IX SIMPOSIO · SYMPOSIUM | 2024
BIOPSIA LÍQUIDA · LIQUID BIOPSY

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

CURRENT RECOMMENDATIONS OF THE ESMO PRECISION MEDICINE WORKING GROUP FOR THE USE OF LIQUID BIOPSY

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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*]

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

LIQUID BIOPSIES VERSUS TISSUE REBIOPSY

Non-invasive

Safe and easy to repeat prospectively through cancer history (helps with temporal heterogeneity)

Theoretically it should recapitulate tumour clones and subclones across body (helps with spatial heterogeneity)

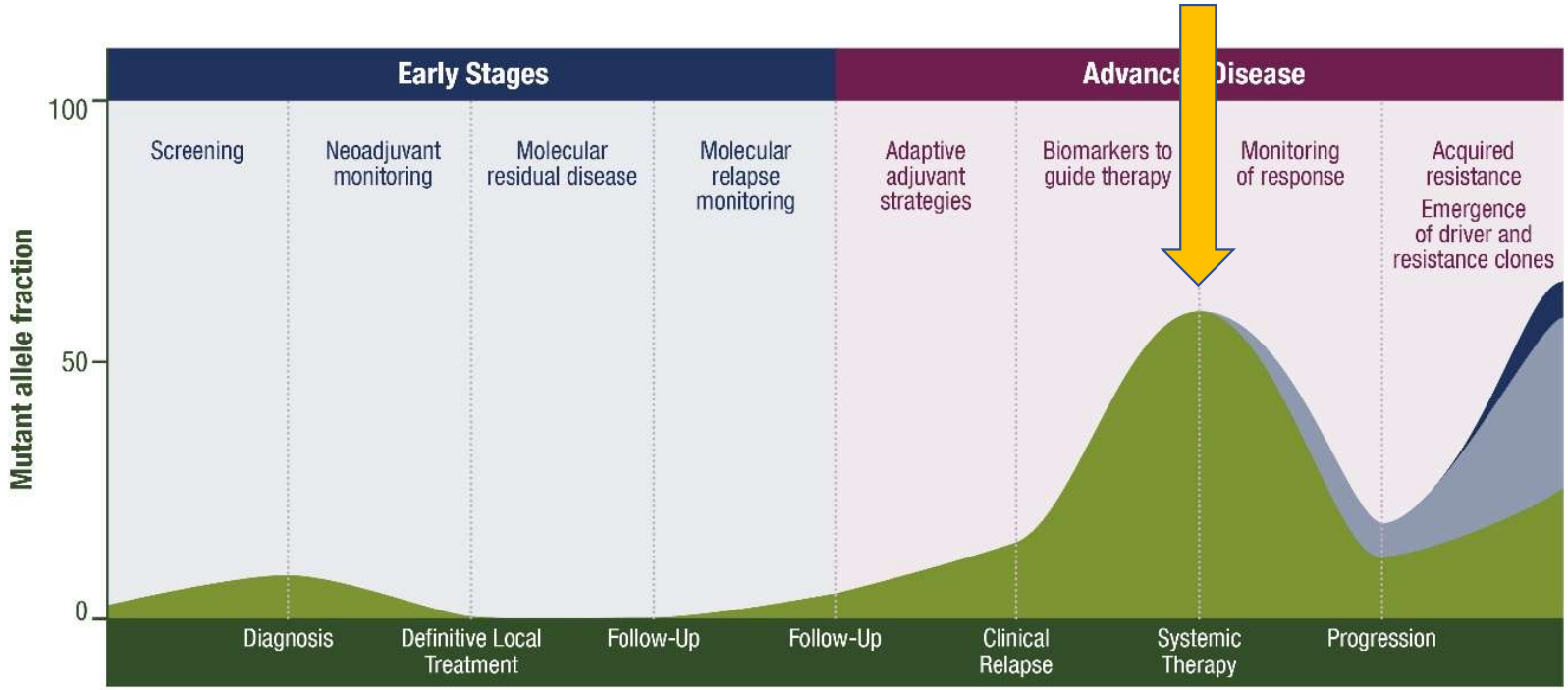
REQUIREMENTS FOR CLINICAL IMPLEMENTATION OF LIQUID BIOPSIES

1. **Analytical validity**
   Test capacity to detect what we want

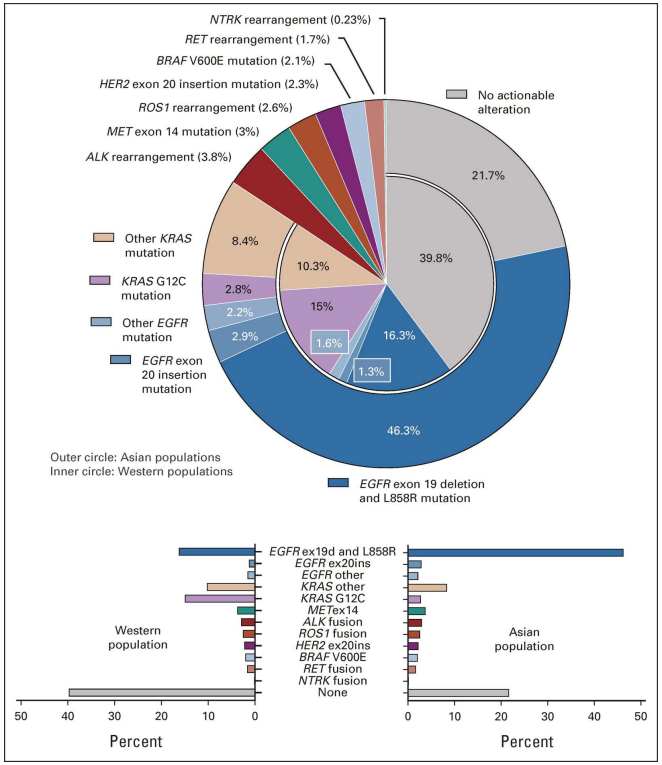
2. **Clinical validity**
   Demonstrate predictive value of the test for the clinical endpoint of interest

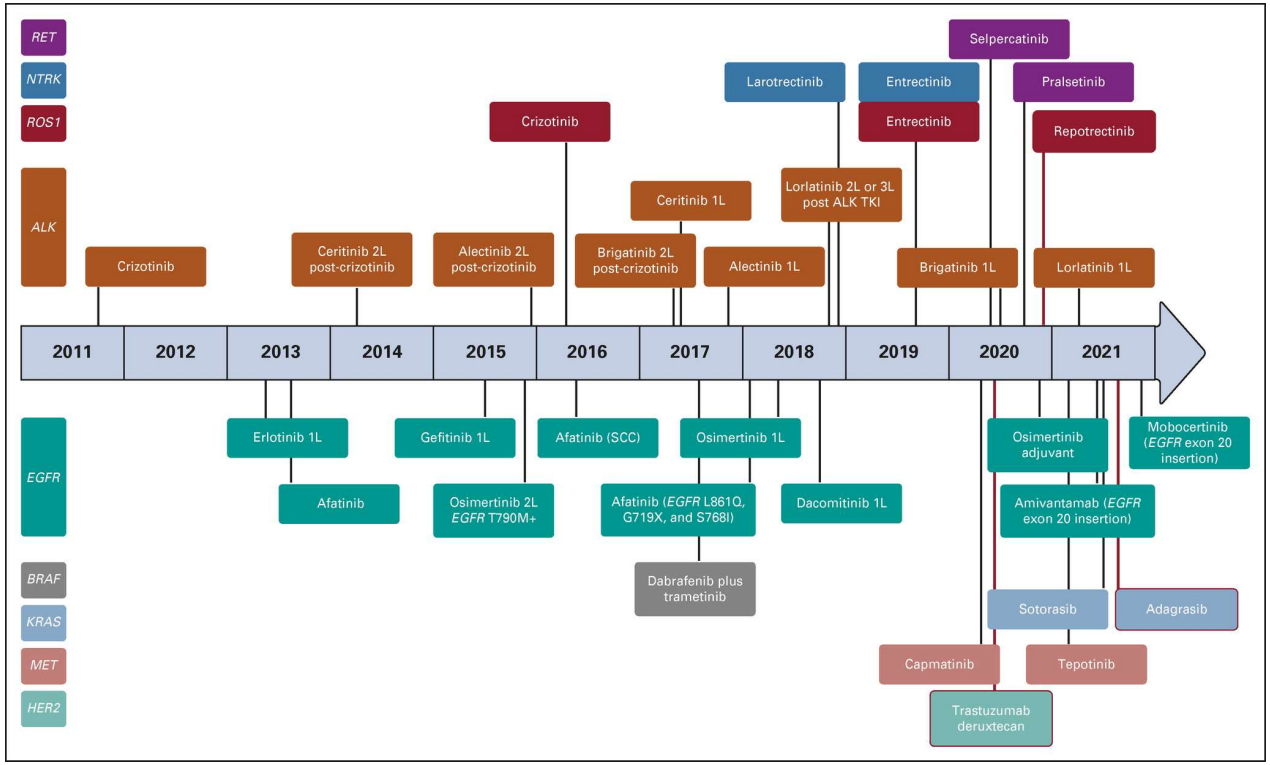
3. **Clinical utility**
   Demonstrate that acting upon the test result can improve health outcomes

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION



GENETIC CHARACTERIZATION FOR TREATMENT SELECTION





GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer

IASLC

"…a **plasma first approach** is already appropriate in the acquired resistance setting for oncogene-driven NSCLC owing to the possibility of overcoming inherent limitations of tissue sampling…"

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

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

"…For patients with advanced cancer, validated and adequately sensitive ctDNA assays have utility in identifying actionable mutations to direct targeted therapy, and may be used in routine clinical practice…**ctDNA assays may be routinely used when faster results will be clinically important, or when tissue biopsies are not possible or inappropriate**…"

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Rolfo C et al. J Thorac Oncol 2021; Pascual J et al. Ann Oncol 2022

