Supplementary Materials

Artificial intelligence and circulating tumor DNA minimal residual disease in perioperative resectable non-small cell lung cancer

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Supplementary Table 1. Completed studies exploring MRD-based interventions

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
Longitudinal Monitoring of Circulating Tumor DNA From Plasma in Patients With Curative Resected Stages I to IIIA EGFR-Mutant Non–Small Cell Lung Cancer	Hyun-Ae Jung, Bo Mi Ku	the Bio & Medical Technology Development Program of the National Research Foundation (NRF), South Korea	2023	Journal of Thoracic Oncology	NA	278 EGFR-M+ NSCLC patients	98 (35%)	180 (65%)	I-IIIA	218(78.4%)	167 (60%)	51 (18%)	34(12%)	28 (10%)	6 (2%)	26 (9%)	26 (9%)	0	0	0	0	0	droplet-digital polymerase chain reaction(ddPCR)	5 years
Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA	Christopher Abbosh	the Cancer Research UK Lung Cancer Centre of Excellence	2023	Nature	TRACERx（NCT01888601）	1,069 plasma samples collected from 197 patients	117 (59%)	80 (41%)	I-III	74 (38%)	not reported	not reported	72 (37%)	not reported	not reported	51 (26%)	not reported	not reported	not reported	0	0	0	AMP patient-specific cfDNA enrichment panels	a median follow-up of 4.6 years

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
		and the CRUK City of London Centre Award (C7893/A26233)				enrolled in the TRACERx study2																	(PSPs)	
Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC	Qiu, Bin	Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital	2021	NATURE COMMUNICATIONS	ChiCTR1900024656	103 NSCLC patients who received surgical resection	67 (65%)	36 (35%)	I-IV	12 (10%)	not reported	not reported	41 (40%)	0	41 (40%)	48 (47%)	48 (47%)	0	0	2 (2%)	not reported	not reported	ultradeep targeted next-generation sequencing (NGS)	not reported
Phylogenetic ctDNA	Charles Swanton	University College	2017	Nature	TRACERx	96 patients	60(62.5%)	36(37.5%)	I-III	59(61.5%)	not report	not report	23(24.0)	not repo	not repo	14(14.5%)	not repo	not repo	not repo	0	0	0	whole exome	775days

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
analysis depicts early-stage lung cancer evolution		London (UCL/12/0279)			（NCT01888601）						ed	ed		rted	rted		rted	rted	rted				sequencing (WES)	（688-945）
Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling	Aadel A Chaudhuri	Stanford Cancer Institute	2017	Cancer Discovery	NCT01385722 和 NCT00349830	255 samples from 40 patients treated with curative intent and 54 healthy adults	27(68%)	13(32%)	I-III	7(18%)	0	7(18%)	7(18%)	3(8%)	4(10%)	26(64%)	15(37%)	11(27%)	0	0	0	0	deep sequencing (CAPP-seq)	35.1months (6.9-56)
Longitudinal Undetectable Molecular Residual Disease Defines	Zhang, Jia-Tao	Guangdong Science and Technology Department Translational Medicine	2022	Cancer Discovery	NA	913 peripheral blood samples from 261 patients	158 (60.5%)	103 (39.5%)	I-III	163(62.4%)	104 (39.8%)	59 (22.6%)	53 (20.3%)	not reported	not reported	45 (17.2%)	not reported	not reported	not reported	0	0	0	deep sequencing (CAPP-seq)	a median follow-up of 19.7months

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																	
Potentially Cured Population in Localized Non–Small Cell Lung Cancer		in Lung Cancer																							
Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer	Gale D	Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Cambridge	2022	Annals of Oncology	LUCID(NCT04153526)	363 plasma samples collected from 88 patients	45(51.1%)	43(48.9%)	IA-IIIB	43(48.9%)	not reported	not reported	25(28.4%)	not reported	not reported	20(22.7%)	not reported	not reported	not reported	0	0	0	whole exome sequencing (WES)	a median of 3 years (42 days- 5 years)
Circulating Tumor DNA Monitoring on	Bruna Pellini	Foundation Medicine, Inc. (R.W.	2023	Clinical Cancer Research	IMpower131(NCT02367794)	221 patients	188(85.1%)	33(14.9%)	IV	0	0	0	0	0	0	0	0	0	0	221(100%)	not reported	not reported	Comprehensive Genomic	not reported

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
Chemo-immunotherapy for Risk Stratification in Advanced Non–Small Cell Lung Cancer		Madison, M.A. Childress, S.T. Miller, O. Gjoerup, R.S.P. Huang, A. Young, G.R. Oxnard)																						Profiling (CGP)	
Circulating tumor DNA and radiological tumor volume identify patients at risk for relapse with resected, early-stage non-small-cell	H. T. Tran	The University of Texas MD Anderson Lung Moon Shot Initiative, UT MD Anderson Cancer	2023	Annals of Oncology	NA	366 serial plasma samples from 85 patients	44 (52%)	41 (48%)	I-III	41 (48%)	not reported	not reported	29 (34%)	not reported	not reported	15 (18%)	not reported	not reported	not reported	0	0	0	next-generation sequencing (NGS)	51 months(2-73)

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
lung cancer		Center																						
Comprehensive Genomic Analysis of Patients With Non-Small-Cell Lung Cancer Using Blood-Based Circulating Tumor DNA Assay: Findings From the BFAST Database of a Single Center in Taiwan	Hsin-Yi Wang	the National Taiwan University Hospital	2024	JCO Precision Oncology	BFAST(NCT03178552)	269 patients	132(49.1%)	137(50.9%)	III-IV	0	0	0	0	0	0	24(8.9%)	not reported	not reported	not reported	245(91.1%)	114(42.4%)	131(48.7%)	next-generation sequencing (NGS)	not reported
Individualized tumor-informed circulating tumor	Kezhong Chen	Research Unit of Intelligence Diagnosis	2023	Cancer Cell	NA	760 plasma samples from 181 prospectivel	105(58%)	76(42%)	I-III	115(63.53%)	78(43.09%)	37(20.44%)	34(18.78%)	not reported	not reported	32(17.68%)	not reported	not reported	not reported	0	0	0	deep sequencing (CAPP-s	1,071 days (987_x0001_—1,137 days)

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
DNA analysis for postoperative monitoring of non_x0002_small cell lung cancer		and Treatment in Early Non-small Cell Lung Cancer, Chinese Academy of Medical Sciences				y enrolled early stage non-small cell lung cancer patients																	eq)	
Dynamic circulating tumor DNA during chemoradiotherapy predicts clinical outcomes for locally advanced non-small cell	Yi Pan	Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical	2023	Cancer Cell	(APPROCH/ CTONG2101， NCT04841811)	761 blood samples from 139 patients with locally advanced non-small cell lung cancer treated with definitive	123 (88.5%)	16 (11.5%)	II-III	0	0	0	6 (4.3%)	0	6 (4.3%)	755(95.7%)	38 (27.3%)	76 (54.7%)	19 (13.7%)	0	0	0	next-generation sequencing (NGS)	every 3–6 months

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
lung cancer patients		Sciences), Southern Medical University, Guangzhou, Guangdong, China				radiation therapy (RT)																		
Circulating Tumor DNA Dynamics Predict Benefit from Consolidation Immunotherapy in Locally Advanced Non-Small Cell Lung Cancer	Everett J. Moding	Department of Radiation Oncology, Stanford University, Stanford, California, USA	2021	HHS Public Access	NCT00349830 和 MDACC lab 09–0983、NCT02525757	218 samples from 65 patients receiving chemoradiation therapy (CRT) for locally advanced NSCLC	35(54%)	30(46%)	IIB-IIIB	0	0	0	6(9%)	0	6(9%)	59(91%)	38(58%)	21(32%)	0	0	0	0	deep sequencing (CAPP-seq)	19 months from the start of CRT
Detection and Monitoring of	Paul van der Leest	Department of	2023	International Journal of	NA	177 cell-free	37 (51%	35 (49%	not repo	not reporte	not report	not report	not report	not repo	not repo	not report	not repo	not repo	not repo	not report	not report	not report	next-generation	not reported

