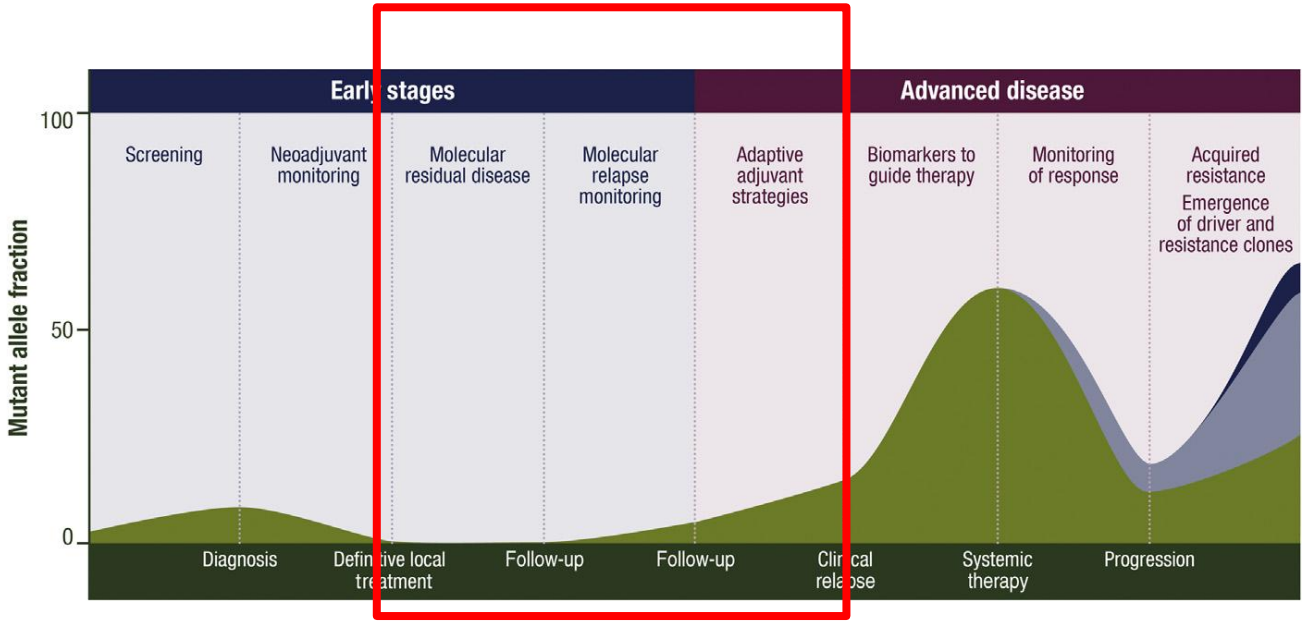
Clinical applications of ctDNA assays for patients with cancer and expected DNA levels in different phases of the disease



Pascual et al Ann Oncol 2022

MRD detection by ctDNA testing in CRC

Table 1. Sensitivity and specificity of the main ctDNA tumor-informed published studies for predicting CRC relapse

Study	Stage	*n*	Assay	Post-operative ctDNA+ rate	Rec. rate in ctDNA+ (PPV)	Sensitivity	Rec. rate in ctDNA− (1 − NPV)	Specificity
Tie et al., 2016[19]	II	178	15-gene panel → Safe-SeqS	8.7%	78.6% (11/14)[a]	40.7% (11/27)[a]	9.8% (16/164)[a]	98% (148/151)[a]
Tie et al., 2019[21]	III	96	15-gene panel → Safe-SeqS	21%	50% (10/20)[a]	41.6% (10/24)[a]	18.4% (14/76)[a]	86.1% (62/72)[a]
Wang et al., 2019[22]	I-III	58	15-gene panel → Safe-SeqS	—	76.9% (10/13)[b]	100% (10/10)[b]	0% (0/45)[b]	93.8% (45/48)[b]
Tarazona et al., 2019[9]	I-III	69	29-gene panel → ddPCR	20.3%	57.1% (8/14)[a] 70% (14/20)[b]	47.1% (8/17)[a] 82.4% (14/17)[b]	16.4% (9/55)[a] 6.1% (3/49)[b]	88.5% (46/52)[a] 88.5% (46/52)[b]
Chen et al., 2021[24]	II-III	240[a] 125[b]	Geneseeq Prime → bespoke assay	8.3%	60% (12/20)[a] 76% (19/25)[b]	37.5% (12/32)[a] 82.6% (19/23)[b]	9.1% (20/220)[a] 4% (4/100)[b]	96.2% (200/208)[a] 94.1% (96/102)[b]
Reinert et al., 2019[28]	I-III	94[a] 75[b]	Signatera	10.6%	70% (7/10)[a] 93.3% (14/15)[b]	41.2% (7/17)[a] 87.5% (14/16)[b]	11.9% (10/84)[a] 3.3% (2/60)[b]	96.1% (74/77)[a] 98.3% (58/59)[b]
Henriksen et al., 2022[8]	III	14[a] 114[b]	Signatera	14%	80% (16/20)[a] 95.5% (21/22)[b]	42.1% (16/38)[a] 87.5% (21/24)[b]	18.3% (22/120)[a] 3.3% (3/92)[b]	96.1% (98/102)[a] 98.9% (89/90)[b]
Reinert et al., 2016[29]	I-IV	11	WGS → ddPCR	—	100% (6/6)[b]	100% (6/6)[b]	0% (0/5)[b]	100% (5/5)[b]
Schøler et al., 2017[4]	I-IV	26	WES → ddPCR	28.6%	100% (14/14)[b]	100% (14/14)[b]	0% (0/12)[b]	100% (12/12)[b]
Henriksen et al., 2024[30]	II-III	797	WES → ddPCR	7.1%	75.4% (43/57)[a]	34.7% (43/124)[a]	10.9% (81/740)[a]	97.9% (659/673)[a]
Kotani et al., 2023[98] (GALAXY trial)	II-IV	1039	Signatera	18%	61.5% (115/187)[a]	58.7% (115/196)[a]	9.5% (81/852)[a]	91.5% (771/843)[a]
Nakamura et al., 2024[33] (GALAXY trial)	II-IV	2240	Signatera	15.9%	78.3% (263/336)[a]	53.0% (263/496)[a]	12.2% (233/1904)[a]	95.8% (1671/1744)[a]
Frydendahl et al., 2024[64]	III	111	WGS → WGS	16%	68.4% (13/19)[a]	46.4% (13/28)[a]	16.3% (15/92)[a]	92.8% (77/83)[a]

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Martinez-Castedo Ann Oncol 2025

MRD detection by cfDNA testing in NSCLC

Tumor type	Patients	Stage	Time point	Method	HR RFS	Author, year
NSCLC/SCLC	37	IB, II, III	1 mo post-surgery	CAPP-seq	43.4	Chaudhuri, 2017
NSCLC	26	I-III	3 d post-surgery	cSMART	7.5	Chen, 2019
NSCLC	77	I-III	2 weeks	cSMART	2.9	Peng, 2020
NSCLC	38	I-III	within 2 weeks	Geneseeq	8.76	Kuang, 2021
NSCLC	123	I-IIIA	within 1 mo	Geneseeq	3.04	Li, 2022
NSCLC	85	I-III	within 1 mo	ATG-Seq	4	Qiu, 2021
NSCLC	534	II-IIIA	before adjuvant chemo	Signatera	NR	Zhou, 2021
NSCLC	330	I-III	3 d/1 mo post-surgery	Genecast MRD	11.1	Xia, 2022
NSCLC	261	I-III	within 1 mo	CAPP-seq	0.08§	Zhang, 2022
NSCLC	278	I-IIIA	4 weeks	ddPCR	NR	Jung, 2023
NSCLC	162	I-III	30 days	PROPHET	16.4	Chen, 2023

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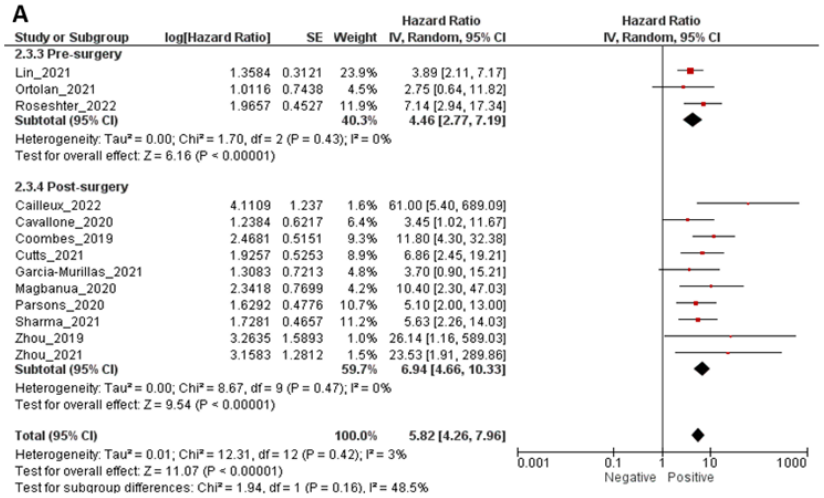
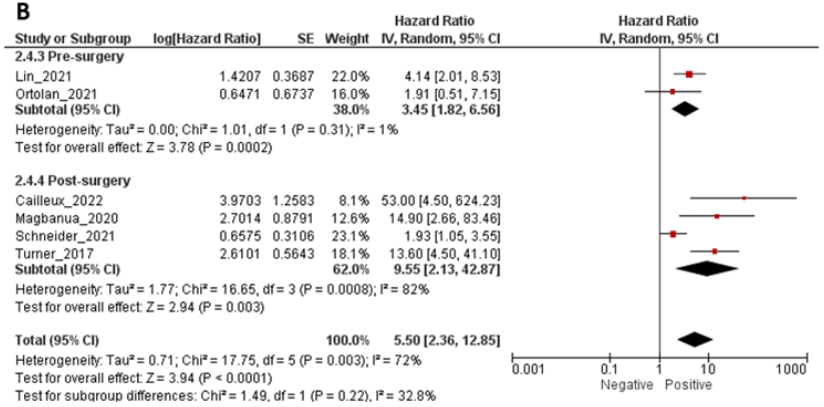
MRD detection by ctDNA testing in BC