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

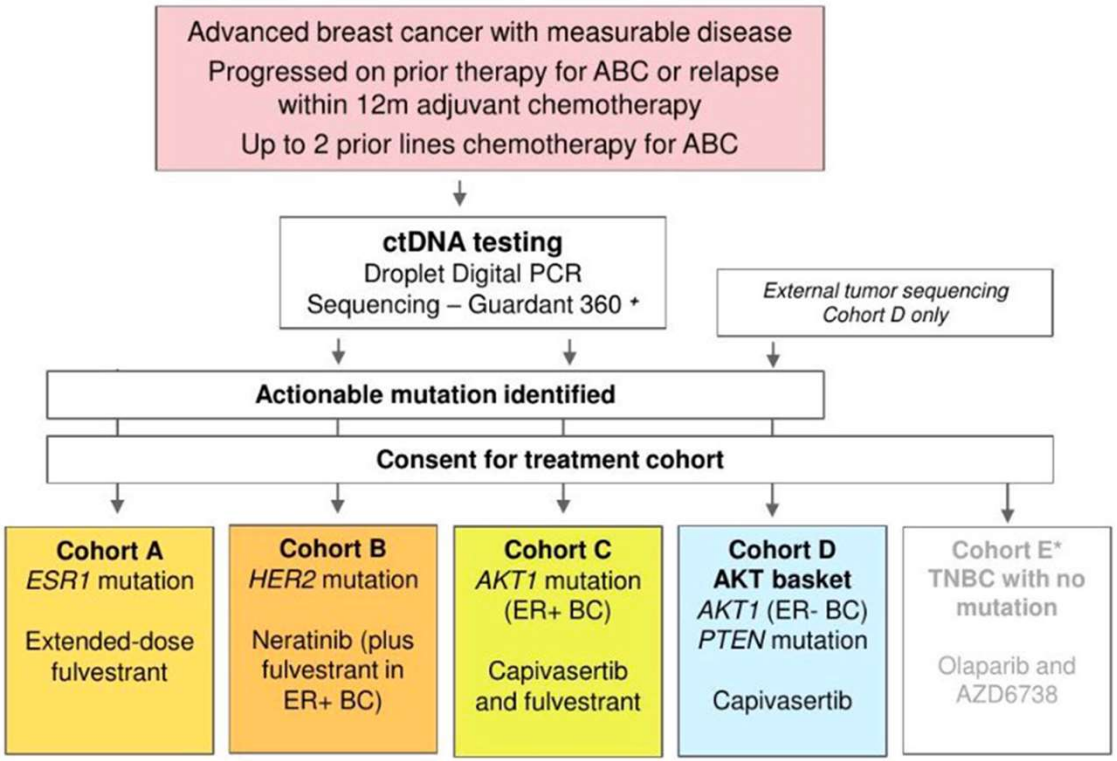
plasmaMATCH study outline

Primary objective

- Response rate of therapies matched to mutations in ctDNA

Secondary objective

- Frequency of targetable mutations
- Accuracy of ctDNA testing
- Proportion of patients entering a cohort
- Activity in clonally dominant vs sub-clonal *ESR1* mutations

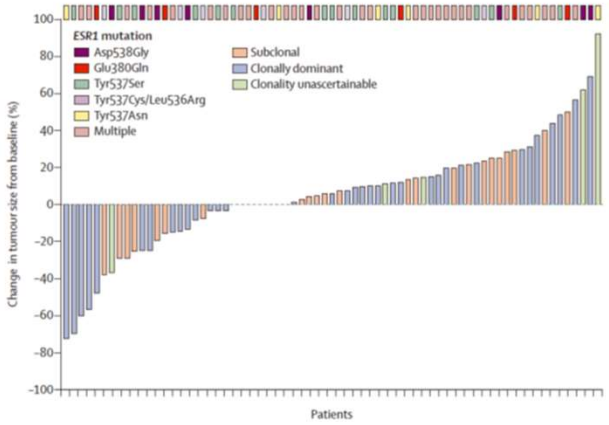


*+ Prospective from part way through recruitment (n=364), retrospective in remaining patients (n=436) *Cohort E to be reported separately*

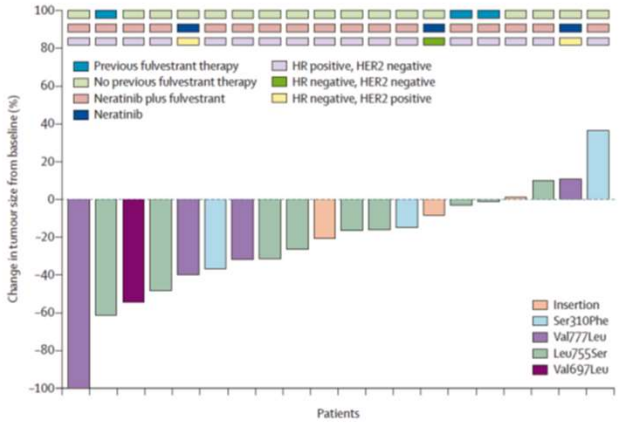
Turner N et al. Lancet Oncol 2020

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

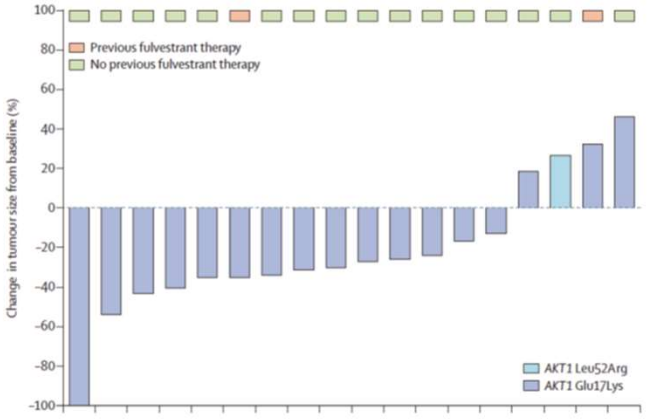
ESR1 mutation -> High dose fulvestrant



ERBB2 mutation -> Neratinib +/- Fulvestrant



AKT1 mutation -> Capivasertib + Fulvestrant



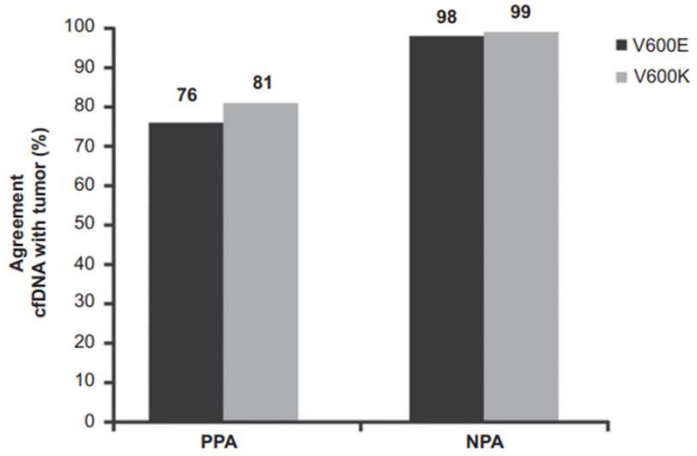
Turner N et al. Lancet Oncol 2020

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

Table 1. Clinical studies overview

Study	Phase	Treatment	Enrollment	Plasma cfDNA tested (% of enrolled)
Break-2 (NCT01153763)	II	Dabrafenib	$N = 92$	$n = 76$ (83)
Break-3 (NCT01227889)	III	Dabrafenib	$N = 187$	$n = 170$ (91)
		DTIC	$N = 63$	$n = 52$ (83)
Break-MB (NCT01266967)	II	Dabrafenib	Cohort A: No prior local brain therapy ($N = 89$)	$n = 61$ (69)
			Cohort B: Prior local brain therapy ($N = 83$)	$n = 69$ (83)
Metric (NCT01245062)	III	Trametinib	$N = 214$	$n = 200$ (93)
		Chemotherapy[a]	$N = 108$	$n = 104$ (96)
Total			$N = 836$	$n = 732$ (88)

[a]Chemotherapy = dacarbazine or paclitaxel.



Santiago-Walker et al. Clin Can Res 2016

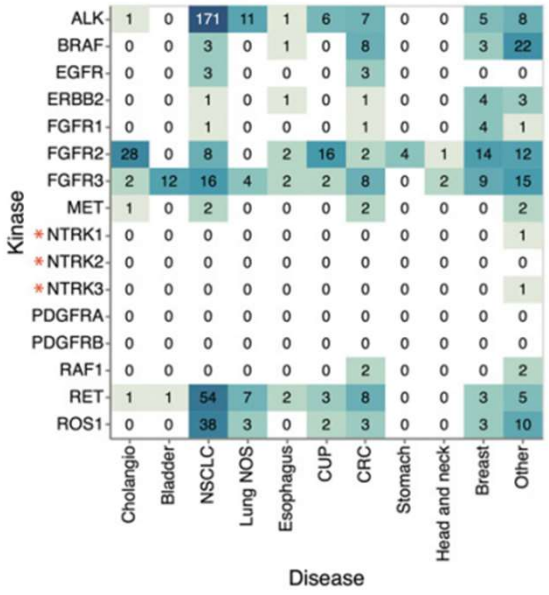
GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