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
Tumor-Derived Mutations in Circulating Tumor DNA Using the UltraSEEK Lung Panel on the MassARRAY System in Metastatic Non-Small Cell Lung Cancer Patients		Pathology (EA10), University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands; p.van.der.leest@umcg.nl (P.v.d.L.); n.rifaela@hotmail.com (N.R.);		Molecular Sciences		plasma samples from 72 NSCLC patients	)	)	rted	d	ed	ed	ed	rted	rted	ed	rted	rted	rted	ed	ed	ed	sequencing (NGS)	

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
		ma_aguirre1@yahoo.com.ar (M.L.A.A.); l.van.kempen@umcg.nl (L.C.v.K.)																						
Perioperative Circulating Tumor DNA as a Potential Prognostic Marker for Operable Stage I to IIIA Non–Small Cell Lung Cancer	Ning Li	Sun Yat-sen University Cancer Center: Guangzhou, Guangdong, CN	2022	American Cancer Society	NCT03465241	123 patients with resectable stage I to IIIA NSCLC	70(59%)	49(41%)	I-III	77(65%)	26(22%)	51(43%)	24(21%)	9(8%)	15(13%)	18(15%)	18(15%)	0	0	0	0	0	next-generation sequencing (NGS)	30.7 months (95% CI, 28.8-32.6 months)
Circulating Tumor DNA as a Prognostic	Muyun Peng	Department of Thoracic Surgery,	2022	Frontiers in Oncology	NA	81 patients diagnosed with	56 (72.7%)	21 (27.3%)	I-III、IV	40 (51.9%)	not reported	not reported	18 (23.4%	not reported	not reported	0	0	0	0	2 (2.6%)	not reported	not reported	high-sensitivity circulati	46 months

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
Biomarker in Localized Non-small Cell Lung Cancer		The Second Xiangya Hospital of Central South University, Changsha, China,				solitary lung nodules																	ng single-molecule amplification and resequencing technology (cSMART) assay	
Early assessment of circulating tumor DNA after curative_x0002_intent resection predicts tumor recurrence in	Silvia Waldeck	Department of Medicine I, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg,	2022	Molecular Oncology	NA	33 consecu-tive patients with stage IA to IIIB NSCLC undergoing curative-intent tumor resection	7 (33%)	14 (67%)	I-III	2(9.5%)	2 (9.5%)	0	9(42.9%)	1 (4.8%)	8 (38.1%)	10(47.6%)	8 (38.1%)	2 (9.5%)	0	0	0	0	next-generation sequencing (NGS)	26.2 months

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
early-stage and locally advanced non-small-cell lung cancer		Freiburg, Germany																						
Circulating tumor DNA integrating tissue clonality detects minimal residual disease in resectable non-small-cell lung cancer	Siwei Wang	Department of Thoracic Surgery, Jiangsu Key Laboratory of Molecular and Translational Cancer Research, Jiangsu Cancer Hospital	2022	Journal of Hematology & Oncology	NA	128 patients with stage I–III NSCLCs who received curative surgical resections	65(56%)	52(44%)	I-III	53(45%)	not reported	not reported	21(18%)	not reported	not reported	43(37%)	not reported	not reported	not reported	0	0	0	Targeted sequencing	144 days
Perioperative	Liang Xia	Institute of	202	American	NCT03317080	950 plasma	161(4	169	I-III	221(67	not	not	60	not	not	49	not	not	not	0	0	0	next-gen	1068 days

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																	
ctDNA-Based Molecular Residual Disease Detection for Non–Small Cell Lung Cancer: A Prospective Multicenter Cohort Study (LUNGCA-1)		Thoracic Oncology and Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China.	2	Association for Cancer Research		samples obtained at three perioperative time points (before surgery, 3 days and 1 month after surgery) of 330 stage I–III NSCLC patients (LUNGCA_x0002_1), as a part of the LUNGCA cohort	8.8%)	（51.2%）		%)	reported	reported	(18.2%)	reported	reported	(14.8%)	reported	reported	reported				eration sequencing (NGS)	

Article title	Author	Institution/ Country	Publish year	Journal	Clinical trial	Sample	Gender		Stage	I	IA	IB	II	IIA	IIB	III	IIIA	IIIB	IIIC	IV	IVA	IVB	ctDNA detection method	Follow-up time
							Male	Female																
Genome-wide cell-free DNA mutational integration enables ultra-sensitive cancer monitoring	Asaf Zviran	New York Genome Center, New York, NY, USA	2020	NATURE MEDICINE	NA	39 LUAD patients	18(46%)	21(54%)	I-IV	26(67%)	18(46%)	8(21%)	7(18%)	5(13%)	2(5%)	5(13%)	5(13%)	0	0	1(2%)	not reported	not reported	deep targeted sequencing	18months(6-36)

MRD: Molecular residual disease; ctDNA: circulating tumor DNA; NSCLC: non-small cell lung cancer; EGFR-M: EGFR-mutant; ddPCR: droplet-digital polymerase chain reaction; NGS: next-generation sequencing; WES: whole-exome sequencing; CAPP-seq: Cancer Personalized Profiling by deep Sequencing; CGP: comprehensive genomic profiling; cSMART: circulating single-molecule amplification and resequencing technology; PSPs: patient-specific cfDNA enrichment panels.

Supplementary Table 2. Ongoing trials exploring MRD-based interventions

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT05254782	Using ctDNA to Detect Minimal Residual Disease After Lung Cancer Resection	Non Small Cell Lung Cancer	NA	Rate of ctDNA Detection, up to 24 Months | Relapse Free Survival, up to 36 Months	University Health Network, Toronto	NA	360	Start: 2021-07-06 Completion: 2025-06-30 Last update: 2023-09-06	Multicenter, Canada
NCT06198868	MRD-guided Prognosis Prediction and Adjuvant Treatment Based on CTC and ctDNA in NSCLC	Non-small Cell Lung Cancer	PROCEDURE: Operable	Progression-free Survival (PFS), up to approximately 3 years	Jiangsu Cancer Institute & Hospital	NA	60	Start: 2024-02-01 Completion: 2027-02-01 Last update: 2024-01-12	Jiangsu Cancer Institute & Hospital, China
NCT05295212	Atezolizumab Combined With Platinum-based Chemotherapy as Neoadjuvant Therapy for Patients With Resectable Stage	Non Small Cell Lung Cancer	DRUG: Atezolizumab	MPR Rate, 1.5 year | MRD negative Rate, 1.5 year	Hunan Province Tumor Hospital	2	120	Start: 2023-02-01 Completion: 2024-07-01 Last update: 2023-03-01	Hunan Cancer hospital, China

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	II-IIIB								
NCT04966663	Using ctDNA to Determine Therapies for Lung Cancer	Non Small Cell Lung Cancer|Complete Surgical Resection|Circulating Tumor DNA	DRUG: Nivolumab|DRUG: Pemetrexed|DRUG: Gemcitabine|DRUG: Cisplatin|DRUG: Carboplatin|PROCEDURE: ctDNA blood test	Relapse Free Survival, 2 years	University Health Network, Toronto	2	66	Start: 2022-03-28 Completion: 2026-12-01 Last update: 2024-07-22	Princess Margaret Cancer Centre, Canada
NCT05460195	Sintilimab Combined With Anlotinib for Perioperative Non-small Cell Lung Cancer Based on MRD Evaluation	Non-small Cell Lung Cancer|Minimal Residual Disease|Immunotherapy|Anti-angiogenesis	DRUG: sintilimab combined with anlotinib|DRUG: sintilimab monotherapy	Major pathologic response (MPR), 2 months	Shanghai Chest Hospital	2	42	Start: 2022-01-01 Completion: 2024-12-31 Last update: 2022-07-15	Shanghai Chest Hospital, China
NCT05236114	GEMINI-NSCLC: NSCLC Biomarker Study	Non-Small Cell Lung Cancer	OTHER: Observation	Real-World Disease Free Survival (rwDFS), 5 years | Real-World Overall Survival	Tempus AI	NA	1200	Start: 2022-06-22 Completion: 2029-06-01 Last update: 2026-02-05	Multicenter, United States