Nader-Marta ESMO Open 2024

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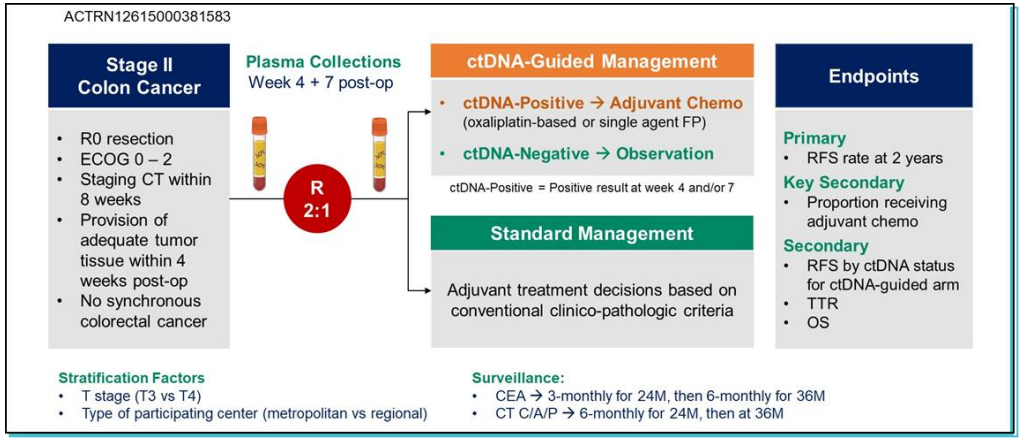
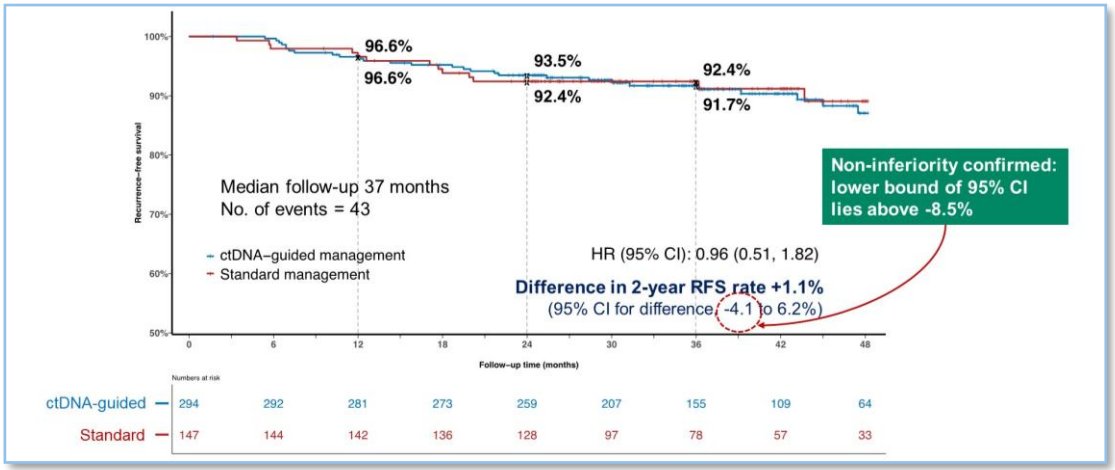
ctDNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer: the DYNAMIC II trial





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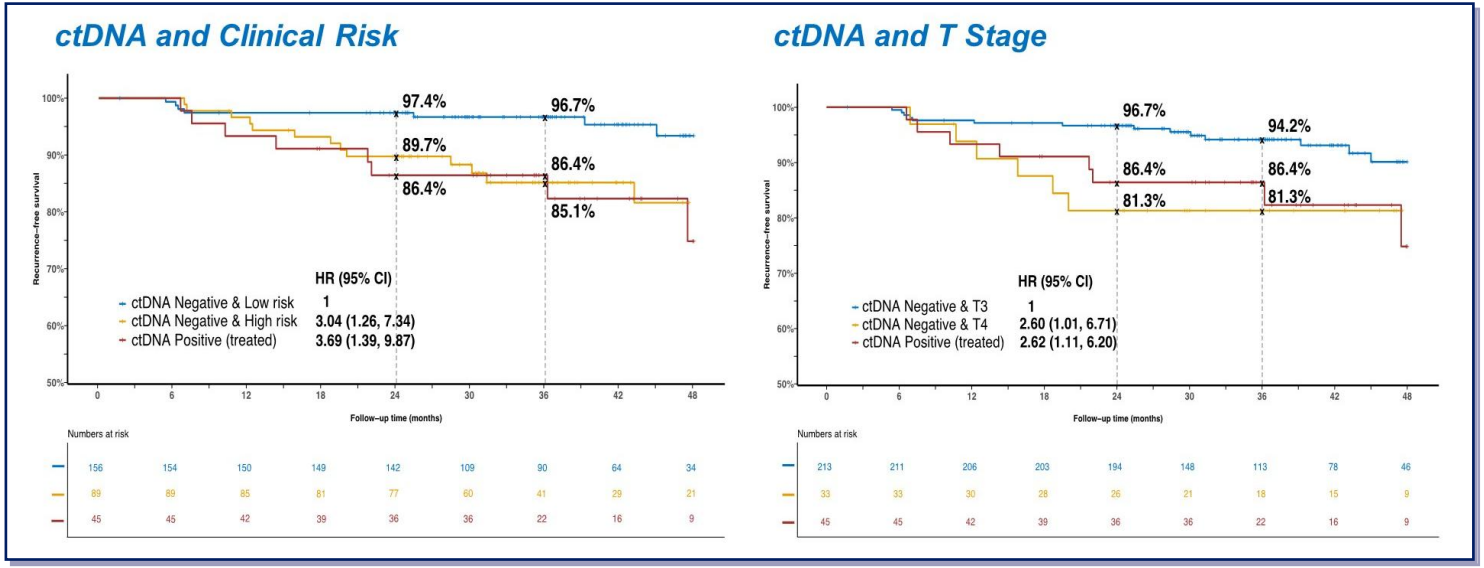
Tie NEJM 2022

DYNAMIC II: ctDNA, Clinical Risk and T Stage



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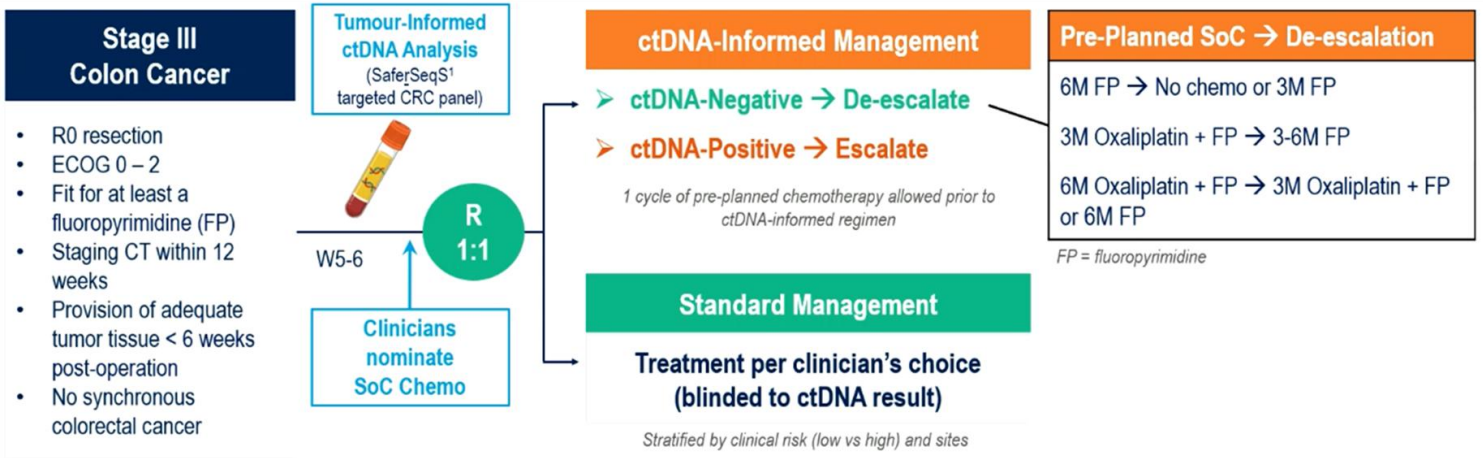
Tie NEJM 2022

ctDNA-guided adjuvant therapy in locally advanced colon cancer: the DYNAMIC III trial



Primary Analysis of ctDNA-Negative Cohort: Endpoints to be Presented Here	
Primary: 3-year recurrence-free survival (RFS)	Secondary: treatment adherence, safety