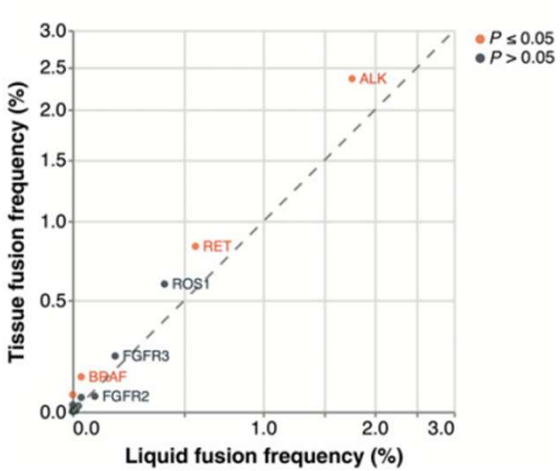
Tumour type	Indications	ESCAT tier and level of evidence	Recommendation
Non-small-cell lung cancer	*EGFR* (for common, uncommon, exon 20 insertions, T790M and other resistance mutations e.g. C797X).	IA[120]	ctDNA genotyping recommended in treatment-naive cancer patients and resistance upon prior TKIs. 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]	
Breast cancer	*PIK3CA* mutations	IA[140]	*ESR1* mutations should preferentially be tested in ctDNA. *ERBB2* amplification and *NTRK* fusions only when advanced tissue biopsy not available.
	ERBB2 amplification	IA[141,142]	
	*BRCA*1/2 mutations	IA[143,144]	
	ESR1 mutations	IB[145,146]	
	MSI-H	IC[147]	
	NTRK 1/2/3 fusions	IC[134]	
Gastric cancer	*ERBB2* amplification	IA[148]	ctDNA testing if tissue not available or when fast turnaround time is needed for urgent therapeutic decision making.
	MSI-H	IC[147]	
	NTRK 1/2/3 fusions	IC[134]	
Pancreatic cancer	*NTRK* 1/2/3 fusions	IC[134]	ctDNA testing if tissue not available.
	MSI-H	IC[147]	
Hepatocellular cancer	MSI-H	IC[147]	ctDNA testing if tissue not available.
	NTRK 1/2/3 fusions	IC[134]	
Cholangiocarcinoma	*IDH1* mutations	IA[149]	ctDNA testing if tissue not available or when fast turnaround time is needed for urgent therapeutic decision making.
	FGFR2 fusions	IA[150]	
	MSI-H	IC[147]	
	NTRK 1/2/3 fusions	IC[134]	
Colorectal cancer	*BRAF* (for V600E mutation)	IA[151]	*KRAS/NRAS/BRAF*^{V600E}/MSI for chemotherapy-naive metastatic colorectal cancer is recommended when tissue testing is not feasible or urgent therapeutic decision making. *KRAS/NRAS/BRAF/EGFR*-ECD for pretreated patients if EGFR rechallenge is planned.
	MSI-H	IA[147,152]	
	NTRK 1/2/3 fusions	IC[134]	
	KRAS/NRAS mutations (exon 2,3,4)	N/A (resistance biomarker)	
	ERBB2 amplification	IB[57,153,154]	
	EGFR-ECD (for mutations in the extracellular domain S492, G465, S464, V441)	IB[73]	
Ovarian cancer	*BRCA*1/2 mutations	IA[155]	In women with no germline pathogenic *BRCA1/2* variant found, testing for *BRCA1/2* pathogenic or likely pathogenic somatic variants may be carried out if tissue not available.
	MSI-H	IC[147]	
Endometrial cancer	MSI-H	IC[147]	ctDNA testing if tissue not available.
Prostate cancer	*BRCA*1/2 mutations	IA[156]	*BRCA1/BRCA2/ATM* for potential PARPi therapy. Caution is needed when interpreting results of ctDNA assays due to false-positive CHIP mutations in DNA repair genes.
	MSI-H	IC[147]	
	ATM mutations	IIA[156]	
	PTEN mutations/deletions	IIA[157]	
	PALB2 mutations	IIB[156,158]	
Urothelial cancers	*FGFR* mutations	IB[159]	ctDNA testing if tissue not available.
	FGFR3 (FGFR3-TACC3) fusions	IB[159]	
	NTRK 1/2/3 fusions	IC[134]	
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]	
Soft tissue sarcoma	*NTRK* 1/2/3 fusions	IC[134]	ctDNA testing if tissue not available.

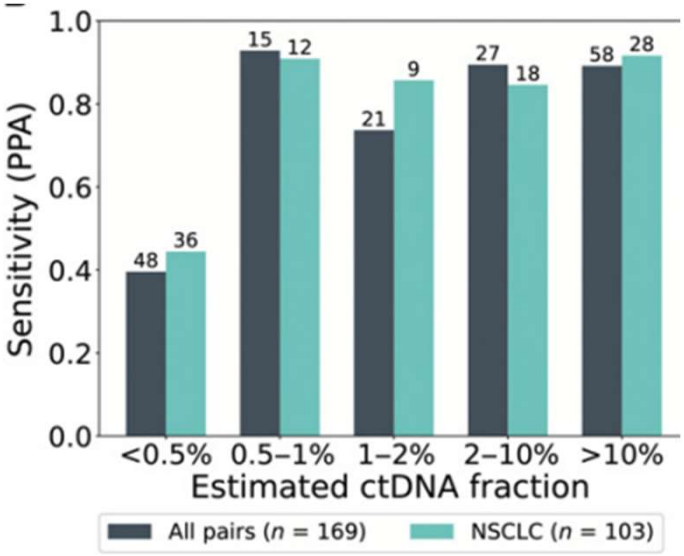
Pascual J et al. Ann Oncol 2022

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

ctDNA assays are still relatively limited for fusions although can be reliable if sufficient tumour purity







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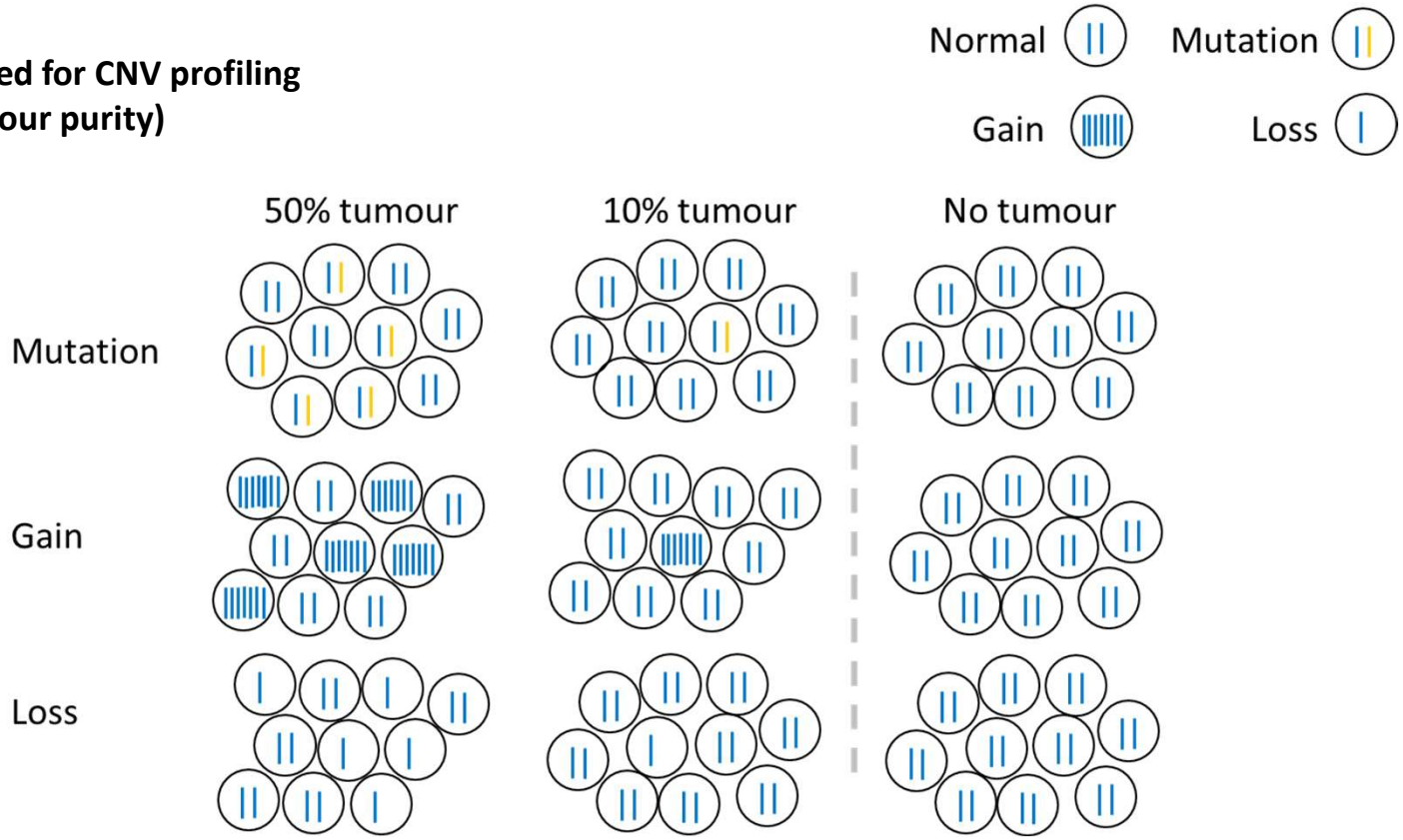
Lee JK et al. Clin Can Res 2022

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

ctDNA assays are still relatively limited for CNV profiling (also challenging in tissue if low tumour purity)



Courtesy of Ben O´Leary

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION

We need to fully understand limitations of results we get back

-Risk of false positive (non-pathogenic mutations, CHIP, CHIP contributing to bTMB, etc)

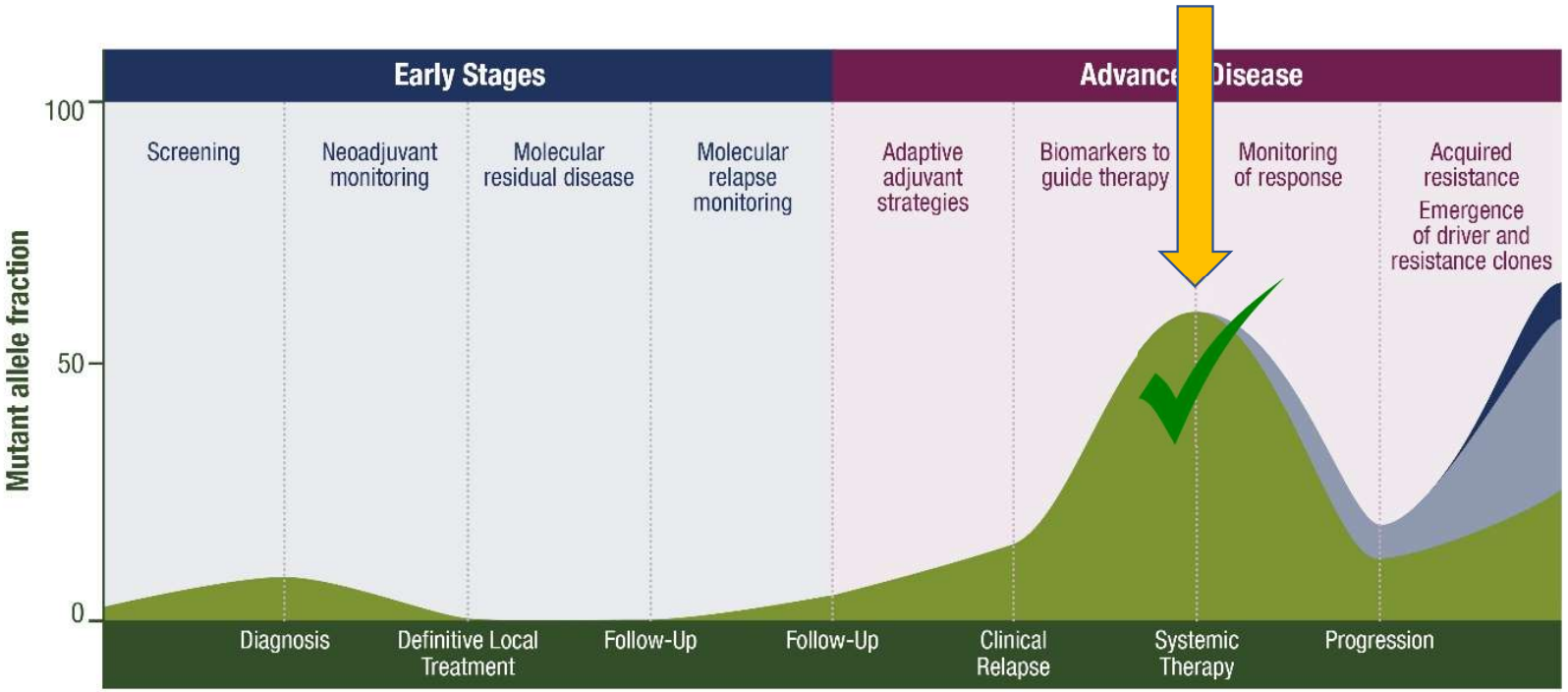
-Risk of false negative (assay sensitivity, genomic coverage, etc)