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
				(rwOS), 3 years					
NCT05536505	Adjuvant Treatment Based on MRD for EGFR Mutant NSCLC	MRD	GENETIC: Adjuvant treatment for MRD positivity	Disease Free Survival, up to 100 months | 3 yeas DFS rate, up to 100 months	Guangdong Association of Clinical Trials	2	180	Start: 2022-09-13 Completion: 2030-10-01 Last update: 2022-09-14	Multicenter, China
NCT06426511	ctDNA-MRD Guided Consolidation Toripalimab in Stage IB-IIIA NSCLC	Lung Cancer, Nonsmall Cell	DRUG: Toripalimab+Chemotherapy|DRUG: Toripalimab+Chemotherapy followed by consolidation toripalimab	The 2-year DFS rate of ctDNA-MRD guided consolidation toripalimab, Baseline to 24 months	Sun Yat-sen University	2	80	Start: 2024-07-01 Completion: 2029-07-01 Last update: 2024-05-23	NA
NCT05219734	MRD Assay Evaluates Recurrence and Response Via a Tumor Informed	Cancer|Solid Tumor|Non Small Cell Lung Cancer|Colorectal Cancer|Bladder Cancer	DIAGNOSTIC_TEST: Personalized Cancer Monitoring (PCM)	Overall survival, up to 5 years | Relapse Free Survival, up to 3	Invitae Corporation	NA	400	Start: 2021-11-29 Completion: 2026-12-01	Multicenter, United States

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	Assessment			years				Last update: 2024-03-12	
NCT06443684	A Study of Molecular Residual, Dynamic Monitoring and Recurrence of Stage III Driver Mutated NSCLC	Non Small Cell Lung Cancer	DIAGNOSTIC_TEST: MRD	Correlation of MRD status in driver gene-positive NSCLC patients with 12-month relapse events, 2022.12--2025.03	Shanghai Chest Hospital	NA	305	Start: 2023-05-08 Completion: 2026-03-31 Last update: 2024-06-05	Multicenter, China
NCT05623267	Sugemalimab as Consolidation Therapy in Patients With LS-SCLC Following cCRT or sCRT	Limited Stage Small Cell Lung Cancer	DRUG: Sugemalimab|DRUG: Placebo	Progress Free Survival(PFS), up to 36 months	Sun Yat-sen University	2|3	346	Start: 2023-07-01 Completion: 2027-03-31 Last update: 2023-08-07	Sun Yat-sen University Cancer Center, China
NCT04950907	Uniportal Tubeless VATS for the Evaluation of Biopsy	NSCLC|Biopsy Technique|VATS|CT Guided Puncture Biopsy|NGS	DIAGNOSTIC_TEST: vats|DIAGNOSTIC_TEST: CT-guided fine needle biopsy	Qualified Rate of Biopsy for Second-generation	Jianxing He	NA	94	Start: 2021-07-15 Completion:	NA

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	for Second-generation Sequencing in Patients With Advanced NSCLC			Tibial Specimens, up to 2 years				2024-06-26 Last update: 2021-07-13	
NCT06111807	Clinical Validation and Benchmarking of Top Performing ctDNA Diagnostics - Stage III NSCLC	Lung Cancer Stage III	DIAGNOSTIC_TEST: ctDNA	Collection of clinical plasma samples at relevant time points, 8 months after end of recruitment	University Medical Center Groningen	NA	248	Start: 2023-11-10 Completion: 2030-07-31 Last update: 2024-02-23	Multicenter, France/Germany/Netherlands
NCT06323148	Adjuvant Target Therapy Guided by ctDNA-MRD in Patients With EGFR-mutant II-IIIA Non-small Cell Lung Cancer (ECTOP-1022)	Lung Cancer|EGFR Gene Mutation|Minimal Residual Disease	DRUG: Osimertinib|DRUG: No adjuvant therapy	The 3-year Disease-Free Survival (DFS) rate between the observation group and the osimertinib treatment group, 3 years	Fudan University	3	226	Start: 2024-04-01 Completion: 2029-03-31 Last update: 2024-03-21	NA

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT05167604	Clinical Value of MRD Monitoring for Adjuvant Therapy in Postoperative NSCLC	Carcinoma, Non-Small-Cell Lung|Next-Generation Sequencing|Chemotherapy, Adjuvant|Neoplasm, Residual|Circulating Tumor DNA	DRUG: Adjuvants, Pharmaceutic	3-year DFS rate, 3 years	Tang-Du Hospital	NA	150	Start: 2021-09-30 Completion: 2024-12-01 Last update: 2021-12-22	The Second Affiliated The Second Affiliated Hospital of Air Force Medical University (Tangdu Hospital), China
NCT05366881	cfDNA Assay Prospective Observational Validation for Early Cancer Detection and Minimal Residual Disease	Brain Cancer|Breast Cancer|Bladder Cancer|Cervical Cancer|Colorectal Cancer|Endometrial Cancer|Esophageal Cancer|Stomach Cancer|Head and Neck Cancer|Hepatobiliary Cancer|Leukemia|Lung Cancer|Lymphoma|Multiple Myeloma|Ovarian Cancer|Pancreatic Cancer|Prostate Cancer|Renal Cancer|Sarcoma|Thyroid Cancer	NA	Detection of cancer, 24 months	Adela, Inc	NA	7000	Start: 2022-05-03 Completion: 2026-12-01 Last update: 2024-02-20	Multicenter, United States
NCT05206812	Window of Opportunity Trial of Durvalumab (MEDI4736) to	Non Small Cell Lung Cancer	DRUG: durvalumab	Major pathologic response, Right after the surgery	Yonsei University	2	25	Start: 2022-03-01 Completion: 2025-12-01	Yonsei University Health System, Korea, Republic of

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	Identify Immune Dynamics in Operable Non-small Cell Lung Cancer (NSCLC) (MIRACLE)							Last update: 2022-02-11	
NCT05079022	ctDNA-MRD Based Adjuvant Targeted Therapy for EGFR Positive Stage I Lung Adenocarcinomas	Adenocarcinoma of Lung	DRUG: Furmonertinib	Clearance of ctDNA at 6 months, 6 months	Peking University People's Hospital	1|2	50	Start: 2021-10-01 Completion: 2024-09-01 Last update: 2021-10-15	Peking University People's Hospital, China
NCT04585490	Personalized Escalation of Consolidation Treatment Following Chemoradiotherapy and Immunotherapy in Stage III NSCLC in Stage III NSCLC	Non Small Cell Lung Cancer|NSCLC, Stage III|Nsclc	DRUG: Durvalumab|DRUG: Carboplatin|DRUG: Pemetrexed|DRUG: Paclitaxel|DRUG: Cisplatin|DEVICE: AVENIO ctDNA Surveillance Kit|DRUG: Tremelimumab	Change in ctDNA Level Following Chemotherapy, 12 weeks	Maximilian Diehn	3	48	Start: 2021-08-25 Completion: 2028-04-01 Last update: 2024-04-17	Stanford University, United States

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT05286957	MRD-guided Adjuvant Tislelizumab and Chemotherapy in Resected Stage IIA-IIIB NSCLC	NSCLC	DRUG: adjuvant tislelizumab and chemotherapy for MRD+ patients|DRUG: adjuvant tislelizumab and chemotherapy for MRD+ patients|DRUG: adjuvant chemotherapy for MRD- patients	2-year PFS rate, up to 36 months after enrollment or study close	The First Affiliated Hospital of Zhengzhou University	2	60	Start: 2022-06-20 Completion: 2027-06-01 Last update: 2023-03-17	The First Affiliated Hospital of Zhengzhou University, China
NCT04944173	SCION: SABR and Checkpoint Inhibition Of NSCLC	Non Small Cell Lung Cancer|Carcinoma, Non-Small-Cell Lung|Non-small Cell Lung Cancer Stage I|Lung Cancer|Lung Cancer Stage I|Lung Adenocarcinoma, Stage I|Lung Squamous Cell Carcinoma Stage I	DRUG: Durvalumab|RADIATION: Stereotactic Body Radiotherapy|DIAGNOSTIC_TEST: Circulating Tumor DNA assay	Overall Risk of Relapse, 18 months	University of British Columbia	2	94	Start: 2023-08-11 Completion: 2027-06-01 Last update: 2024-05-24	Multicenter, Canada
NCT05165160	Residual Disease Evaluation of Resected NSCLC by cirDNA Analysis	Nsclc	DIAGNOSTIC_TEST: Blood sample	Recurrence-free survival probability according to MiTest at one year after surgery (RFS1), The year after surgery	University Hospital, Montpellier	NA	133	Start: 2022-02-15 Completion: 2025-08-15 Last update: 2023-12-26	University Hospital, France