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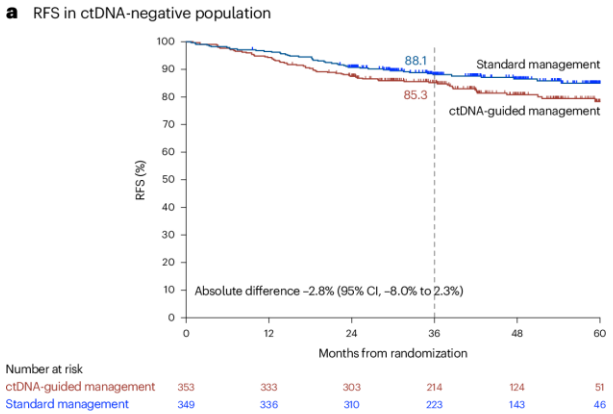
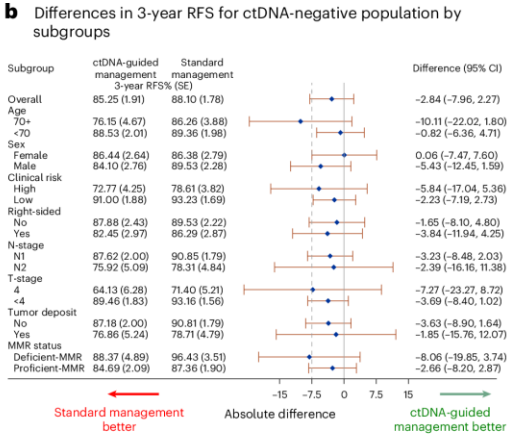
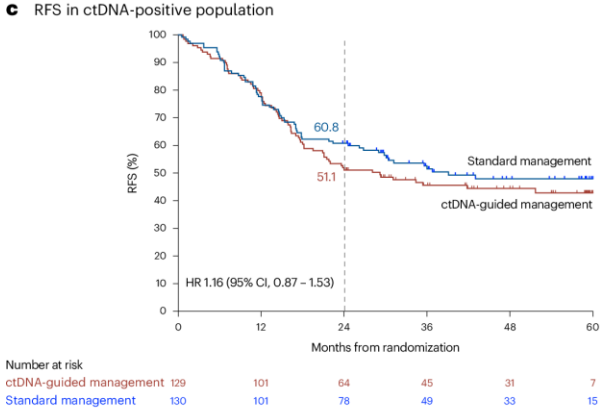
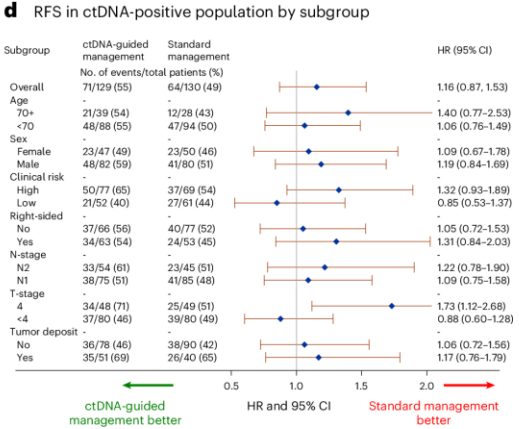
DYNAMIC III trial: RFS with ctDNA-guided versus standard-of-care adjuvant therapy









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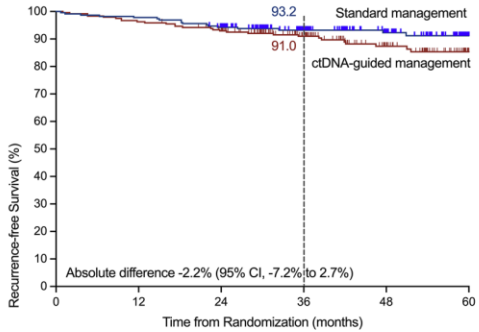
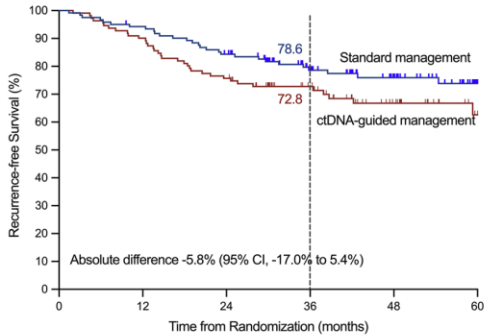
DYNAMIC III trial: RFS with ctDNA-Guided versus Standard-of-Care Adjuvant Therapy for ctDNA-Negative Patients, According to Clinical Risk

A Clinical Low-Risk (T1-3N1)



No. at Risk						
ctDNA-guided management	242	233	219	160	93	39
Standard management	227	222	209	152	95	32

B Clinical High-Risk (T4 and/or N2)



No. at Risk						
ctDNA-guided management	111	100	84	54	31	12
Standard management	122	114	101	71	48	14

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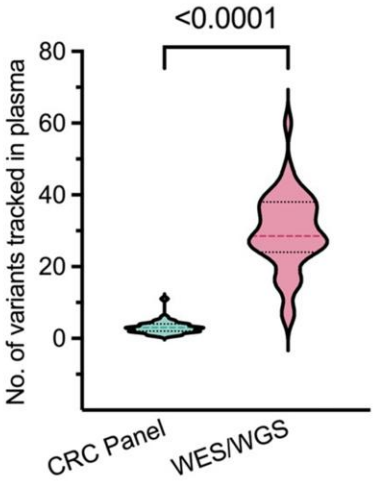
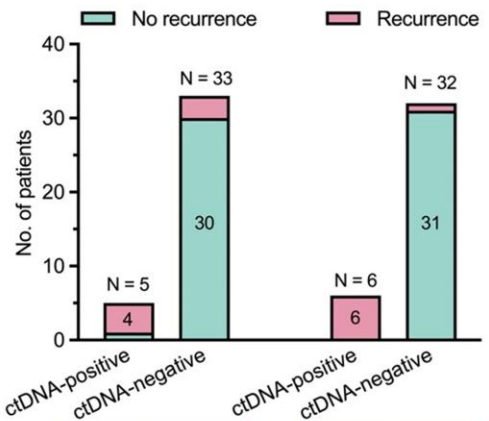
Tracking More Variants Identified in Tumor Improves Testing for MRD

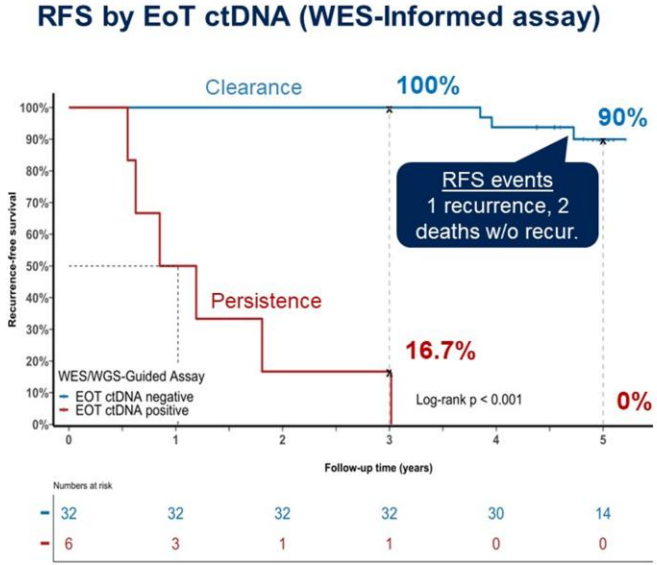
EoT plasma samples (N = 38 with residual samples)



# Variants	CRC panel	WES*
Median (IQR)	**3** (2, 4)	**29** (24, 38)



CRC Panel	WES-Informed
Sensitivity 57.1% **Specificity 96.8%** **PPV 80.0%** **NPV 90.9%**	**Sensitivity 85.7%** **Specificity 100%** **PPV 100%** **NPV 96.9%**

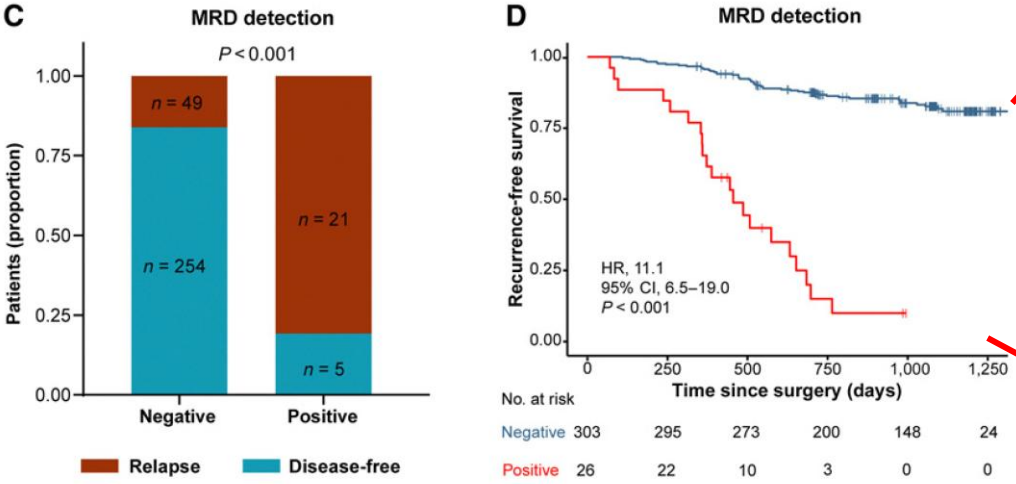


**WGS (whole genome sequencing) in 3 patients due to low no. of suitable variants by WES (whole exome sequencing)*

PRESENTED BY: Jeanne Tie, MBChB FRACP MD

MRD detection: open issues

Prognostic value of postoperative ctDNA in NSCLC patients



- A fraction of MRD negative patients still has a disease recurrence
- It is not clear whether this is due to limited sensitivity of the assays or to biological features of the tumor
- In MRD negative patients, recurrence is more frequently lorocoregional or in lymph nodes or intracranial

- Almost all MRD positive patients have a disease recurrence
- Interventional studies are needed to develop effective therapeutic strategies to eradicate MRD