Table 1. Recommended reporting elements and approaches for ctDNA assays

Reporting element	Examples and considerations
Pre-analytical variables	Date of sample acquisition and treatment exposure (on/off treatment) at time of acquisition should be reflected.
Result	Cases where a variant is not detected are reported as 'non-informative' or 'not detected', instead of 'negative'.
Potential germline variants	Follow recommendations from ESMO Precision Medicine Working Group on germline-focused analysis of tumour-only sequencing.[45] This includes: • Flagging deleterious and/or pathogenic variants in genes associated with heritable cancer predisposition that are identified at an allele frequency consistent with germline origin. • Providing patient informed consent before follow-up clinical testing of germline DNA to determine whether the variant is germline or somatic.
Variants potentially associated with CHIP	Variants in genes commonly implicated in CHIP should be flagged to caution the clinician about the potential non-tumour origin of these variants.
Variant allele fractions for quantitative assays	Variant allele fractions should be reported as they may provide information suggestive of possible germline origin, clonal relatedness of variants in the same panel and the potential for a false-positive result.
Targeted variant or regions examined by assay	This could range from a single variant for digital PCR assays (e.g. *EGFR*, c.2369C>T, p.T790M) to hundreds of genes for an expanded NGS-based panel.
Variant type and/or genomic features detected by assay	SNVs, small insertions/deletions, amplifications, copy number losses, gene fusions, MSI, TMB and LOH.
Limit of detection for different variant types	The limit of detection for each variant type should be determined and reported, ideally with an associated confidence interval. In cases where input plasma DNA is limiting, the reported sensitivity is adjusted or a warning is inserted in the report.
Assay limitations	Currently, many ctDNA assays have a substantial amount of discordance with tumour testing, so reporting language should communicate this potential discordance, especially in cases where a variant is not detected.

Pascual J et al. Ann Oncol 2022

GENETIC CHARACTERIZATION FOR TREATMENT SELECTION



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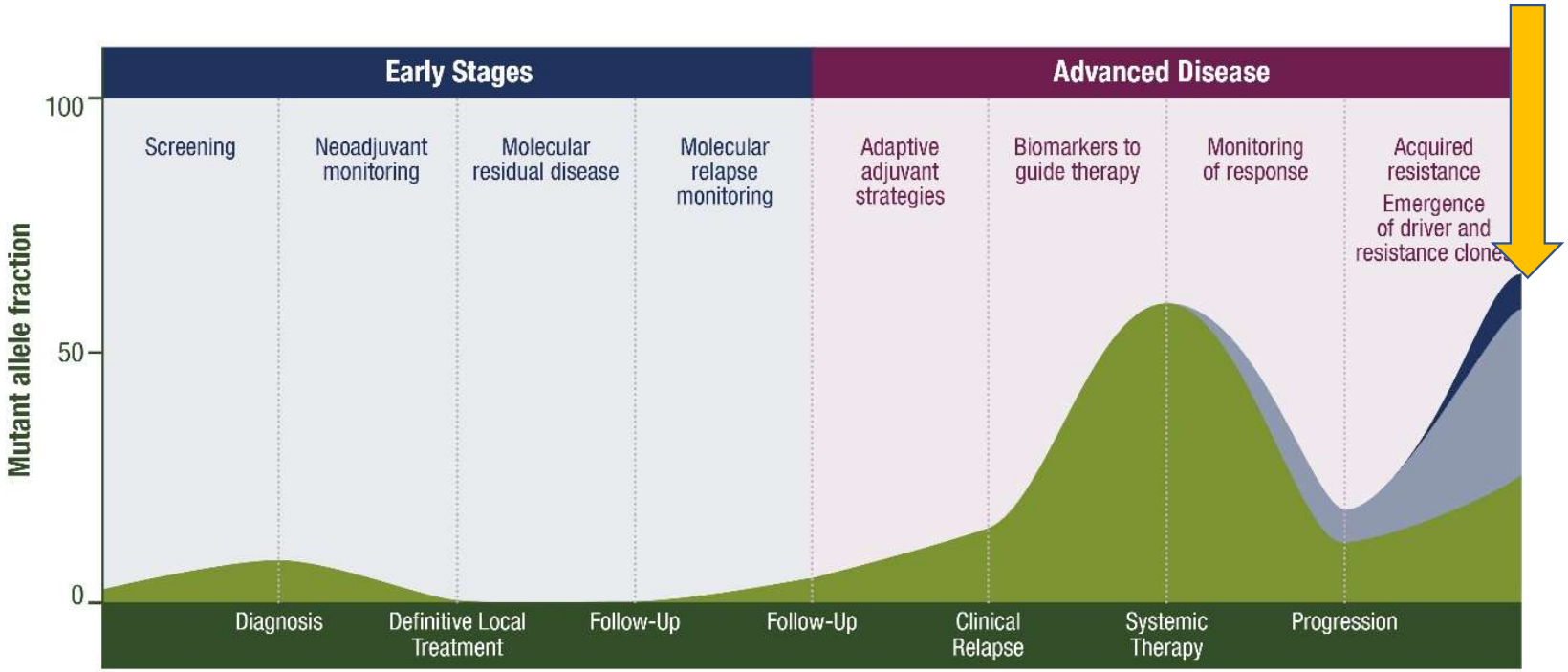
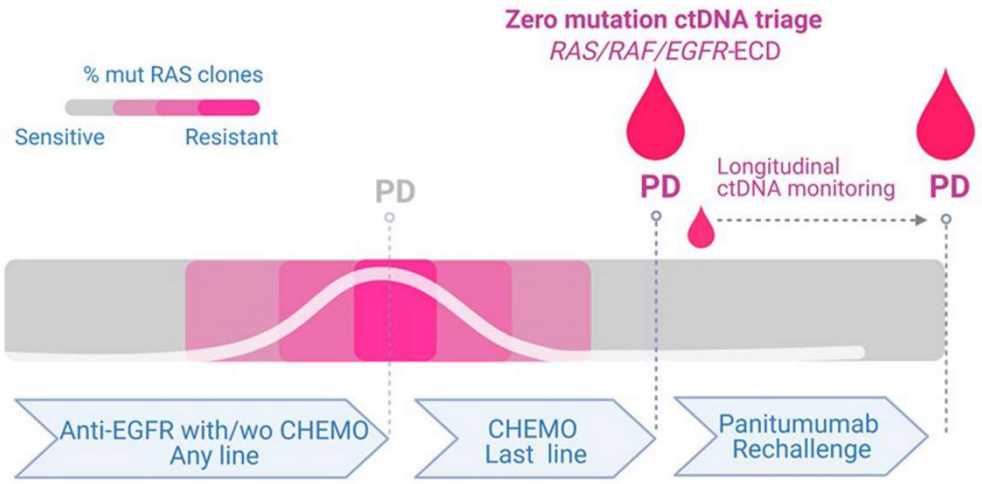
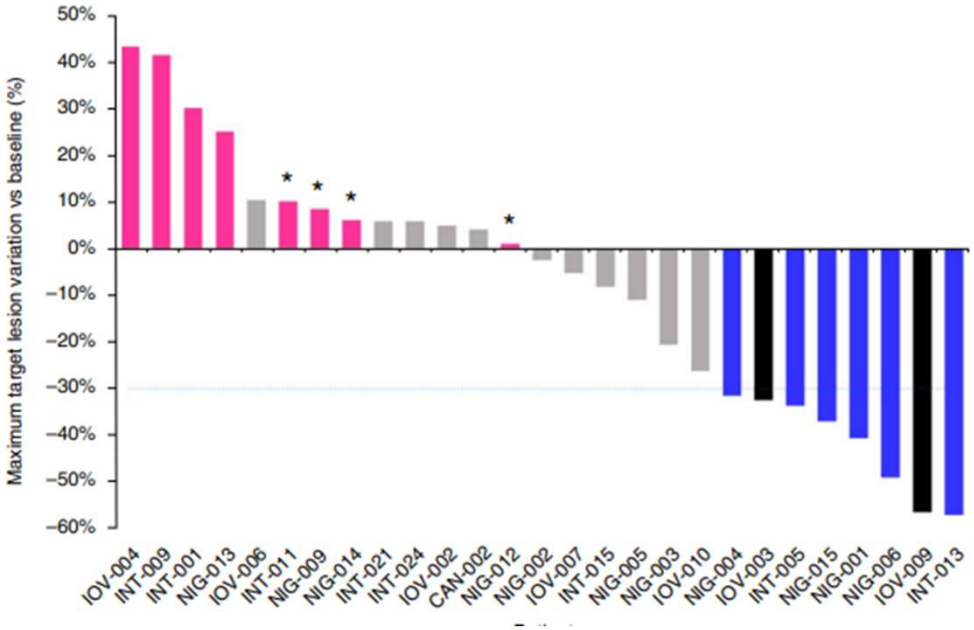
RESISTANCE MECHANISMS