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT04585477	Adjuvant ctDNA-Adapted Personalized Treatment in Early Stage NSCLC (ADAPT-E)	Non-small Cell Lung Cancer|Non-small Cell Lung Cancer Stage I|Non-small Cell Lung Cancer Stage II|Non-small Cell Lung Cancer Stage III	DEVICE: AVENIO ctDNA Surveillance Kit|DRUG: Durvalumab	Decrease in ctDNA Level, 8 weeks	Stanford University	2	80	Start: 2021-04-08 Completion: 2026-12-30 Last update: 2024-06-21	Stanford University, United States
NCT04367311	Adjuvant Treatment With Cisplatin-based Chemotherapy Plus Concomitant Atezolizumab in Patients With Stage I (Tumors ≥ 4cm), IIA, IIB, and Select Stage III [Any T1-3 N1-2 and T4N0-2] Resected Non-small Cell Lung Cancer (NSCLC) and the Clearance of Circulating Tumor	Lung Cancer|NSCLC	DRUG: Atezolizumab|DRUG: Docetaxel|DRUG: Cisplatin|DRUG: Pemetrexed	Percentage of patients with undetectable ctDNA after 4 cycles of adjuvant chemotherapy + Atezolizumab plus up to 13 additional cycles of Atezolizumab in patients with stage I (tumors ≥ 4cm), IIA, IIB, and select stage III	Nasser Hanna	2	100	Start: 2020-05-22 Completion: 2025-01-01 Last update: 2024-08-09	Multicenter, United States

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	DNA (ctDNA)			[any T1-3 N1-2 and T4N0-2], Up to 17 cycles (13 months)					
NCT06381960	Clinical Study on the Prevention and Treatment of Postoperative Metastasis of Lung Cancer by Fuzheng Quxie Recipe	Lung Cancer	DRUG: Fuzheng Quxie Recipe|DRUG: Fuzhengquye Fang Recipe simulant	Disease-free survival, up to 5 years	Jianhui Tian	2	356	Start: 2023-03-01 Completion: 2025-12-31 Last update: 2024-05-03	Multicenter, China
NCT04758949	FL-101 in Surgically Resectable Non-Small Cell Lung Cancer	Non-Small Cell Lung Cancer	DRUG: FL-101|DRUG: Nivolumab|DRUG: Placebo	Number of patients with treatment related adverse events as assessed by NCI CTCAE v.5.0, From time of first dose to 3 months after surgery	Flame Biosciences	2	0	Start: 2021-08-25 Completion: 2021-12-22 Last update: 2022-01-11	NA

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT06524518	A Multicenter Randomized Controlled Study of Interventional Treatment for Operable Stage II-III Non-small Cell Lung Cancer With Potential Recurrence as Minimal Residual Disease(MRD) Positive	DFS	DRUG: Chemotherapy combined with immunization	DFS, 3 years	Xuanwu Hospital, Beijing	2	213	Start: 2024-08-01 Completion: 2029-12-01 Last update: 2024-08-06	Xuanwu Hospital, China
NCT06086574	Developing Circulating and Imaging Biomarkers Towards Personalised Radiotherapy in Lung Cancer	Lung Cancer Stage III	NA	Prognostic model built using baseline and longitudinal circulating-tumour DNA, 2.5 years	University of Manchester	NA	80	Start: 2023-03-24 Completion: 2025-09-24 Last update: 2023-10-17	The Christie NHS Foundation Trust, United Kingdom
NCT06262386	Combined Relapse Prediction Model for	Lung Cancer|Relapse/Recurrence	DRUG: Cisplatin based chemottherapy	Accuracy of proposed relapse	Chang Gung	NA	358	Start: 2023-08-01	Ching-Yang Wu, Taiwan

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	Resectable Non-Small Cell Patients - a Prospective Clinical Feasibility Trial			prediction model, follow up in 3 month-interval | early relapse rate, follow up in 3 month-interval	Memorial Hospital			Completion: 2028-07-31 Last update: 2024-02-16	
NCT03774758	Biomarkers for Risk Stratification in Lung Cancer	Nodule Solitary Pulmonary|Non-small Cell Lung Cancer	DIAGNOSTIC_TEST: Guardant Health ct-DNA LUNAR assay	Sensitivity and specificity of ct-DNA LUNAR Assay | Prospective negative predictive value of ct-DNA LUNAR assay	University of California, San Francisco	NA	590	Start: 2017-12-17 Completion: 2024-12-31 Last update: 2023-09-21	Multicenter, United States
NCT04965831	Furmonertinib as Perioperation Therapy in Stage IIIA-IIIB (N1-N2) Resectable EGFR Mutated Lung	Lung Adenocarcinoma	DRUG: Furmonertinib	Objective Response Rate (ORR), Approximately 8 weeks following	Tianjin Medical University Cancer Institute	2	40	Start: 2021-08-01 Completion: 2026-05-01 Last update:	NA

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	Adenocarcinoma (FRONT)			the first dose of study drug	and Hospital			2021-07-16	
NCT05059444	ORACLE: Observation of ResiduAl Cancer With Liquid Biopsy Evaluation	Bladder Carcinoma|Ureter Carcinoma|Renal Pelvis Carcinoma|Non-small Cell Lung Cancer|Invasive Breast Carcinoma|Cutaneous Melanoma|Esophageal Carcinoma|Gastroesophageal Junction Carcinoma|Gastric Adenocarcinoma|Pancreatic Adenocarcinoma|Squamous Cell Carcinoma of the Head and Neck|Epithelial Ovarian Carcinoma|Fallopian Tube Carcinoma|Endometrial Carcinoma|Renal Cell Carcinoma	DIAGNOSTIC_TEST: Guardant Reveal	Distant Recurrence Free Interval (D-RFi), 6 years	Guardant Health, Inc.	NA	1000	Start: 2021-09-07 Completion: 2028-02-01 Last update: 2022-09-09	Redwood City, United States
NCT04025216	A Study of CART-TnMUC1 in Patients With	Non-Small Cell Lung Cancer|Ovarian Cancer|Fallopian Tube Cancer|Triple Negative Breast Cancer|Multiple	BIOLOGICAL: CART-TnMUC1|DRUG: Cyclophosphamide|DRUG:	Dose Escalation: Dose Identification of	Kite, A Gilead Company	1	16	Start: 2019-10-10 Completion:	Multicenter, United States

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	TnMUC1-Positive Advanced Cancers	Myeloma|Pancreatic Ductal Adenocarcinoma	Fludarabine	CART-TnMUC1, Up to 2 years | Cohort Expansion: Objective Response in solid tumors, Up to 2 years				2022-12-02 Last update: 2024-01-24	
NCT07472478	Phase II Neoadjuvant Study of Garsorasib Followed by Ivonescimab Plus Chemotherapy in Resectable Stage IIA-IIIB KRAS G12C-Mutant NSCLC (GIVEN Study)	Lung Cancer (NSCLC)|KRAS G12C Lung Cancer	DRUG: Garsorasib|DRUG: Ivonescimab Combined With Chemotherapy|PROCEDURE: Surgery|DRUG: Garsorasib|DRUG: Ivonescimab|BEHAVIORAL: Observation	Pathologic complete response (pCR) rate assessed according to the IASLC recommendations for pathologic evaluation of lung cancer neoadjuvant therapy, 14-24 weeks	Guangdong Provincial People's Hospital	2	32	Start: 2026-03-15 Completion: 2028-03-31 Last update: 2026-03-16	NA