MRD: Minimal residual disease

Xia Clin Cancer Res 2022

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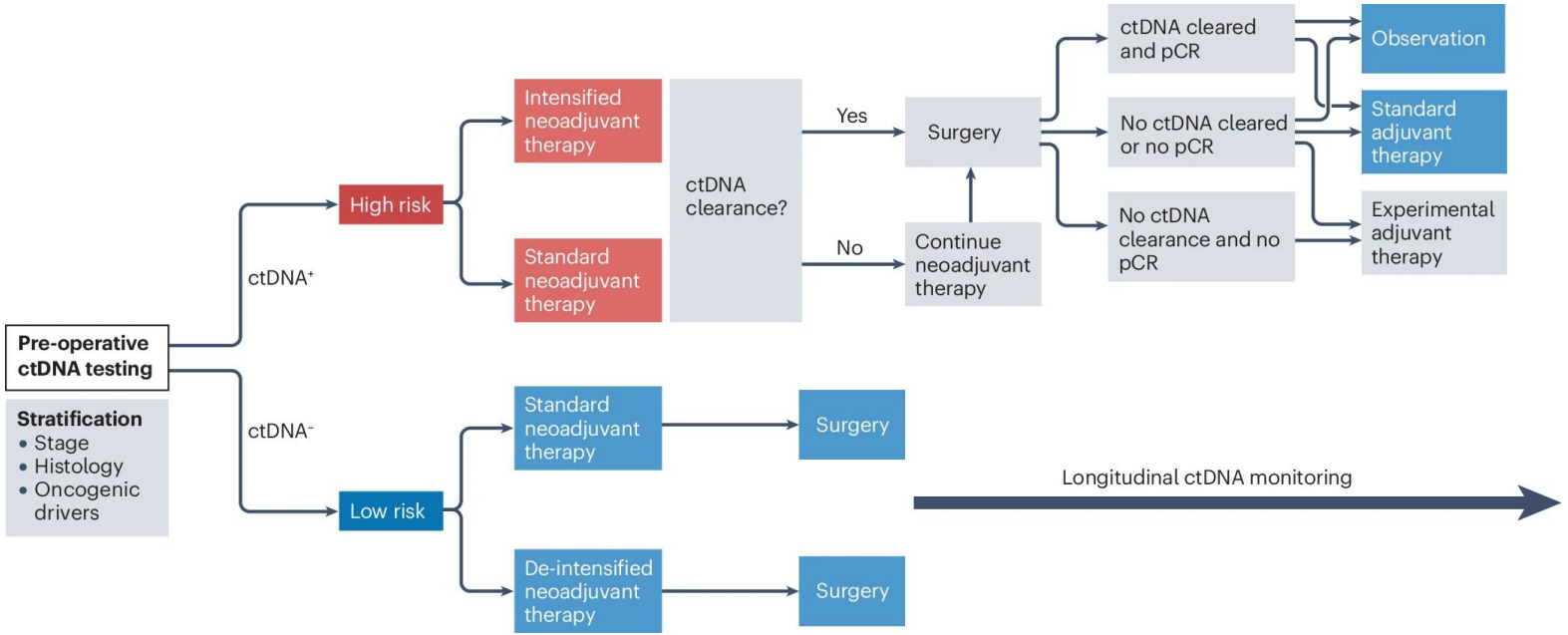
Prospective interventional studies testing perioperative ctDNA in patients with early stage NSCLC



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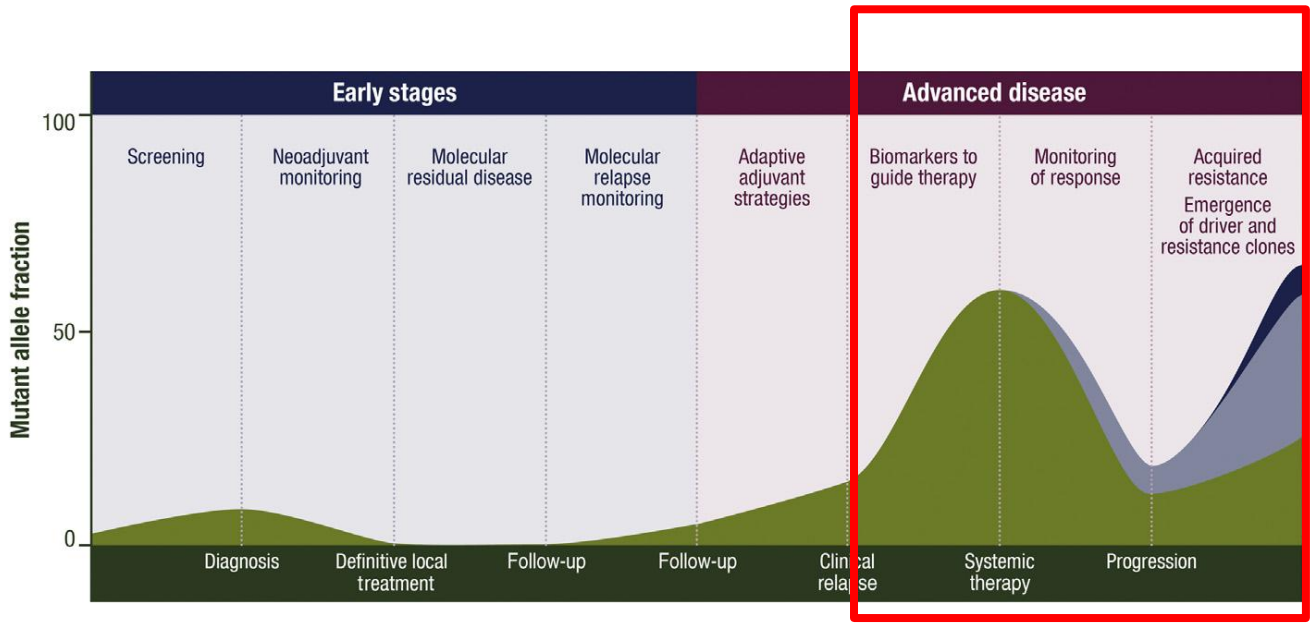
Clinical applications of ctDNA assays for patients with cancer and expected DNA levels in different phases of the disease



Pascual et al Ann Oncol 2022

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]

Tumour type	Indications	ESCAT tier and level of evidence	Recommendation
Non-small-cell lung cancer	*EGFR* (for common, uncommon, exon 20 insertions, T790M and other resistance mutations e.g. C797X).	IA[120]	ctDNA genotyping recommended in treatment-naive cancer patients and resistance upon prior TKIs. Caution should be kept as ctDNA assays will miss histological trans-differentiation. ctDNA testing may not have adequate sensitivity to detect *MET* true high copy number gain as resistance mechanism to osimertinib or lorlatinib. Amplification and fusion detection is suboptimal with ctDNA assays, and should be repeated in tissue where possible.
	ALK (for fusions and acquired resistance kinase domain mutations).	IA[121-125]	
	MET (for exon 14 splice site mutations, and acquired resistance mutations)	IB[126,127]	
	KRAS (for G12C and non-tier 1 other *KRAS* mutations)	IB[128]	
	BRAF (for V600E)	IB[129,130]	
	RET (for fusions and acquired resistance kinase domain mutations)	IB[131]	
	ROS1 (for fusions and acquired resistance kinase domain mutations)	IB[132,133]	
	NTRK 1/2/3 (for fusions and acquired resistance mutations)	IC[134]	
	MET (for high-level copy number gain/amplification)	IIA[135]	
	ERBB2 (for exon 20 insertions and transmembrane mutations, and amplification)	IIB[136-138]	
	BRAF (for non-V600E class I-III mutations)	IIB[139]	
Thyroid cancer	*BRAF* mutations	IB[160,161]	ctDNA testing if tissue not available.
	RET mutations	IB[162,163]	
	NTRK 1/2/3 fusions	IC[134]	

ctDNA assays can be undertaken in treatment-naive patients and is especially recommended when a significant delay is expected in obtaining tumour tissue for genotyping, when invasive procedures may be risky or contraindicated, or bone is the only site that could be biopsied

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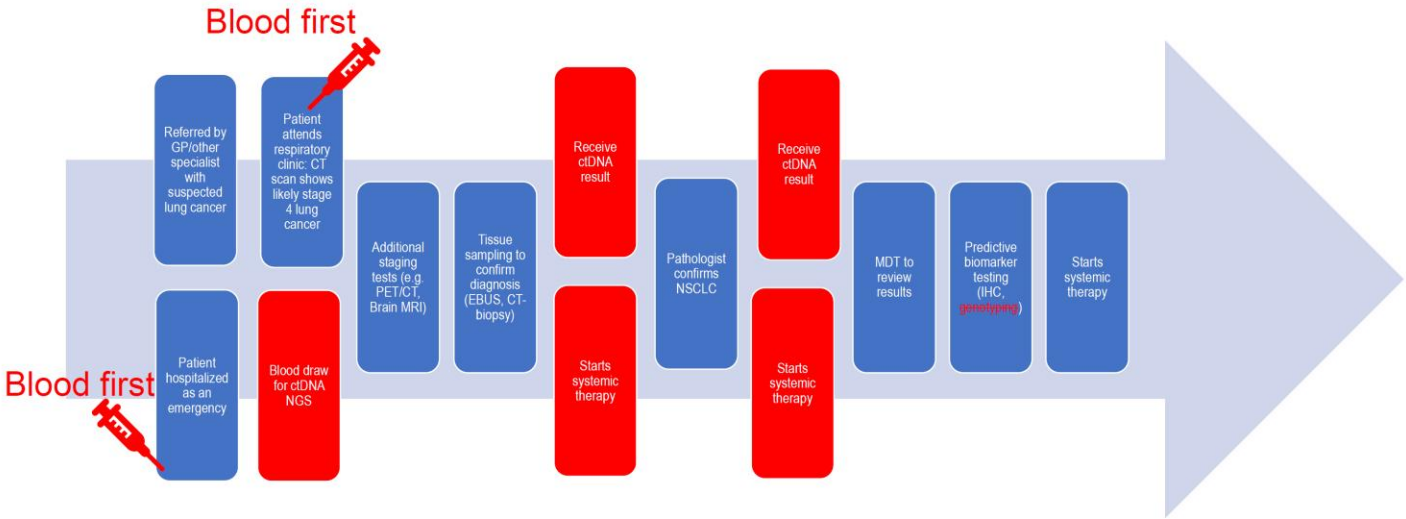
The new diagnostic algorithm

For image-suspected stage 3-4 lung cancer



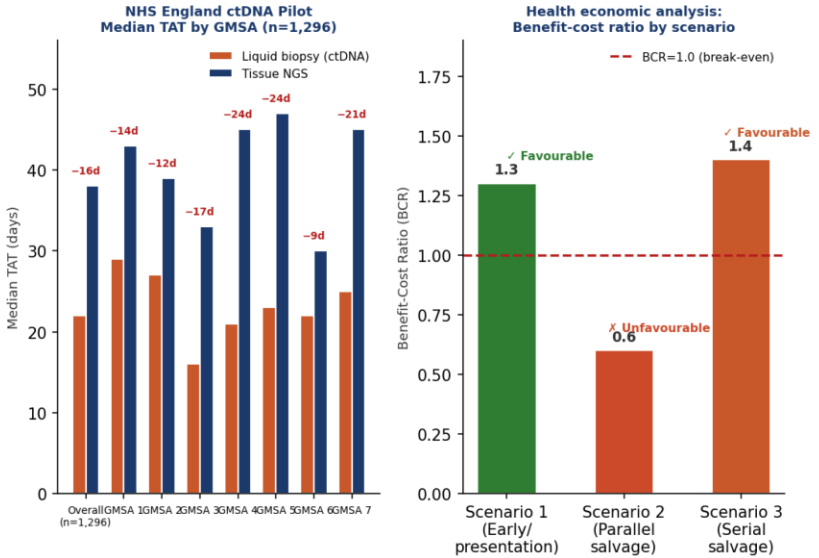
Sanjay Popat FRCP PhD

Results of the health economic evaluation

What did we find?