RESISTANCE MECHANISMS

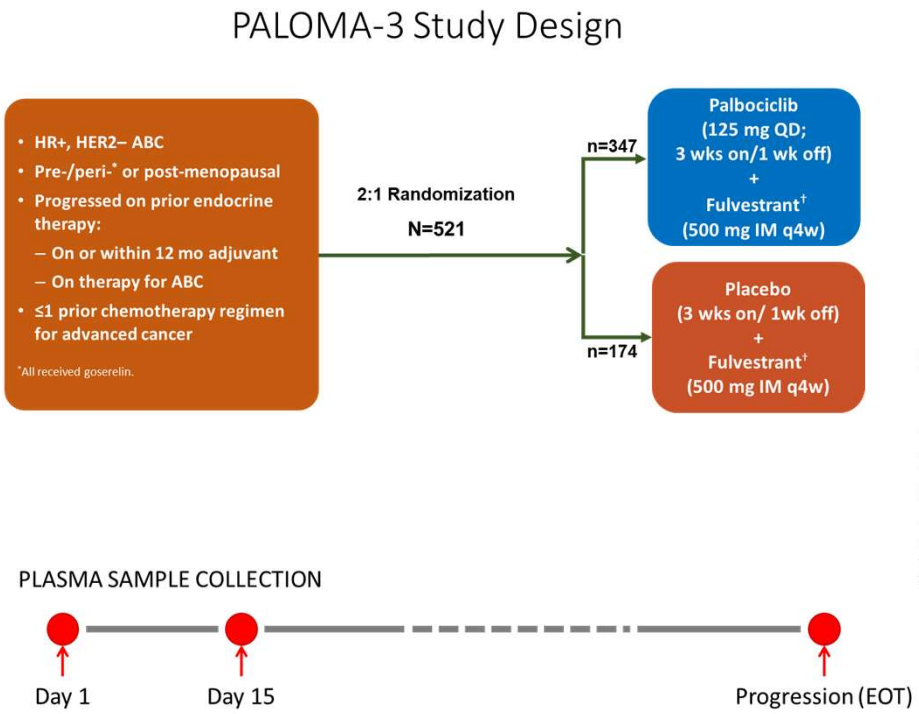
Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial

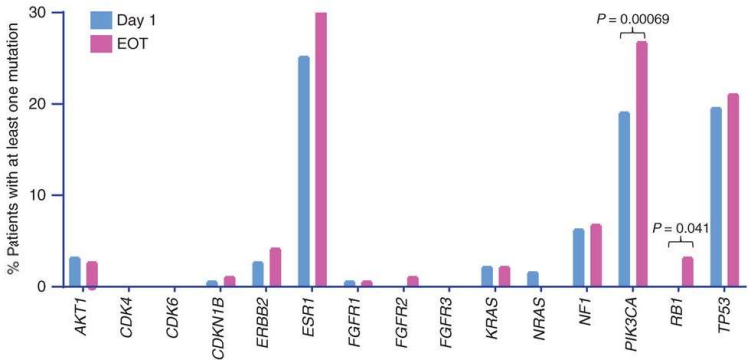


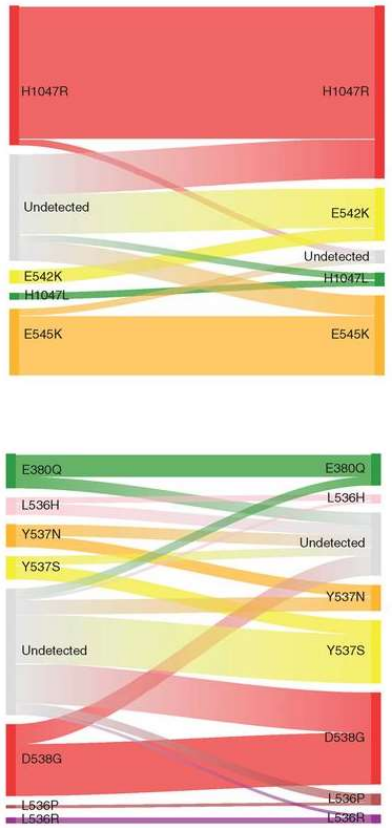


Sartori-Bianchi A et al. Nat Med 2022

RESISTANCE MECHANISMS







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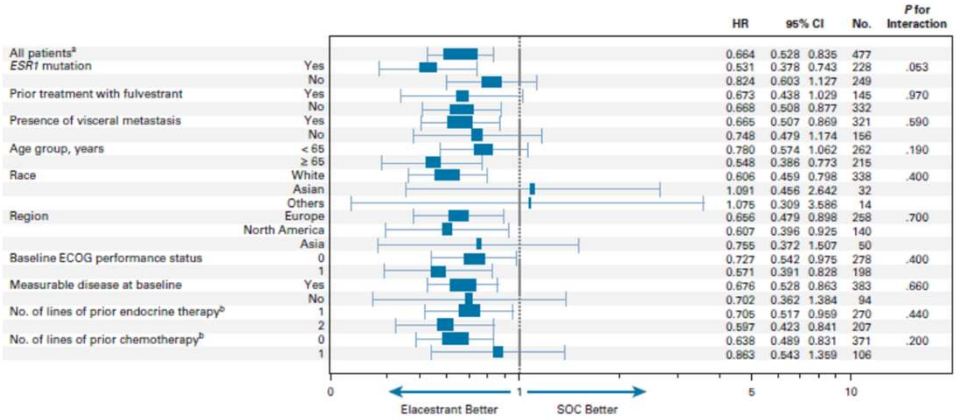
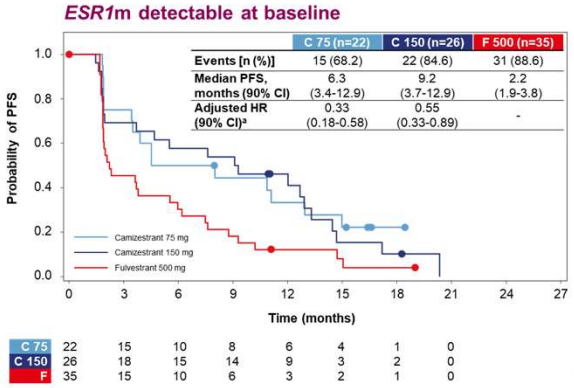
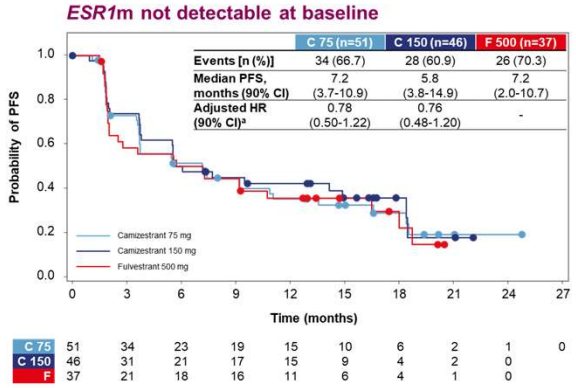
O´Leary B et al. Cancer Discovery 2018