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT07450183	Perioperative Cemiplimab for Resectable Non-Small Cell Lung Cancer With High PD-L1	Lung Cancer (NSCLC)	DRUG: Cemiplimab|DRUG: Adjuvant chemotherapy	Pathologic Complete Response Rate, At surgical resection visit	Henry Ford Health System	2	33	Start: 2026-06-01 Completion: 2027-12-01 Last update: 2026-03-04	Henry Ford Health, United States
NCT07291921	To Conduct Multi-omics Integrated Studies in Peripheral Blood, Such as Fragment Omics, Metabolomics and Epigenetics, and Establish Non-invasive Dynamic Follow-up Monitoring Programs During Perioperative and Postoperative Periods	Lung Neoplasms|Neoadjuvant Therapy|Immunotherapy|Minimal Residual Disease	NA	Two-year recurrence-free survival rate	Peking University People's Hospital	NA	100	Start: 2025-05-08 Completion: 2027-10-31 Last update: 2026-03-03	Peking University People's Hospital, China

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	(Observational Study)								
NCT07119190	A Perioperative Comprehensive Diagnosis and Treatment System for Lung Cancer in the Era of Neoadjuvant Immunotherapy	Non-Small Cell Lung Cancer	NA	Pathological Complete Response (pCR), At surgery (typically 3-6 months post-treatment initiation)	Peking University People's Hospital	NA	350	Start: 2025-08-06 Completion: 2027-10-30 Last update: 2025-08-12	NA
NCT06856798	Construction of a Prognostic and Prediction Model for Perioperative Immunotherapy in NSCLC: a Multi - Omics Perspective	NSCLC Stage IIIA/B|NSCLC Stage II	NA	Pathological response after immune neoadjuvant therapy, From enrollment to surgery at 18 weeks	Ziming Li	NA	120	Start: 2025-03-10 Completion: 2028-02-09 Last update: 2025-03-04	NA
NCT06734182	Neoadjuvant Envafolimab Plus	Non-small Cell Lung Cancer	DRUG: Envafolimab injections+intravenous Disitamab	MPR rate, up to 7 weeks after	Guangdong Provincial	2	25	Start: 2024-06-22	Guangdong Provincial People's Hospital, China

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
	Disitamab Vedotin and Carboplatin in Resectable HER2-Mutant Non-Small-Cell Lung Cancer		Vedotin+carboplatin	neoadjuvant	People's Hospital			Completion: 2028-06-22 Last update: 2024-12-16	
NCT06332274	tislelizUMaB in canceR Patients With molEcuLar residuaL Disease	Cancer|Lung Cancer|Colo-rectal Cancer|Pancreas Cancer|Soft Tissue Sarcoma	DRUG: Tislelizumab|OTHER: Blood sampling|DRUG: Placebo	Efficacy of tislelizumab compared to placebo as measured by DFS (Disease-free survival), relapse/death assessed up to 60 months and at 12 months, 24 months, 48 months and 60 months	Gustave Roussy, Cancer Campus, Grand Paris	3	717	Start: 2025-04-16 Completion: 2030-04-01 Last update: 2025-05-13	Gustave Roussy, France

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
NCT05822284	ctDNA-MRD in Stage IIIB-C NSCLC Patients Treated With Induction Chemoimmunotherapy	Non-small Cell Lung Cancer	DIAGNOSTIC_TEST: NGS and ctDNA-MRD detection	Predicting Progression Free Survival, up to 5 years | Predicting pathologic complete response, Up to 1 year | Predicting Overall Survival, up to 5 years	Second Xiangya Hospital of Central South University	NA	50	Start: 2023-04-01 Completion: 2029-03-01 Last update: 2023-04-20	Second Xiangya Hospital of Central South University, China
NCT05648370	Liquid Biopsy in Advanced Oligometastatic NSCLC Receiving Surgery	Non-small Cell Lung Cancer|Oligometastatic Disease	GENETIC: ctDNA testing and whole exome sequencing	Association between perioperative ctDNA-MRD characteristics and rogression-free survival, 2-year PFS | Construction of a survival-predictio	Guangdong Provincial People's Hospital	NA	60	Start: 2022-07-01 Completion: 2025-06-30 Last update: 2022-12-13	Guangdong Lung Cancer Institute, China

NCT	Study title	Condition	Interventions	Primary outcome measures	Sponsor	Phases	Enrollment	Timeline	Location
				n model, up to 5 years					

ctDNA: Circulating tumor DNA; MRD: molecular residual disease; NSCLC: non-small cell lung cancer; NCT: National Clinical Trial number; PFS: progression-free survival; DFS: disease-free survival; MPR: major pathologic response; rwDFS: real-world disease-free survival; rwOS: real-world overall survival; EGFR: epidermal growth factor receptor; VATS: video-assisted thoracoscopic surgery; NGS: next-generation sequencing; ORR: objective response rate; pCR: pathologic complete response; IASLC: International Association for the Study of Lung Cancer; PD-L1: programmed death-ligand 1; KRAS: Kirsten rat sarcoma viral oncogene homolog; HER2: human epidermal growth factor receptor 2.

Supplementary Table 3. Ongoing trials utilizing AI/ML for ctDNA analysis in NSCLC

NCT	Study title	Study status	Conditions	Interventions	Sponsor	Study type
NCT06163846	Image Mining and ctDNA to Improve Risk Stratification and Outcome Prediction in NSCLC Applying Artificial Intelligence.	RECRUITING	Non Small Cell Lung Cancer	DIAGNOSTIC_TEST: Assess the role of baseline image mining, ctDNA data and their combination in patient staging and risk stratification	IRCCS San Raffaele	OBSERVATIONAL
NCT06810609	Immunochemotherapy, Surgery or Chemoradiation, and Durvalumab for Stage IIIA/B NSCLC	RECRUITING	Lung Cancer Non-Small Cell Cancer (NSCLC)	PROCEDURE: surgery (any volume) and / or pharmaceuticals treatment initiated or planned or only dynamic observation, in accordance with current clinical guidelines|RADIATION: Chemoradiotherapy|DRUG: Immunotherapy	Eleni Gkika	INTERVENTIONAL
NCT05736029	Predicting Responsiveness in Oncology Patients Based on Host Response Evaluation During Anti Cancer Treatments, Using Multiomics	RECRUITING	Non Small Cell Lung Cancer|Healthy	OTHER: blood, stool and tissue samples collection	OncoHost Ltd.	OBSERVATIONAL
NCT03519958	Epidermal Growth Factor Receptor (EGFR) T790M Mutation Testing Practices in Hong Kong	WITHDRAWN	Non-small Cell Lung Cancer	DIAGNOSTIC_TEST: Plasma-tissue testing	AstraZeneca	OBSERVATIONAL
NCT06105177	Implementation of Up-front ctDNA Into Lung Cancer Care and Development of Liquid Biopsy-based Decision Support Models - LM Study	RECRUITING	Lung Cancer		Catharina Ziekenhuis Eindhoven	OBSERVATIONAL
NCT05732974	A Machine Learning Approach to Identify Patients With Resected Non-small-cell Lung	RECRUITING	Non-small Cell Lung Cancer Stage IIIA	OTHER: Resected non small cell lung cancer	University Hospital,	OBSERVATIONAL