- N=1,296, equal gender balance, 18% never smokers
- 24% emergency hospitalizations
- 10% could not undergo tissue biopsy; 20% underwent ≥1 biopsy; 6% complication rate of biopsies
- 62% confirmed NSCLC; 11% SCLC; 12% other cancers/benign
- Genomics turnaround time: **39d vs 22d** from sampling to genomics report (44% turnaround time improvement)

➢ **Cost effective** for ctDNA at presentation with **£11M savings** to NHS: avoiding additional procedures, better treatment, start treatment quicker, improved QOL



Edge Health / NHS England HEA Report 2024 (commissioned by NHSE Genomics Unit) — Fig 22 & Tables 4–6

Sanjay Popat FRCP PhD

https://norththamesgenomics.nhs.uk/wp-content/uploads/2026/01/Edge-Health-Health-economics-evaluation-of-ctDNA-testing-in-NSCLC-for-pub4.pdf

Organisers

Partners

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ctDNA NGS ctDNA pilot implementation roadmap

Commercial partnerships with the NHS via technology transfer

	Dates	Programme	Content	ctDNA Provider
Evaluation	February – December 2022	Phase 0	Discussions, agreements, funding	N/A
	January – July 2023	Phase 1	700 tests, (selected hospitals)	2 commercial providers:
	August – March 2024	Phase 2	1,800 tests, (selected hospitals) Health economic evaluation	1 NHS provider:
Implementation	April 2024 – March 2025	Phase 3	10,000 tests, (all hospitals)	2 NHS providers:
	April 2025 onwards	Routinely NHS-funded service (England only)	Patients with radiologically suspected stage III/IV lung cancer, likely unsuitable for curative intent surgery or radical radiotherapy and ECOG 0-3	3 NHS providers:

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Organisers

Partners

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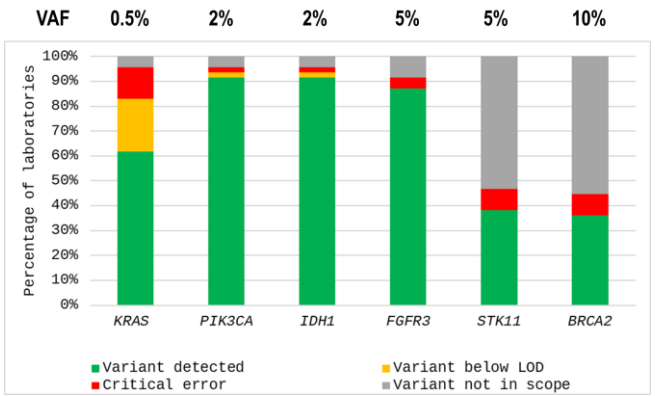
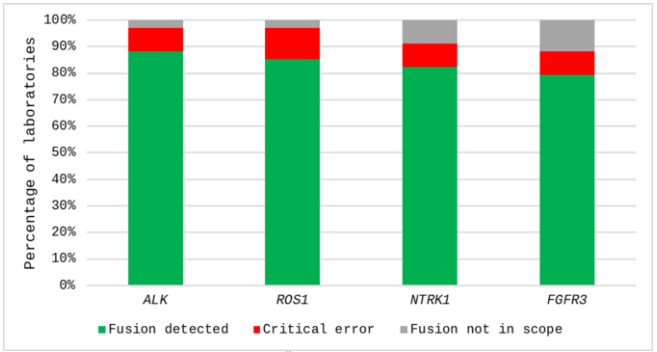
Pilot EQA for Multibiomarker Testing in cfDNA





- Sixty laboratories from 17 different countries
- Five artificial plasma samples were distributed for testing
- Two samples contained multiple biomarkers and participating laboratories were assessed for genotyping
- The program is coordinated by GenQA (Jenny Fairley) on behalf of IQN Path

Variants	VAF Range (Avg)	Number of laboratories			
		Detected variant	Did not detect the variant		
Case 3 ***EGFR*** c.2303_2304insTGTGGCCAG p.(Ala767_Val769dup)	**Expected 4%** 2.5%-7.5% (4.1%)	32 (86%)	5 (14%)	Out of scope	1
				Critical error	4 (10.8%)
Case 4 ***BRAF*** c.1799T>A p.(Val600Glu)	**Expected 1%** 0.3%-1.5% (0.87%)	36 (94.8%)	2 (5.2%)	Out of scope	1 (2.6%)
				Below LOD? Stated as 1%	1 (2.6%)
Case 5 ***EGFR*** c.2238_2252del p.(Glu746_Thr751delinsAla) (deletion in exon 19) AND	**Expected 1%** 0.4%-3.2% (0.94%)	35 (92%)	3 (8%)	Below LOD? Stated as 0.5% and 1%	2 (5.3%)
				Critical error	1 (2.6%)
EGFR c.2369C>T p.(Thr790Met)	**Expected 0.5%** 0.3%-1.0% (0.61%)	34 (89.4%)	4 (10.6%)	Critical error	4 (10.6%)

Actionable genomic alterations in breast cancer

Table 3. List of genomic alterations level I/II according to ESCAT in advanced breast cancer

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched	References
ERBB2	Amplifications	15%-20%	IA	Anti-HER2 monoclonal antibodies HER2 TKIs Anti-HER2 ADCs	Baselga et al., *N Engl J Med* 2012[55] Krop et al., *Lancet Oncol* 2014[56] Lin et al., *J Clin Oncol* 2020[57] Saura et al., *J Clin Oncol* 2020[58] Rugo et al., *JAMA Oncol* 2021[59]
	Hotspot mutations	4%	IIB	Pan-HER TKIs Anti-HER2 ADCs	Hyman et al., *Nature* 2018[51] Smyth et al., *Cancer Discov* 2020[60] Li et al., *Ann Oncol* 2023[61]
PIK3CA	Hotspot mutations	30%-40%	IA (ER-positive HER2-negative ABC)	α-specific PI3K inhibitors	André et al., *N Engl J Med* 2019[62] Rugo et al., *Lancet Oncol* 2021[63]
ESR1	Mutations	30%-40%	IA (ER-positive HER2-negative ABC resistant to AI)	SERDs	Bidard et al., *J Clin Oncol* 2022[64] Bardia et al., *Cancer Res* 2023[65]
BRCA1/2	Germline pathogenic/likely pathogenic variants	4%	IA	PARP inhibitors	Litton et al., *N Engl J Med* 2018[66] Robson et al., *Eur J Cancer* 2023[67]
	Somatic mutations	3%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68]
PTEN	Mutations/deletions	7%	I/II	AKT inhibitors	Schmid et al., *J Clin Oncol* 2020[69] Turner et al., *N Engl J Med* 2023[70]
AKT	Mutations (p. E17K)	5%	I/II	AKT inhibitors	Kalinsky et al., *JAMA Oncol* 2021[71] Turner et al., *N Engl J Med* 2023[70]
PALB2	Germline pathogenic/likely pathogenic variants	1%	IIB	PARP inhibitors	Tung et al., *J Clin Oncol* 2020[68] Gruber et al., *Nat Cancer* 2022[72]

It is recommended to carry out tumour NGS of a tumour (or plasma) sample from a patient with hormone receptor-positive/HER2-negative advanced breast cancer as standard of care.

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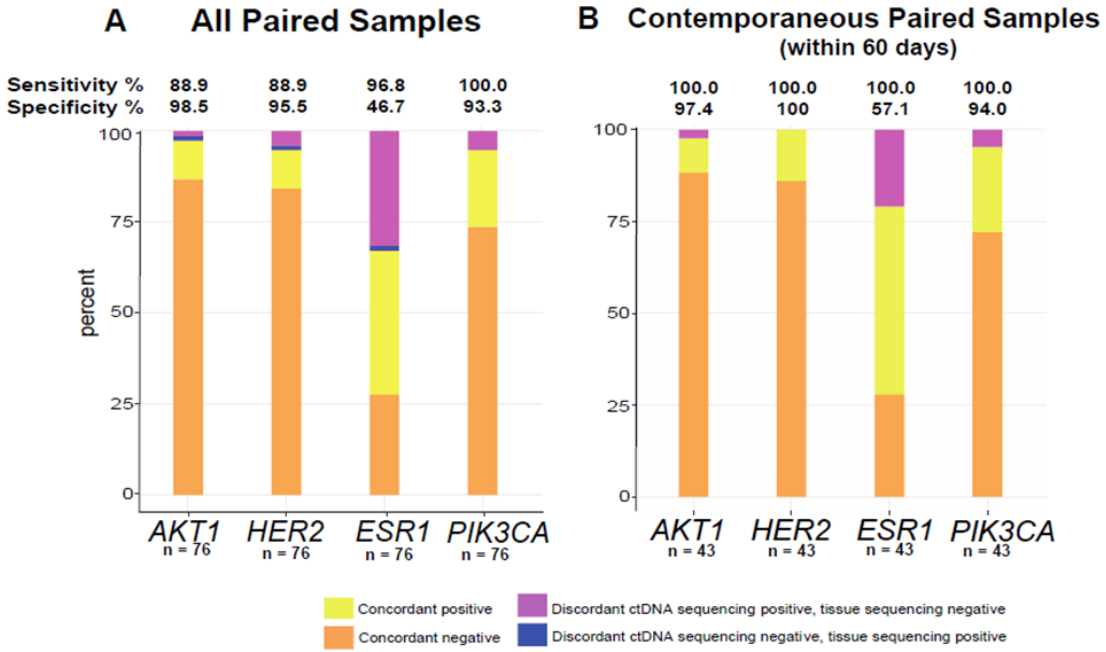
Mosele Ann Oncol 2024