RESISTANCE MECHANISMS



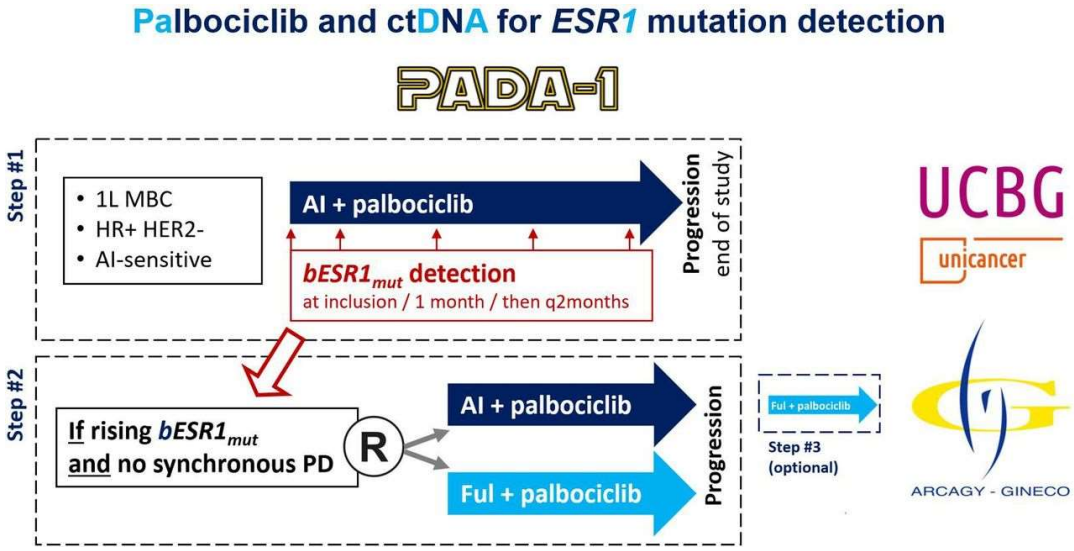
PFS in patients by detectable *ESR1*m

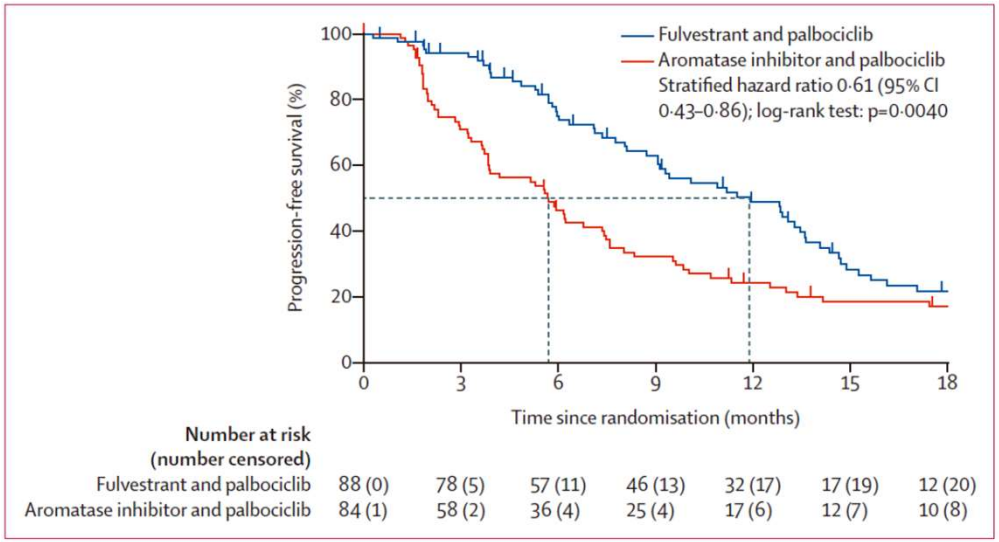




Bidard FC et al. JCO 2022; Oliveira M. SABCS 2022

RESISTANCE MECHANISMS





Bidard FC et al. Lancet Oncol 2022

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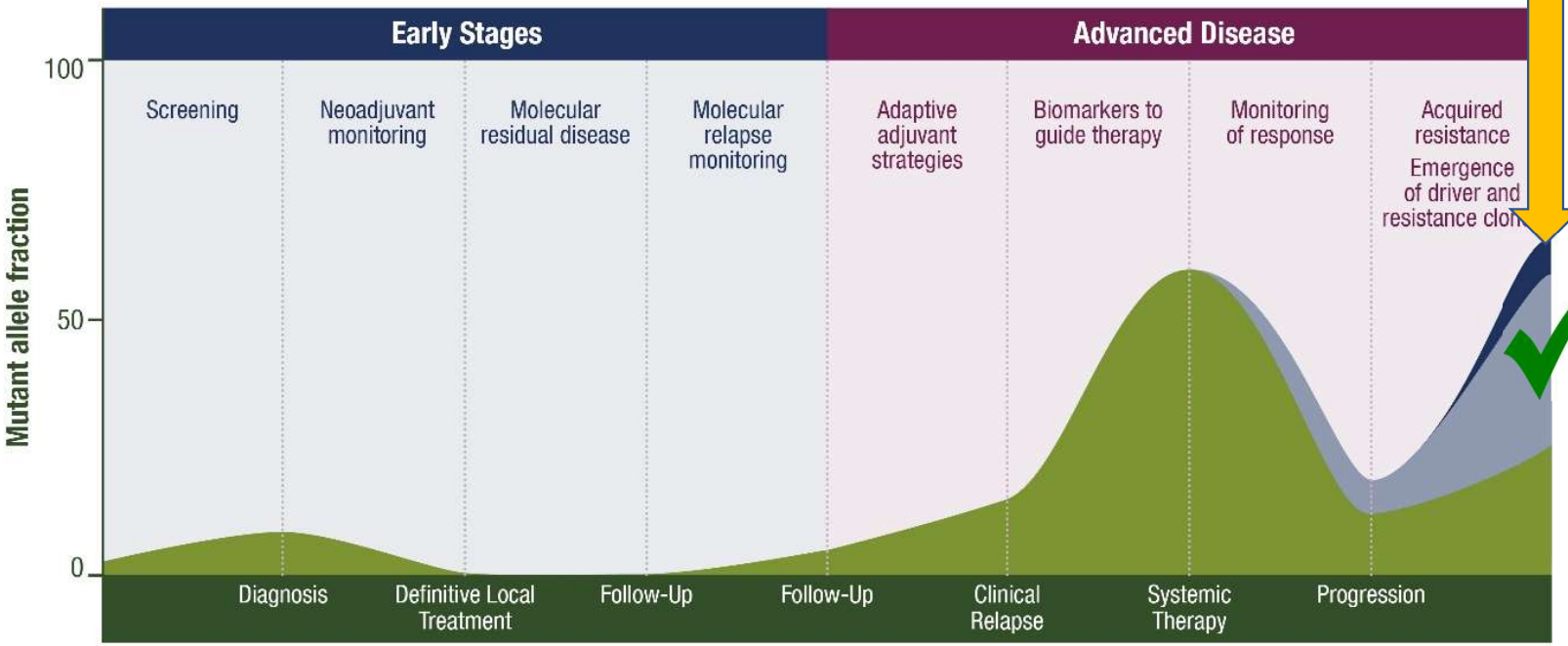

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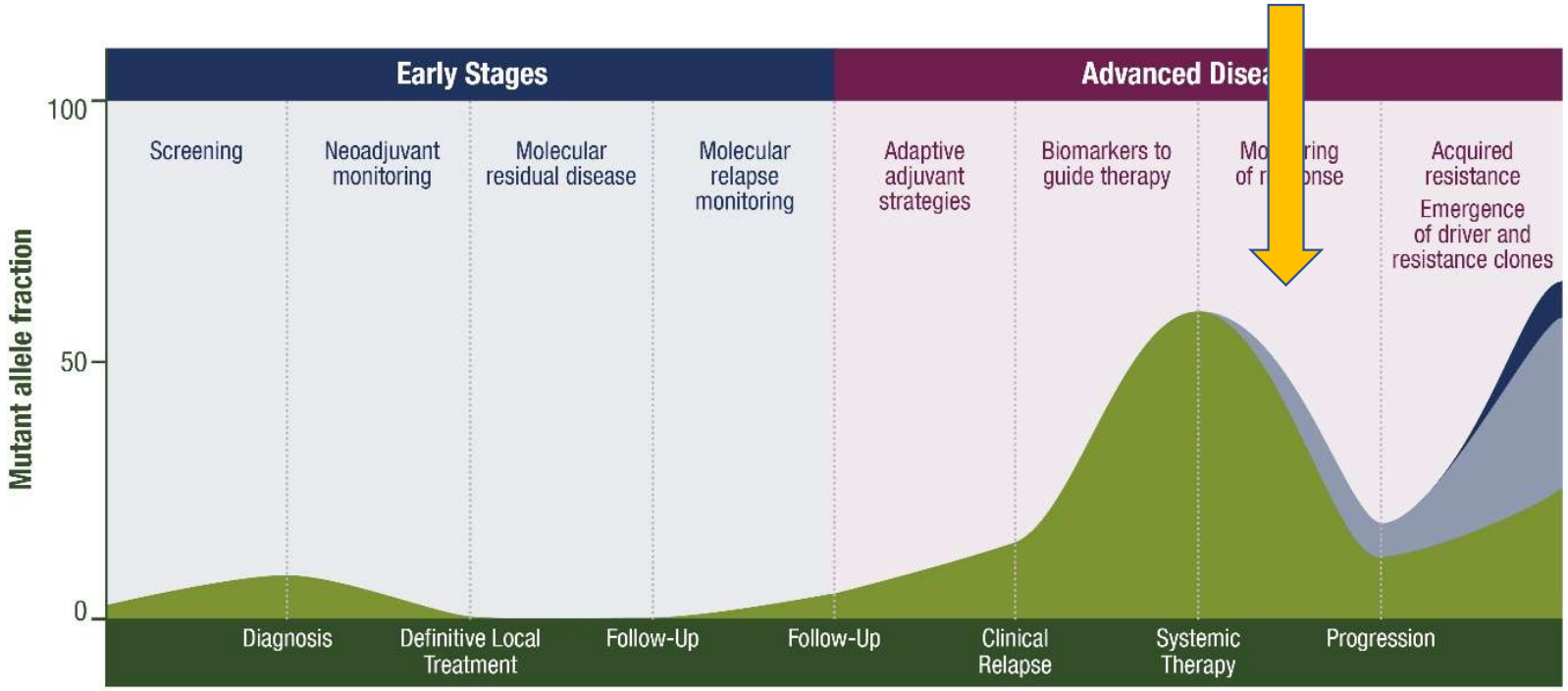
EARLY ON-TREATMENT DYNAMICS FOR EFFICACY PREDICTION



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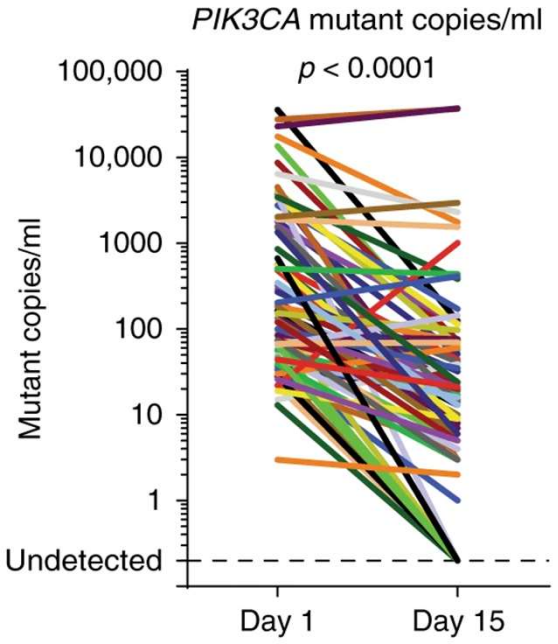