NCT	Study title	Study status	Conditions	Interventions	Sponsor	Study type
	Cancer With High Risk of Relapse				Toulouse	
NCT04529915	Multicenter Clinical Research for Early Diagnosis of Lung Cancer Using Blood Plasma Derived Exosome	UNKNOWN	Lung Cancer	DIAGNOSTIC_TEST: Exosome sampling	Korea University Guro Hospital	OBSERVATIONAL
NCT06086574	Developing Circulating and Imaging Biomarkers Towards Personalised Radiotherapy in Lung Cancer	RECRUITING	Lung Cancer Stage III		University of Manchester	OBSERVATIONAL
NCT05066776	Liquid Biopsy With PET/CT Versus PET/CT Alone in Diagnosis of Small Lung Nodules	TERMINATED	Lung Cancer|Solitary Pulmonary Nodule|Multiple Pulmonary Nodules		Palo Alto Veterans Institute for Research	OBSERVATIONAL
NCT06717295	The CCANED-CIPHER Study: Early Cancer Detection and Treatment Response Monitoring Using AI-Based Platelet and Immune Cell Transcriptomic Profiling	NOT_YET_RECRUITING	Brest Cancer|Lung Cancer (NSCLC)|Pancreatic Cancer, Adult|Prostate Cancers|Ovarian Cancer|Colorectal Cancer|Glioblastoma (GBM)|Liver Carcinoma	DIAGNOSTIC_TEST: DiNanoQ: A multi-cancer early detection (MCED) blood test|OTHER: DiNanoTrack: Therapeutic Response Monitoring Blood Test	Javier Toledo	OBSERVATIONAL
NCT06440018	INSPIRE: a Multi-Cancer Early Detection Study	RECRUITING	Lung Cancer|Gastric Cancer|Liver Cancer|Colorectal Cancer|Pancreatic Cancer|Esophageal Cancer|Breast Cancer|Cervical Cancer|Ovarian		Singlera Genomics Inc.	OBSERVATIONAL

NCT	Study title	Study status	Conditions	Interventions	Sponsor	Study type
			Cancer|Endometrial Cancer|Bladder Cancer|Prostate Cancer|Cholangiocarcinoma			
NCT04315766	Optimised Lung Cancer Screening to Prevent Cardiovascular and Pulmonary Diseases Coupled With Primary Prevention	UNKNOWN	Lung Cancer|Cardiovascular Disease (CVD)|Chronic Obstructive Pulmonary Disease (COPD)		Istituto Clinico Humanitas	OBSERVATIONAL
NCT07285434	Clinical Study of the Therapeutic Effectiveness of In-silico-Designed, Machine Learning Inspired, and Quantum-molecularly Coupled Personalized Neoantigenic Vaccines Microlyvaq™ in Patients With Advanced Non-small Cell Lung Cancer (Microlyvaq™)	ENROLLING_BY_INVITATION	NSCLC (Non-small Cell Lung Cancer)|Squamous Lung Cancer With FGFR1 Amplification|Non-Squamous Non Small Cell Lung Cancer	BIOLOGICAL: Microlyvaq™(Personalized Multi-Epitope Immunotherapeutic)	Biogenea Pharmaceuticals Ltd.	INTERVENTIONAL
NCT07286539	Precision Physical Exercise for Personalized Onco-Hematology.	NOT_YET_RECRUITING	Hematologic Cancer|Colon Cancer|Breast Cancer|Lymphoma|Chronic Lymphocytic Leukemia (CLL)|Lung Cancer	OTHER: Supervised Intervention|OTHER: Home-based Intervention	University of Salamanca	INTERVENTIONAL
NCT07291921	To Conduct Multi-omics Integrated Studies in Peripheral Blood, Such as Fragment Omics, Metabolomics and Epigenetics, and Establish Non-invasive Dynamic Follow-up Monitoring	RECRUITING	Lung Neoplasms|Neoadjuvant Therapy|Immunotherapy|Minimal Residual Disease		Peking University People's Hospital	OBSERVATIONAL

NCT	Study title	Study status	Conditions	Interventions	Sponsor	Study type
	Programs During Perioperative and Postoperative Periods (Observational Study)					
NCT07370077	Research on Early Screening and Diagnosis of Pulmonary Nodules Based on Novel Non-invasive Technologies.	RECRUITING	Lung Cancer	DIAGNOSTIC_TEST: Employing multi-omics diagnostic approaches to enhance diagnostic efficacy	Chen KeZhong	OBSERVATIONAL
NCT07399210	Noninvasive Detection of Lung Nodule Malignancy Using cfDNA Fragmentomics	RECRUITING	Lung Cancer (Diagnosis)|Fragmentomics	OTHER: This study did not include intervention between two cohorts	Baohui Han	OBSERVATIONAL
NCT07458425	The SENTINL-1 Study: Evaluating Patient-Reported Outcomes of AI-Inferred Lung Cancer Risk	NOT_YET_RECRUITING	Lung Cancer	DIAGNOSTIC_TEST: Artificial Intelligence (AI) test|DIAGNOSTIC_TEST: Research-use-only multimodal AI risk model	University of Illinois at Chicago	INTERVENTIONAL
NCT07492121	Screening for Brain Metastases	NOT_YET_RECRUITING	Lung Cancer Stage IV|Melanoma Stage IV|Breast Cancer Metastatic	OTHER: gadopiclenol (contrast agent)|OTHER: standard contrast agent	University of Zurich	INTERVENTIONAL

AI: artificial intelligence; ML: machine learning; ctDNA: circulating tumor DNA; NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; cfDNA: cell-free DNA; MCED: multi-cancer early detection; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; GBM: glioblastoma; CLL: chronic lymphocytic leukemia.

Supplementary Table 4. Ongoing trials utilizing AI/ML for liquid biopsy analysis in NSCLC

NCT number	Study title	Study URL	Study status	Conditions	Interventions	Sponsor	Study type
NCT05254132	Artificial Intelligence for Help Non-Small Cell Lung Cancer: Measure Cancer Biology and Treatment Response Via Imaging	https://clinicaltrials.gov/study/NCT05254132	UNKNOWN	Non Small Cell Lung Cancer	PROCEDURE: Liquid biopsy	OncoRadiomics	OBSERVATIONAL
NCT06122077	Clinical Validation of Freenome Multiomics Blood Test for Lung Cancer Screening	https://clinicaltrials.gov/study/NCT06122077	RECRUITING	Lung Cancer Diagnosis	DIAGNOSTIC_TEST: blood draw	Freenome Holdings Inc.	OBSERVATIONAL
NCT06270992	Oral Microbiome Diagnostics of Lung Cancer	https://clinicaltrials.gov/study/NCT06270992	RECRUITING	Lung Cancer	DIAGNOSTIC_TEST: NCCN (National Comprehensive Cancer Network) diagnosis	TC Erciyes University	OBSERVATIONAL
NCT04522284	PRECISE CURATE.AI Pilot Clinical Trial	https://clinicaltrials.gov/study/NCT04522284	UNKNOWN	Solid Tumor	DEVICE: CURATE.AI|DRUG: Capecitabine|DRUG: XELOX|DRUG: XELIRI|DRUG: Ibrutinib	National University Hospital, Singapore	INTERVENTIONAL
NCT04558255	A Preliminary Study on the Detection of Plasma Markers in Early Diagnosis for Lung Cancer	https://clinicaltrials.gov/study/NCT04558255	UNKNOWN	Lung Cancer	DIAGNOSTIC_TEST: A machine-learning method which can robustly discriminate early-stage lung cancer patients from controls	Peking University People's Hospital	OBSERVATIONAL
NCT05175235	Nivolumab and Pembrolizumab Dose Optimisation in Solid Tumours With CURATE.AI Platform and Sequential ctDNA Measurements	https://clinicaltrials.gov/study/NCT05175235	UNKNOWN	Solid Tumor	DEVICE: CURATE.AI|DRUG: Nivolumab, Pembrolizumab	National University Hospital, Singapore	INTERVENTIONAL

NCT number	Study title	Study URL	Study status	Conditions	Interventions	Sponsor	Study type
NCT05381038	Optimizing and Personalising Azacitidine Combination Therapy for Treating Solid Tumours QPOP and CURATE.AI	https://clinicaltrials.gov/study/NCT05381038	RECRUITING	Solid Tumor|Gastrointestinal Cancer|Breast Cancer	DEVICE: QPOP|DEVICE: CURATE.AI|DRUG: Azacitidine + docetaxel|DRUG: Azacitidine + paclitaxel|DRUG: Azacitidine + irinotecan	National University Hospital, Singapore	INTERVENTIONAL

AI: Artificial intelligence; ML: machine learning; NSCLC: non-small cell lung cancer; NCT: National Clinical Trial number; NCCN: National Comprehensive Cancer Network; ctDNA: circulating tumor DNA.