ctDNA testing identifies more ESR1 positive patients compared to tissue testing



ctDNA tested with Guardant360® CDx

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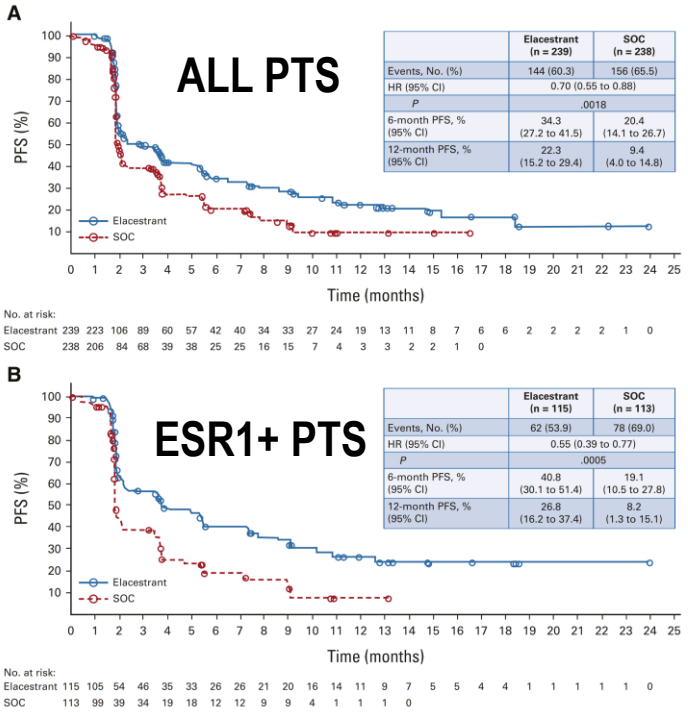
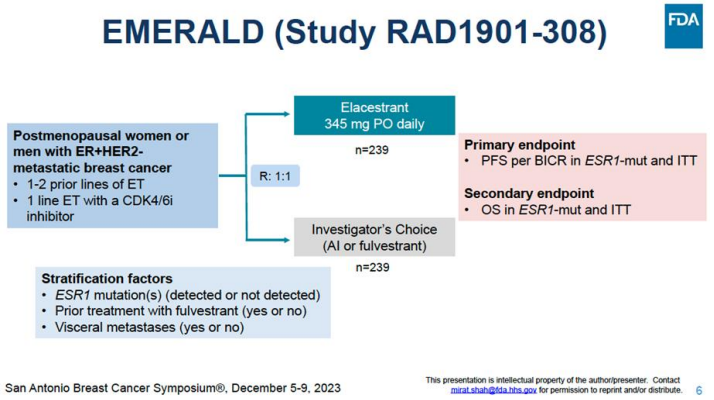
Turner et al, Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH), suppl mat, Lanc. Onc.2020

ELACESTRANT in ESR1 mutation positive BC pts





- ESR1 testing in cfDNA at a central laboratory using the Guardant360 CDx assay
- ESR1 mutations were defined as any missense mutation in codons 310-547
- Frequency of ESR1 variants: 47.8%
- VAF up to 0.03%

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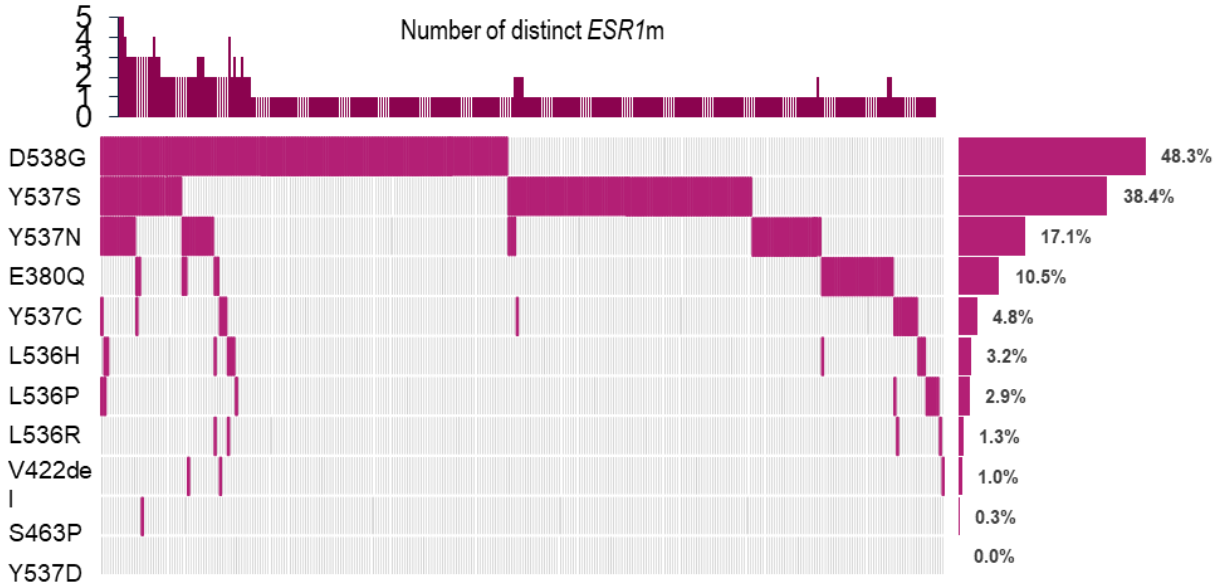
Bidard JCO 2022

SERENA-6: *ESR1*m distribution and baseline sVAF

Randoised patients, n=315

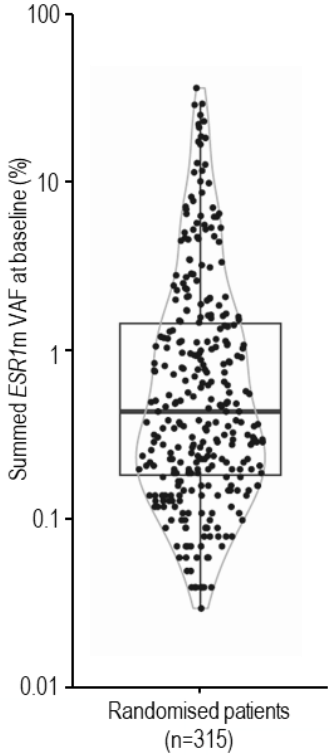
94% of randomised patients had at least 1 of the 4 most common mutations

18% of randomised patients had >1 distinct *ESR1*m detected



(s)VAF, (summed) variant allele frequency.

Baseline *ESR1*m sVAF



EMBER3

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Imlunestrant		Standard Therapy		Imlunestrant–Abemaciclib
	Patients with *ESR1* Mutations (N=138)	All Patients (N=331)	Patients with *ESR1* Mutations (N=118)	All Patients (N=330)	All Patients (N=213)
ESR1 mutation — no. (%)¶	138 (100)	138 (41.7)	118 (100)	118 (35.8)	67 (31.5)

42% ESR1m Detection Rate (138/331)

VERITAC-2

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients with *ESR1* Mutations		All Patients	
	Vepdegestrant (N=136)	Fulvestrant (N=134)	Vepdegestrant (N=313)	Fulvestrant (N=311)
ESR1 mutation — no. (%)¶	136 (100.0)	134 (100.0)	136 (43.5)	134 (43.1)

>43% ESR1m Detection Rate (136/313; 134/311)

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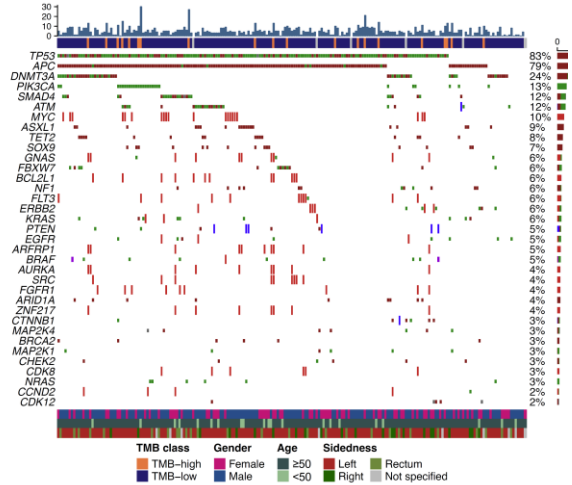
Tissue/liquid biopsy concordance in CRC

Table 1. Tissue and plasma *KRAS* and *NRAS* status

Tissue *KRAS/NRAS* mutational status, *n*		Plasma *KRAS/NRAS* mutational status (*n*)	
		Mutated	Wild-type
Mutated	33	23	10
Wild-type	59	10	49
Total	92	33	59

Normanno et al Ann Oncol 2018



Ciardiello et al Ann Oncol 2024

	Baseline	8 weeks	PD	3mo from PD
Cases KRAS/NRAS/BRAF mutant on plasma/ wt on tissue at baseline	6/37 (16.2%)	6/31 (19.3%)	14/37 (37.8%)	2/21 (9.5%)