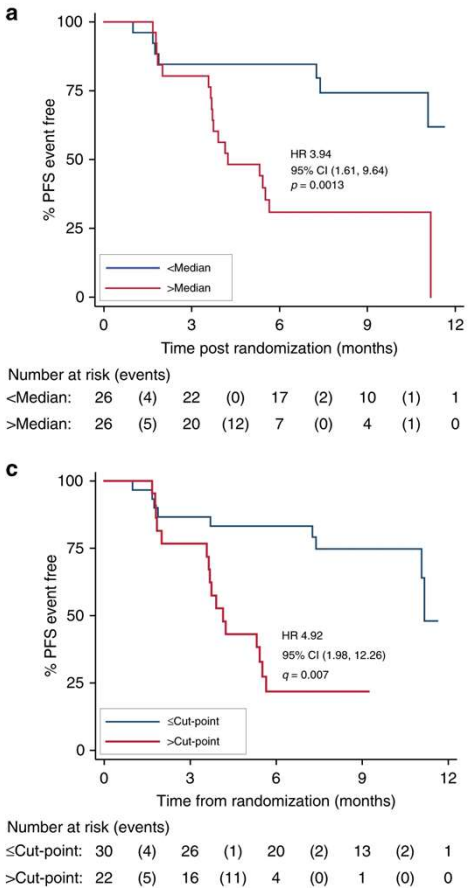

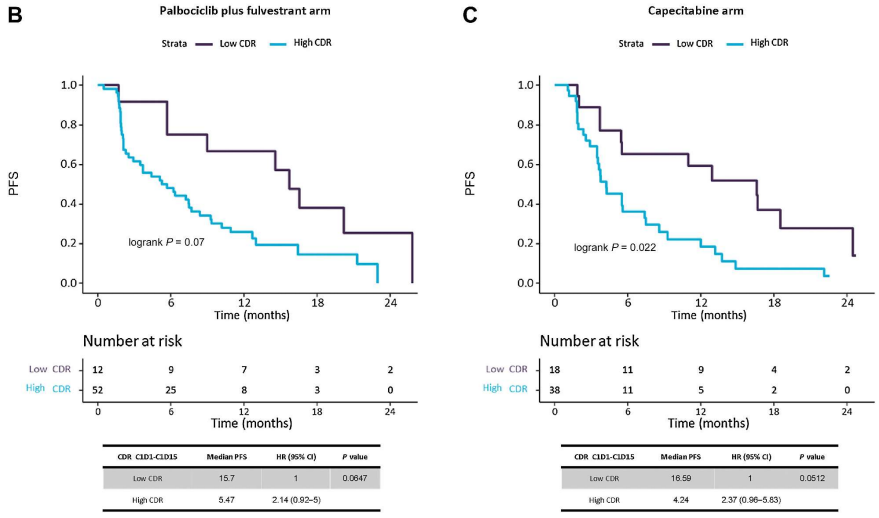

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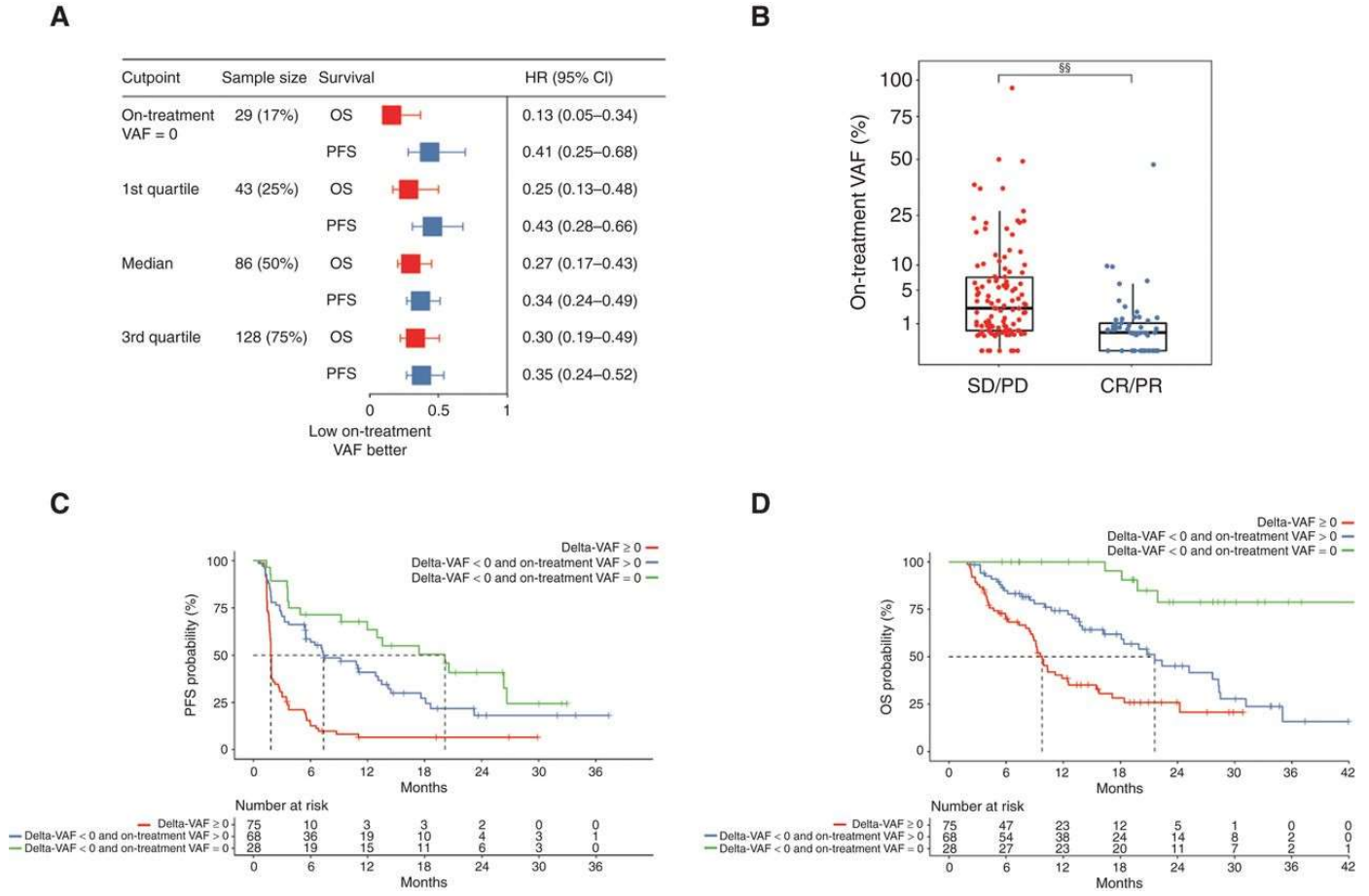
O´Leary B et al. Nat Comms 2018; Pascual J et al. Cancer Discovery 2021; Pascual J et al. Clin Can Res 2023

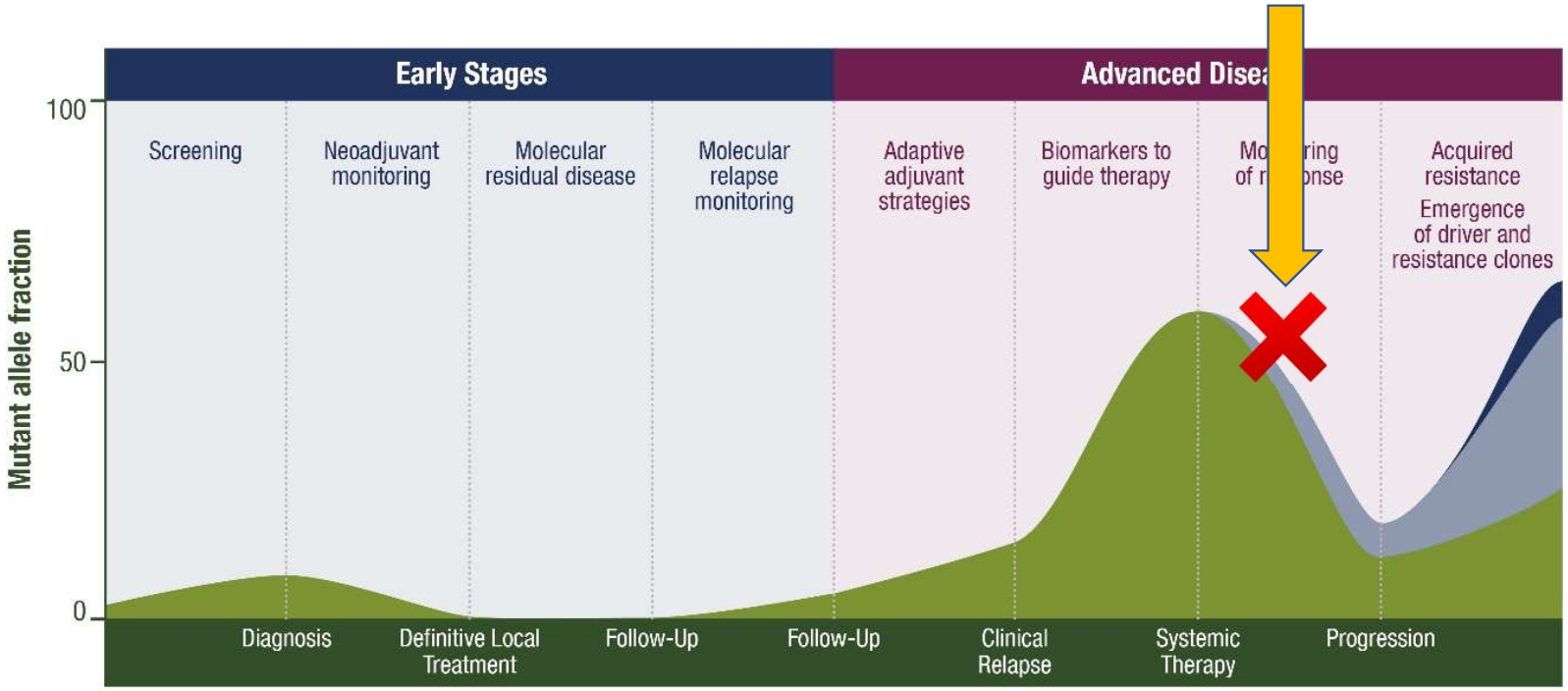
EARLY ON-TREATMENT DYNAMICS FOR EFFICACY PREDICTION

Urothelial
NSCLC
SCLC
Gastroesophageal
TNBC
Ovarian
….