Supplementary Table 5. Comparative summary of key AI/ML studies for perioperative ctDNA-MRD in resectable NSCLC

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Wang *et al.*, 2023[44]	Postsurgical NSCLC landmark MRD; plasma collected at 7 days and 6 months after surgery.	87 resected NSCLC patients; 23 relapses; 163 plasma samples.	WGS cfDNA fragmentomics plus targeted sequencing.	Penalized Cox model (Coxnet, scikit-survival); separate 7-day and 6-month models.	Direct: postoperative MRD/recurrence	Leave-one-out cross-validation; internal only.	Post-op recurrence / RFS; high-risk HR 4.6 at 7 days and 8.3 at 6 months; pooled sensitivity 78.3%.	Single-center cohort; small relapse count; internal validation only; code not reported.	Direct evidence that fragmentomics can improve postoperative recurrence sensitivity over mutation-only MRD.	Data: EGA EGAD00001010300, controlled access. Code/weights: not reported.
Zhang *et al.*, 2026[48] (LAMPAD)	Resected stage I-III NSCLC; focused on patients with landmark-undetectable MRD.	Training *n* = 163; multiple validation cohorts, including pooled validation reported in the article.	Perioperative ctDNA-MRD and cfDNA quantitative features plus clinicopathologic variables.	LASSO feature selection plus XGBoost-Cox model; SHAP interpretation.	Direct: perioperative MRD risk stratification	Multiple validation cohorts across fixed-panel and personalized ctDNA-MRD approaches.	DFS / potential-cure risk; training 2-year DFS 97.8% vs 71.6%; pooled validation 94.3% vs 72.4%.	Retrospective/modeling evidence; prospective treatment-guidance utility remains unproven.	Direct domain-matched AI/ML evidence for perioperative NSCLC MRD risk stratification, pending prospective decision testing.	Data: GSA-Human HRA008684. Code/weights: not reported in available text.

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Widman *et al.*, 2024[42] (MRD-EDGE)	Early-stage NSCLC perioperative MRD component within a mixed CRC/NSCLC MRD-EDGE platform; NSCLC patients received neoadjuvant durvalumab with/without SBRT before intended surgery.	NSCLC n = 22; postoperative plasma n = 16; recurrence analysis in 14 resected patients.	Plasma WGS integrating genome-wide SNV and CNV signals.	Deep-learning / ML-guided MRD-EDGE signal enrichment.	Direct-adjacent: neoadjuvant-treated perioperative MRD	Analytical testing plus small clinical cohort; internal only.	Post-op MRD / recurrence; 5/8 MRD-positive patients relapsed vs 0/6 MRD-negative patients.	Very small neoadjuvant-treated NSCLC component; mixed-cancer development; internal only; no prospective decision testing.	Direct-adjacent perioperative NSCLC evidence for genome-wide ML signal enrichment; not a pure post-surgery/no-neoadjuvant target domain.	Data: EGA EGAS00001007306 and EGAS00001007545. Code: on request via Cornell CTL, non-commercial license. Weights: restricted / not public.

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Zhu *et al.*, 2025[45] (Fragle)	Multi-cancer ctDNA quantification model with resected early-stage lung cancer MRD/risk-stratification application.	Multi-cohort development; resected-lung MRD *n* = 162; ctDNA-negative risk-stratification *n* = 158.	cfDNA fragment-length density distribution from low-pass WGS; also compatible with off-target targeted-sequencing reads.	Tumor-naive multi-stage deep-learning model estimating ctDNA fraction.	Direct-adjacent: resected-lung MRD application	Cross-validation and multiple independent cohorts; benchmarked against tumor-naive ichorCNA / panel approaches.	ctDNA quantification and MRD risk stratification; stratified ctDNA-negative resected lung cancer and outperformed tumor-naive panel.	Primary task is ctDNA quantification rather than prospective treatment-decision modeling; MRD thresholds require validation.	Supports fragment-length deep learning as an orthogonal tumor-naive MRD signal source; clinical task remains direct-adjacent rather than a recurrence model.	Data: EGA EGAD50000000167, restricted access. Code/software: https://github.com/skandlab/FRAGLE. Weights/model: available with software, not separately specified.
Zviran *et al.*, 2020[43] (MRDetect)	Mixed-cancer genome-wide cfDNA MRD method paper with an early-stage LUAD postoperative arm.	LUAD *n* = 39 pre-op and *n* = 22 post-op; plus CRC *n* = 19, melanoma *n* = 2, and controls.	Genome-wide cfDNA WGS integrating SNV and CNA signals.	SVM denoising plus ML signal integration (MRDetect-SNV / MRDetect-CNA).	Direct-adjacent: postoperative LUAD MRD	Synthetic admixtures plus internal clinical validation.	MRD detection / DFS association; LUAD pre-op AUC 0.82; operable CRC detection SNV AUC 0.97.	Small mixed-cancer cohorts; internal validation; predecessor to MRD-EDGE; restricted code.	Foundational feasibility evidence for ultra-sensitive genome-wide postoperative MRD detection.	Data: pending at EGA in original text; accession not specified in available text. Code: non-commercial license via Cornell CTL. Weights: restricted / not public.

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Wang *et al.*, 2026[47] (PRIME)	Curative-intent stage I-III NSCLC across radical surgery and definitive CRT cohorts.	493 patients; 781 blood samples; training n = 345, validation n = 148.	ctDNA-MRD, pretreatment ctDNA mutations, and clinical-therapeutic features.	Interpretable neural-network PRIME model selected from six ML algorithms; SHAP interpretation.	Direct-adjacent: mixed curative-intent NSCLC	Four training cohorts and two validation cohorts.	Progression / treatment-failure risk; AUC 0.85 in training and 0.82 in validation.	Surgery and definitive CRT pooled; treatment modality is a model input; surgical subgroup calibration needed.	Supports interpretable integration of MRD, mutations, and clinical variables after curative-intent treatment.	Data: GSA-Human HRA011737 and HRA001346; survival data on request. Code/weights: not reported.
Assaf *et al.*, 2023[29]	Metastatic non-squamous NSCLC from IMpower150; longitudinal on-treatment sampling.	466 patients; 1,954 samples across 5 timepoints.	FoundationOne Liquid CDx at baseline plus custom 330 kb panel; PBMC and algorithmic CH/germline correction.	ML model integrating longitudinal ctDNA features, including VAF change and number of alterations.	Metastatic-active-disease: longitudinal monitoring	Internal development plus independent OAK validation.	OS risk; stable-disease subgroup HR 3.2; partial-response subgroup HR 3.3; OAK validation HR 3.73.	Metastatic high-tumor-fraction setting; dense sampling; OS endpoint rather than post-op recurrence.	Mature longitudinal template, but model, sampling schedule, and thresholds cannot transfer unchanged to postoperative MRD.	Data/R code: EGA EGAS00001006703, controlled access. Weights: not separately reported.

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Yuan *et al.*, 2025[49]	Metastatic non-squamous NSCLC from IMpower150; treatment-agnostic ctDNA kinetics modeling.	466 selected patients; 348 ctDNA-detectable; train/test n = 181/167.	IMpower150 ctDNA data; median allele fraction of pathogenic mutations.	Two-step joint model: nonlinear mixed-effects disease submodel plus survival submodel.	Metastatic-active-disease: joint OS modeling	Internal train/test split within the same trial; no external perioperative validation.	Dynamic OS prediction beyond 21-week landmark; median-AF model AUC 0.75/0.73 at year 2 and 0.70/0.77 at year 3 (train/test).	Same metastatic source trial; not perioperative; OS rather than recurrence endpoint.	Useful dynamic-modeling template requiring refitting and external validation in postoperative cohorts.	Data: EGA EGAS00001006703, controlled access. Code/weights: not reported.
van 't Erve *et al.*, 2024[69] (DELFI-TF)	Tumor-fraction estimation and treatment monitoring, mainly in advanced CRC with NSCLC validation.	CRC: 689 samples / 153 patients; NSCLC validation: 47 samples / 15 stage III/IV patients.	Low-coverage WGS cfDNA fragmentome, mutation-independent.	Locked random-forest regression model estimating tumor fraction.	Metastatic-active-disease: tumor-fraction monitoring	Internal CV plus independent CRC and NSCLC validation.	Tumor fraction, OS, and treatment-response dynamics; baseline OS HR 9.84; dynamics HR 3.12.	Advanced active-disease development; tiny NSCLC validation; not postoperative MRD.	Supports mutation-independent fragmentomic monitoring, but postoperative NSCLC MRD use remains unvalidated.	Data: EGA EGAS00001006695. Code: https://github.com/delfidiagnostics/CAIRO5_Public. Weights: with code / not separately specified.