Normanno et al ASCO 2018

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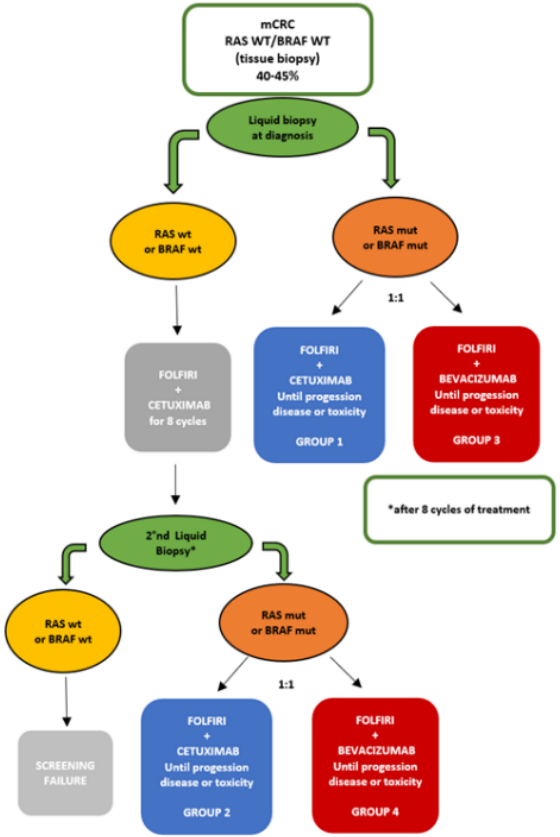
The LIBImAb study



I Random

II Random

Blood samples collected into two 10.0 mL Cell-free DNA BCT (Streck) at:

- baseline for all enrolled patients (screening);
- after 8 cycles of treatment for patients with RAS^{WT} liquid biopsy at baseline, who did not progress (re-screening);
- at progression of the disease, for all randomized patients.
- Plasma samples at baseline and after 8 cycles will be immediately tested, while samples at progression will be also stored for retrospective analyses.

PIs Carmine Pinto & Nicola Normanno; Funded by AIFA (Italian Drug Agency)

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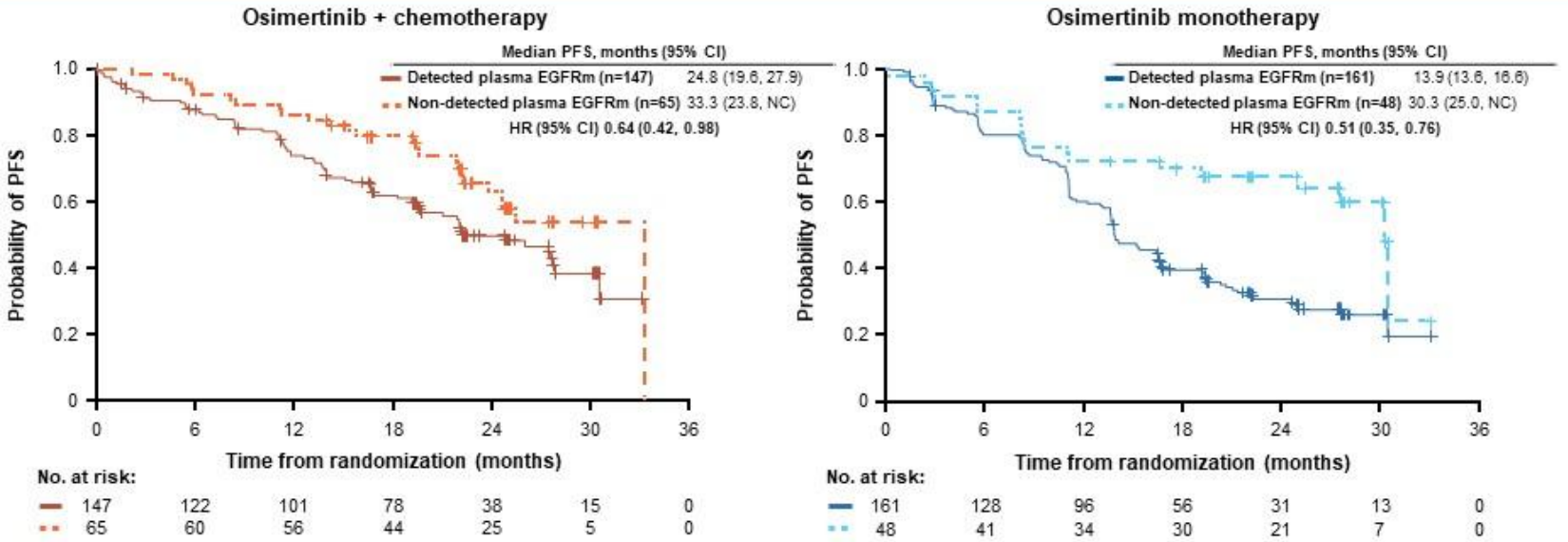
Baseline detected plasma EGFRm correlated with PFS in the ctDNA analysis set across both treatment arms



- Patients with baseline detected plasma EGFRm had shorter median PFS (24.8 and 13.9 months) compared with those with baseline non-detected plasma EGFRm (33.3 and 30.3 months) in the osimertinib plus chemotherapy and osimertinib monotherapy arms, respectively

ctDNA analysis set. HR was calculated by an unstratified log-rank test
CI, confidence interval; ctDNA, circulating tumor DNA; EGFRm, epidermal growth factor receptor mutation; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

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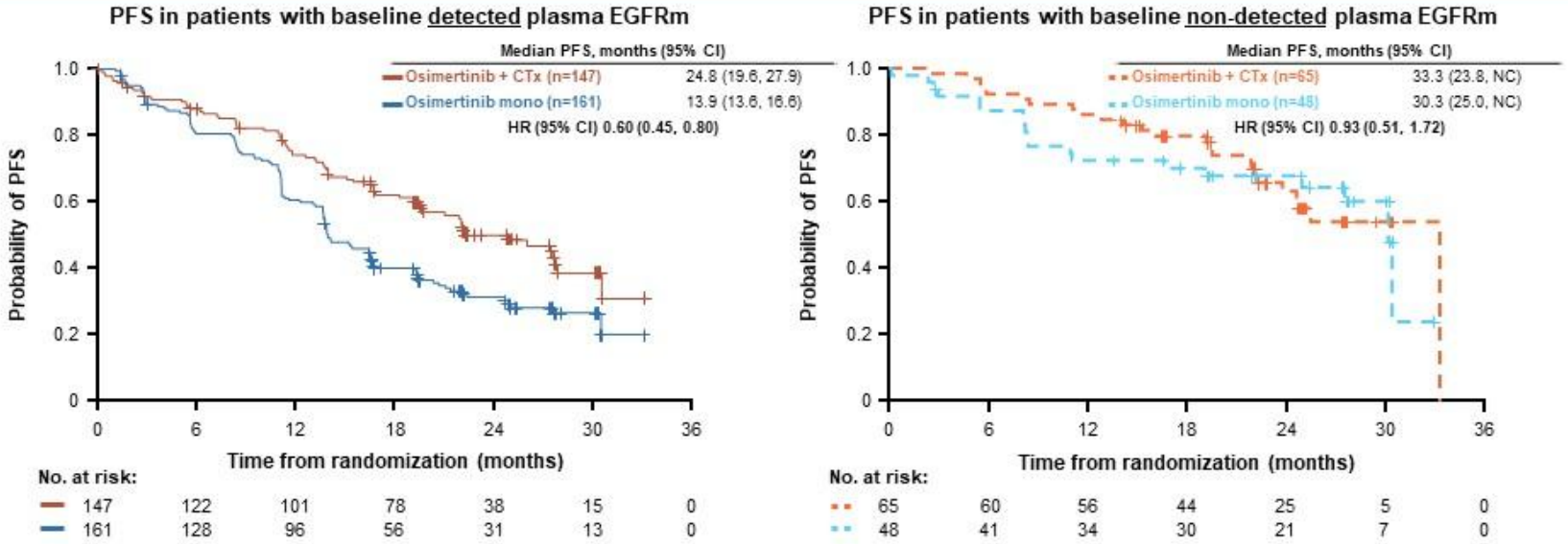
PFS improved with osimertinib plus chemotherapy in patients with baseline detected plasma EGFRm versus osimertinib alone



Baseline detected plasma EGFRm was prognostic and may select for a higher degree of clinical benefit with osimertinib plus chemotherapy versus osimertinib alone

HR was calculated by an unstratified log-rank test
CI, confidence interval; CTx, chemotherapy; EGFRm, epidermal growth factor receptor mutation; HR, hazard ratio; mono, monotherapy; NC, not calculable; PFS, progression-free survival