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Bahado-Singh and Vlachos, 2022[40]	Lung cancer case-control detection using cfDNA methylation.	30 total: 10 cancer cases and 20 controls.	Genome-wide cfDNA DNA methylation using Illumina EPIC array.	Informative-CpG feature selection plus multiple supervised classifiers, including deep learning.	Screening-diagnosis: diagnostic case-control detection	Internal resampling only; no external cohort.	Cancer-versus-control detection; AUC up to 1.00; deep-learning model 100% sensitivity/specificity.	Tiny sample size and perfect metrics create major overfitting concern; detection task differs from MRD.	Illustrates multifeature methylation integration, but should be framed as proof-of-concept only.	Data/code/model weights: not reported in available text.
Kim *et al.*, 2024[41]	NSCLC diagnosis versus healthy controls.	198 total: 142 NSCLC and 56 healthy controls.	Targeted enzymatic methylation sequencing panel with fragment-size features.	CNN applied to a two-dimensional methylation-by-fragment-size matrix.	Screening-diagnosis: diagnosis	Internal CV plus dilution experiment; no external cohort.	NSCLC diagnosis / low-tumor-fraction detection; AUC 0.87; 0.1% tumor fraction detected at 80% specificity.	Diagnostic cohort; internal validation; low-TF specificity may be insufficient for MRD decisions.	Supports weak-signal feature integration, but postoperative operating points need re-estimation.	Data: K-BDS KAP240715 and KoNA KAP230731. Code: https://github.com/minjung826/MFS_model. Weights: within repository / not separately specified.
Mathios *et al.*, 2021[67] (DELFI)	Lung cancer detection in symptomatic/high-risk cohorts.	365 baseline samples plus independent validation of 385 non-cancer and 46 cancer samples.	Low-coverage WGS cfDNA fragmentome plus CEA / clinical variables in DELFImulti.	Gradient-boosted ML using genome-wide fragmentation profiles.	Screening-diagnosis: early detection	Repeated 5-fold CV plus fixed-model independent validation.	Lung cancer detection; AUC 0.90 in LUCAS, 0.93 in no-prior-cancer subgroup; stage I AUC 0.76.	Prevalent cancer detection differs from low-burden postoperative MRD; stage I performance weaker.	Supports fragmentomic ML and external validation practice, but not direct MRD performance.	Data: EGA EGAS00001005340 plus SRA / dbGaP / GEO. Code: https://github.com/cancer-genomics/reproduce_lucas_wflow. Weights: with code / not separately specified.

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Mazzone *et al.*, 2024[68] (DELFI)	Prospective lung-cancer early-detection validation.	1,646 enrolled; 958 evaluable; training *n* = 576, validation *n* = 382.	Low-coverage WGS cfDNA fragmentome.	Locked, prespecified ML fragmentation classifier.	Screening-diagnosis: screening validation	Prospective case-control validation on held-out set.	Screening augmentation; validation sensitivity 84%, specificity 53%; stage I sensitivity 71% in clinical-validation subgroup.	High-sensitivity / low-specificity screening operating point is not equivalent to postoperative MRD.	Shows prospective validation of fragmentome classifiers; MRD requires different false-positive tolerance.	Data: EGA EGAS00001005340 / EGAC00001001180, partly restricted. Code: reference tracks on GitHub; model code/weights not reported.
Fairchild *et al.*, 2023[30]	Pan-cancer real-world cfDNA variant-origin classification.	4,324 clinical cfDNA samples; NSCLC subset *n* = 521.	Clinical cfDNA NGS with matched sequencing labels in training subset.	Random forest plus logistic regression to classify CH-derived versus tumor-derived variants.	CH-filtering: variant-origin attribution	10-fold CV, 15% held-out test, and separate validation set.	Variant-origin classification; auROC 0.90 / 0.90; F1 0.91 / 0.89.	Not a disease-state or recurrence model; pan-cancer and mostly non-perioperative setting.	Improves MRD specificity conceptually by reducing false-positive tumor attribution.	Data: paper/supplement plus requests through clinicalstudydatarequest.com. Code: https://zenodo.org/badge/latestdoi/421601612. Weights: with code / not separately specified.

Study	Clinical setting	Sample size	Assay type	AI/ML method	Domain	Validation strategy	Endpoint / key performance	Major limitations	Relevance to perioperative NSCLC	Code/data/model weights
Arango-Argoty *et al.*, 2025[58] (MetaCH)	Plasma-only CH versus tumor variant classification.	cfDNA training: Razavi *n* = 124 (436 tumor + 914 CH variants). Sequence training: 57,210 tumor + 6,745 CH variants. External sets include 85 NSCLC, 100 breast, 50 gastric, and pan-cancer Zhang data.	cfDNA NGS with tumor/blood sequence embeddings; no matched WBC required at inference.	Three-stage ML framework: METk embeddings, base classifiers, logistic-regression meta-classifier.	CH-filtering: plasma-only variant-origin attribution	Cross-validation, multiple external validation sets, and ablation.	Variant-origin classification; external gastric auPR / auROC 0.89 / 0.84; overall external auROC 0.79.	Not an MRD outcome model; low-VAF false positives remain a concern.	Relevant when matched leukocyte sequencing is unavailable, but needs perioperative NSCLC evaluation.	Data: TCGA / cBioPortal / public resources. Code: https://github.com/gaarangoa/MetaCH and https://github.com/gaarangoa/METk. Weights: open-source / with code.

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Palizban *et al.*, 2024[59]	Non-NSCLC cfDNA mutation-origin classification using a curated SNV catalog, prostate cfDNA development samples, and glioma independent validation.	Approximately 25,000 SNVs; prostate development used SNVs from 20 cfDNA samples in 48 triplets; glioma validation used 3 cfDNA samples with matched tumor/WBC.	cfDNA SNV genomic-coordinate and nucleotide-composition features.	Semi-supervised GAN with DNN generator and discriminator / classifier plus ensemble feature ranking.	CH-filtering: variant-origin attribution	Internal validation plus 3-sample glioma validation; weak external generalization reported in later MetaCH benchmarking.	Variant-origin classification; internal AUC/accuracy around 95-96%. Later MetaCH benchmarking reported SSGAN auPR / auROC 0.54 / 0.48 on the external Leal gastric set.	Non-NSCLC and non-perioperative; weak external generalization; no clinical outcome linkage.	Cautionary example that high internal AI performance may not transfer to MRD deployment.	Data: EGA EGAD00001004526 and NCBI SRP268702. Code: https://github.com/FPalizban/SSGAN plus Colab notebook. Weights: with code / not separately specified.

AI: Artificial intelligence; auPR: area under the precision-recall curve; AUC: area under the receiver-operating-characteristic curve; CH: clonal hematopoiesis; cfDNA: cell-free DNA; CNA/CNV: copy-number alteration/variation; CNN: convolutional neural network; CRC: colorectal cancer; CRT: chemoradiotherapy; ctDNA: circulating tumor DNA; DFS: disease-free survival; EGA: European Genome-phenome Archive; GSA: Genome Sequence Archive; HR: hazard ratio; LUAD: lung adenocarcinoma; ML: machine learning; MRD: molecular residual disease; NSCLC: non-small cell lung cancer; OS: overall survival; PBMC: peripheral blood mononuclear cell; RFS: recurrence-free survival; SBRT: stereotactic body radiation therapy; SHAP: SHapley Additive exPlanations; SNV: single-nucleotide variant; SVM: support vector machine; VAF: variant allele fraction; WBC: white blood cell; WGS: whole-genome sequencing.