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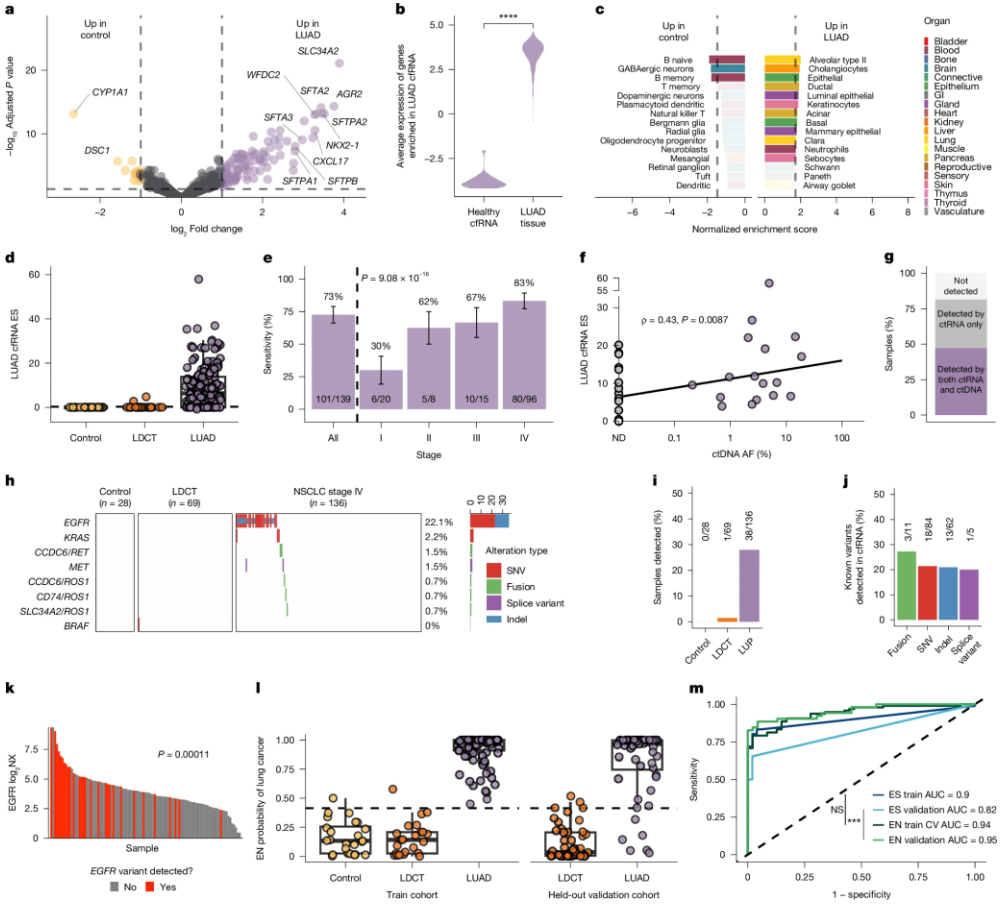
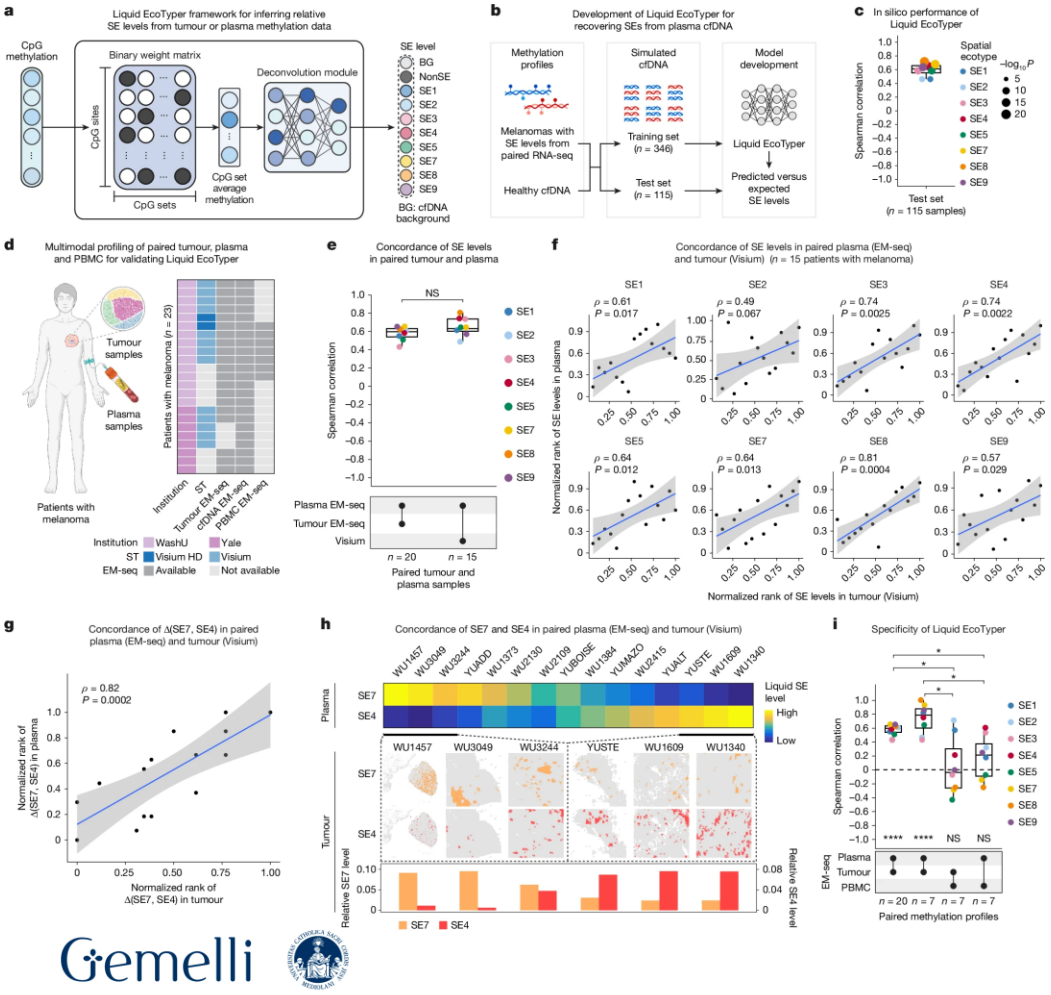
Detection of ctRNA in plasma from patients with NSCLC



Nesselbush Nature 2025

Non-invasive detection of the TME from plasma cell-free DNA



Zhang Nature 2026

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ctDNA CLINICAL USE, INTERPRETATION AND REPORTING IN ADVANCED CANCER

Clinical Guidelines and ctDNA Use

- **Pascual J et al.** ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer. *Ann Oncol. 2022;33(8):750–768.*
- **van de Haar J et al.** ESMO Recommendations on clinical reporting of genomic test results for solid cancers. *Ann Oncol. 2024;35(11):954–967.*
- **Burstein HJ et al.** Testing for ESR1 Mutations to Guide Therapy for HR+/HER2– Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol. 2023;41(18):3423–3427.*

Reporting and Interpretation

- **de Jager VD et al.** Reporting of molecular test results from cell-free DNA analyses: expert consensus recommendations from the 2023 ELBS ctDNA Workshop. *eBioMedicine. 2025;114:105636.*
- **Hadd AG, Silvestro A et al.** Establishing a Common Lexicon for Circulating Tumor DNA Analysis and Molecular Residual Disease: Insights From the BLOODPAC Consortium. *Clin Transl Sci. 2025;18:e70185.*
- **Li MM et al.** Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: Joint Consensus Recommendation of AMP, ASCO, and CAP. *J Mol Diagn. 2017;19(1):4–23.*

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Assay Validation and Quality Assurance

- **Lockwood CM et al.** Recommendations for Cell-Free DNA Assay Validations: A Joint Consensus Recommendation of AMP and CAP. *J Mol Diagn. 2023;25(12):876–897.*
- **Fairley JA, Cheetham MH, Patton SJ et al.** Results of a worldwide external quality assessment of cfDNA testing in lung cancer. *BMC Cancer. 2022;22:759*
- **Edge Health.** A Health Economics Evaluation of ctDNA testing in NSCLC. *NHS England Report. 2024.*

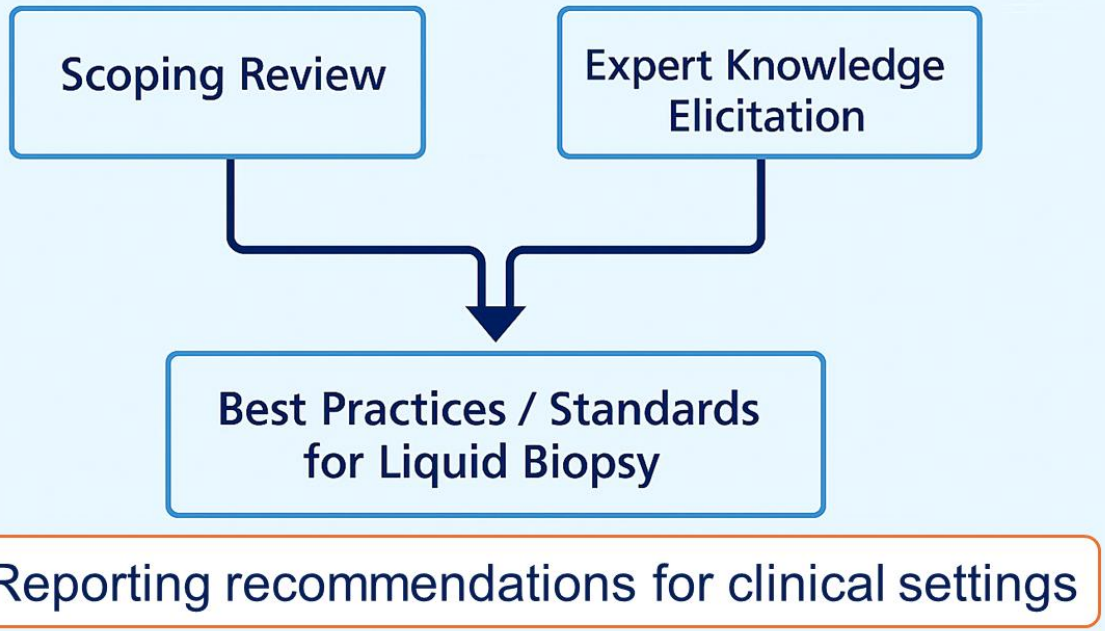
Clonal Haematopoiesis and Germline Findings

- **Tell R, Zehir A et al.** Lexicon for Clonal Hematopoiesis in Liquid Biopsy. *Clin Transl Sci. 2026;19:e70463.*
- **Kuzbari Z et al.** Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations. *Ann Oncol. 2023;34(3):215–241.*

IQNPath
International Quality Network for Pathology

IC3R
collaboration for cancer classification

LIQUID BIOPSY PROTOCOL FOR ONCOLOGY (LUPO)



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Take home messages

- Multi-omic and multi-modal approaches are under development for early cancer diagnosis
- In patients receiving neoadjuvant therapy, ctDNA clearance is highly prognostic and correlates with pCR
- After surgery, detection of MRD by ctDNA testing is associated with a significantly increased risk of recurrence
- Novel technologies will allow detection of complex biomarkers by ctDNA and ctRNA testing
- Results of interventional clinical trials demonstrating the clinical utility of ctDNA testing in directing treatment are needed to move this biomarker in clinical practice
- Standardization of methods for ctDNA testing is necessary to harmonize results from clinical trials

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