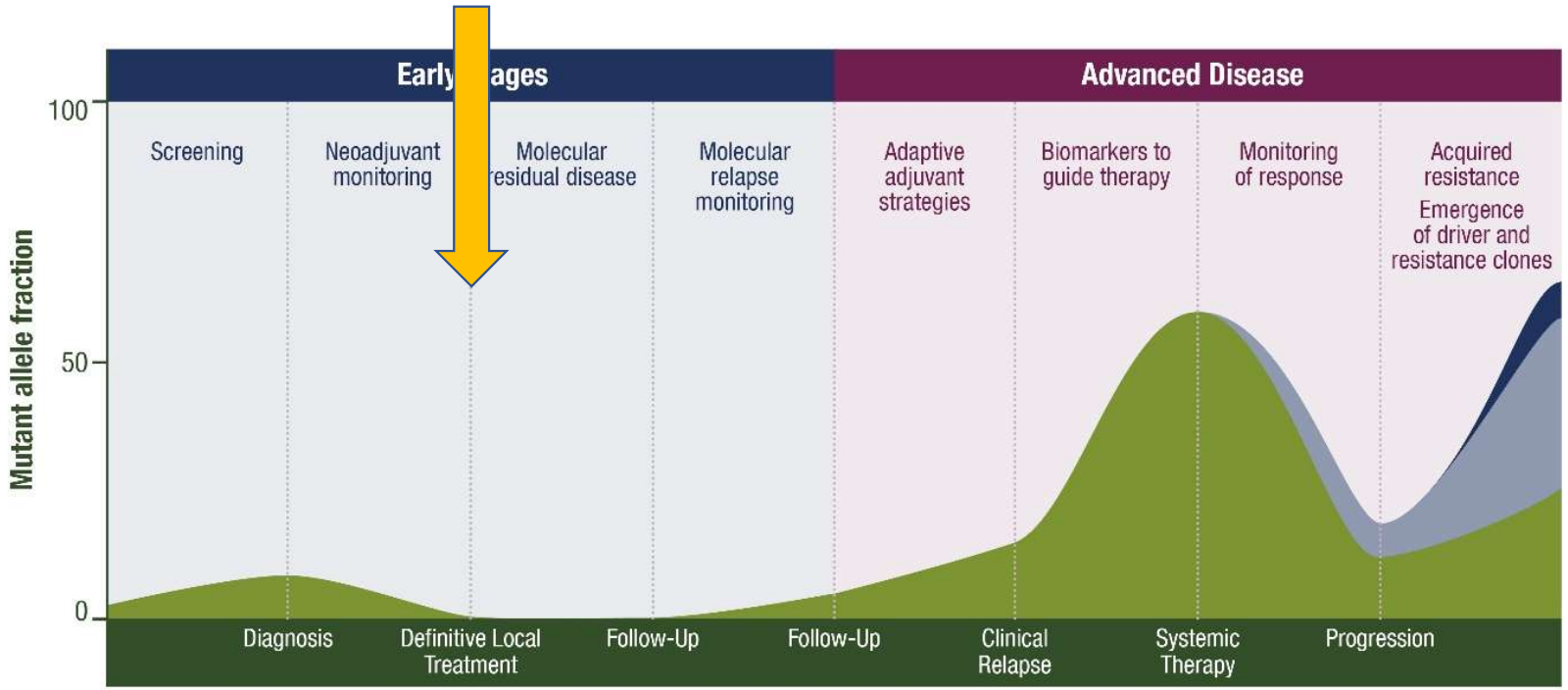


Zhang et al. Cancer Discovery 2020

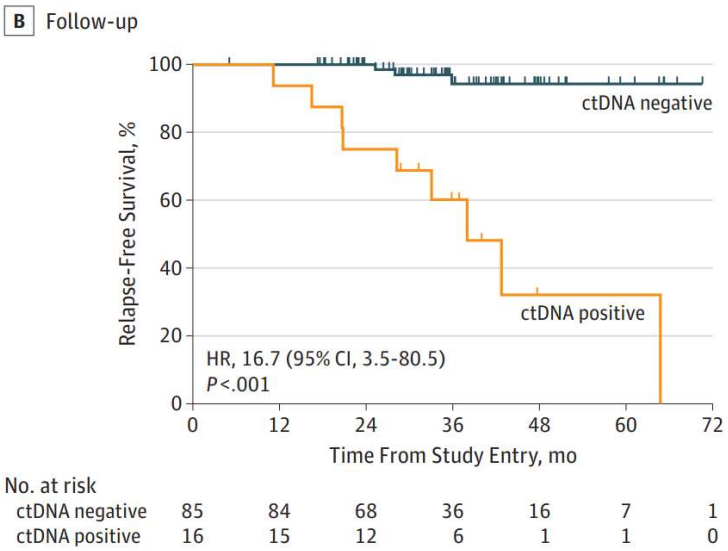
EARLY ON-TREATMENT DYNAMICS FOR EFFICACY PREDICTION



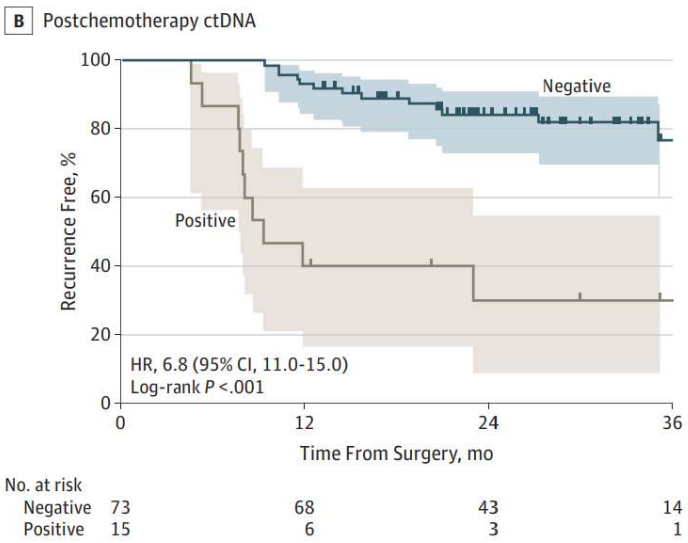
MOLECULAR RESIDUAL DISEASE FOR RELAPSE PREDICTION

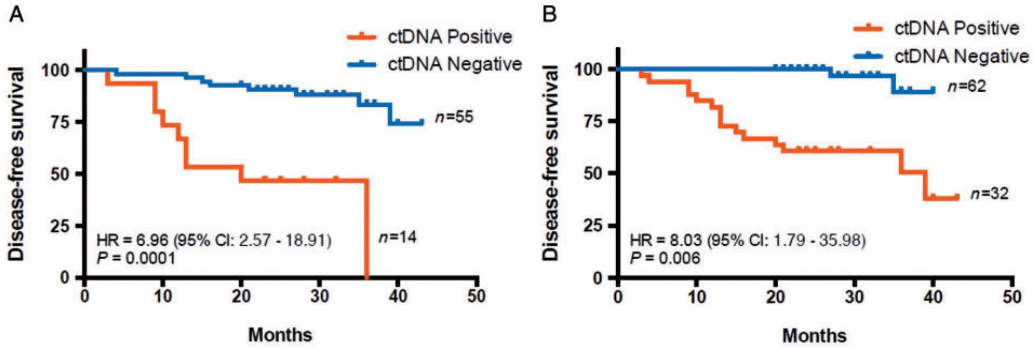


MOLECULAR RESIDUAL DISEASE FOR RELAPSE PREDICTION



Clinical validity





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Garcia-Murillas I et al. JAMA Oncol 2019; Tie J et al. JAMA Oncol 2019; Tarazona N et al. Ann Oncol 2019

MOLECULAR RESIDUAL DISEASE FOR RELAPSE PREDICTION

The NEW ENGLAND JOURNAL of MEDICINE

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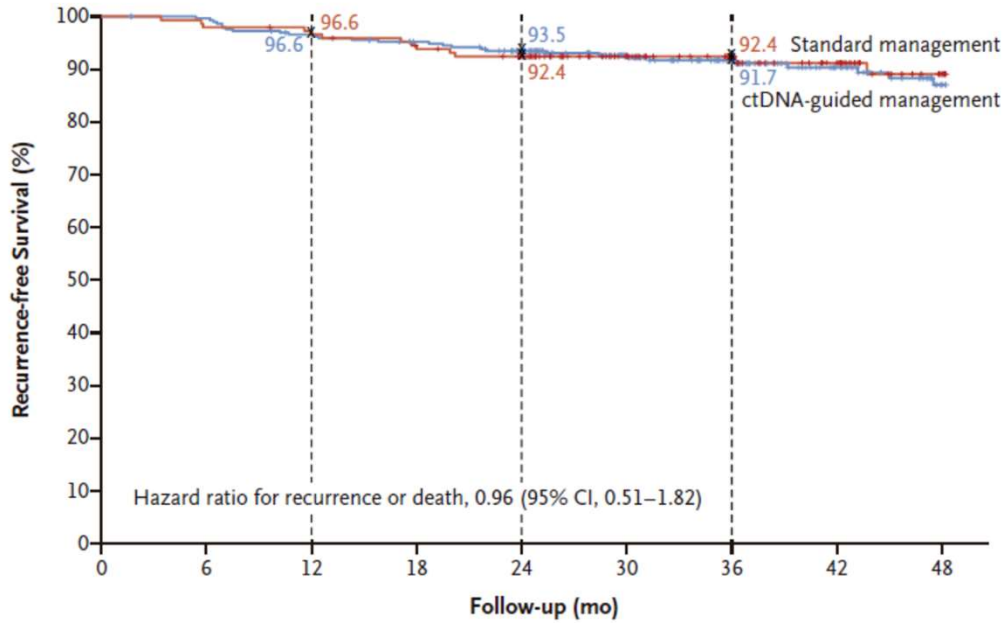
Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Jeanne Tie, M.D., Joshua D. Cohen, M.Phil., Kamel Lahouel, Ph.D., Serigne N. Lo, Ph.D., Yuxuan Wang, M.D., Ph.D., Suzanne Kosmider, M.B., B.S., Rachel Wong, M.B., B.S., Jeremy Shapiro, M.B., B.S., Margaret Lee, M.B., B.S., Sam Harris, M.B., B.S., Adnan Khattak, M.B., B.S., Matthew Burge, M.B., B.S., Marion Harris, M.B., B.S., James Lynam, M.B., B.S., Louise Nott, M.B., B.S., Fiona Day, Ph.D., Theresa Hayes, M.B., B.S., Sue-Anne McLachlan, M.B., B.S., Belinda Lee, M.B., B.S., Janine Ptak, M.S., Natalie Silliman, B.S., Lisa Dobbyn, B.A., Maria Popoli, M.S., Ralph Hruban, M.D., Anne Marie Lennon, M.D., Ph.D., Nicholas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Bert Vogelstein, M.D., Cristian Tomasetti, Ph.D., and Peter Gibbs, M.D., for the DYNAMIC Investigators*



No. at Risk									
Standard management	147	144	142	136	128	97	78	57	33
ctDNA-guided management	294	292	281	273	259	207	155	109	64

Tie J et al. NEJM 2022

MOLECULAR RESIDUAL DISEASE FOR RELAPSE PREDICTION

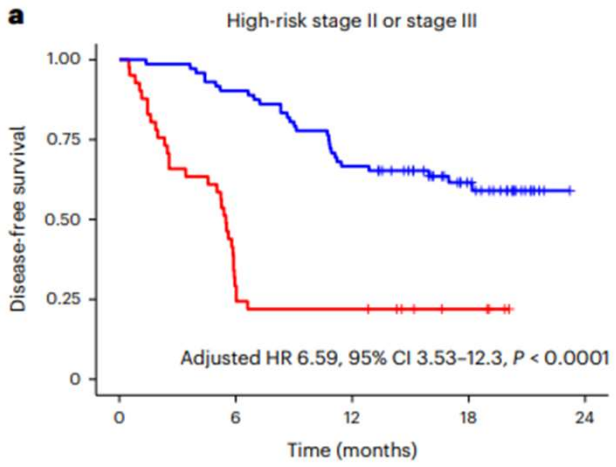
nature medicine

Article

https://doi.org/10.1038/s41591-022-02115-4

Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer

ctDNA+ four weeks after surgery

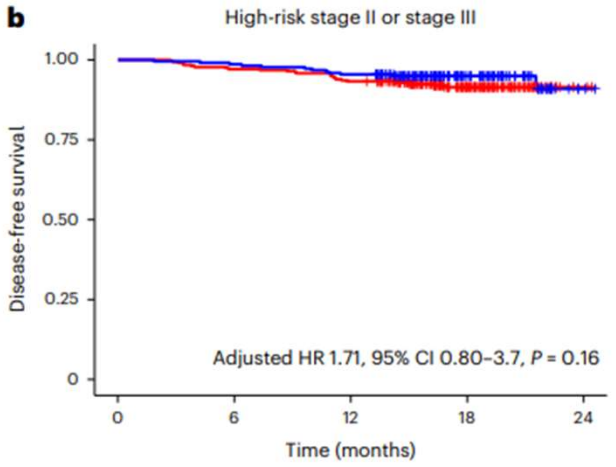


Number at risk

Observation	41	12	9	4	0
ACT	72	65	48	26	0

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	32 out of 41	29.3% (16.4–43.4)	22.0% (10.9–35.5)	22.0% (10.9–35.5)
ACT	28 out of 72	90.3% (80.7–95.2)	66.7% (54.5–76.3)	61.6% (49.0–71.9)

ctDNA- four weeks after surgery



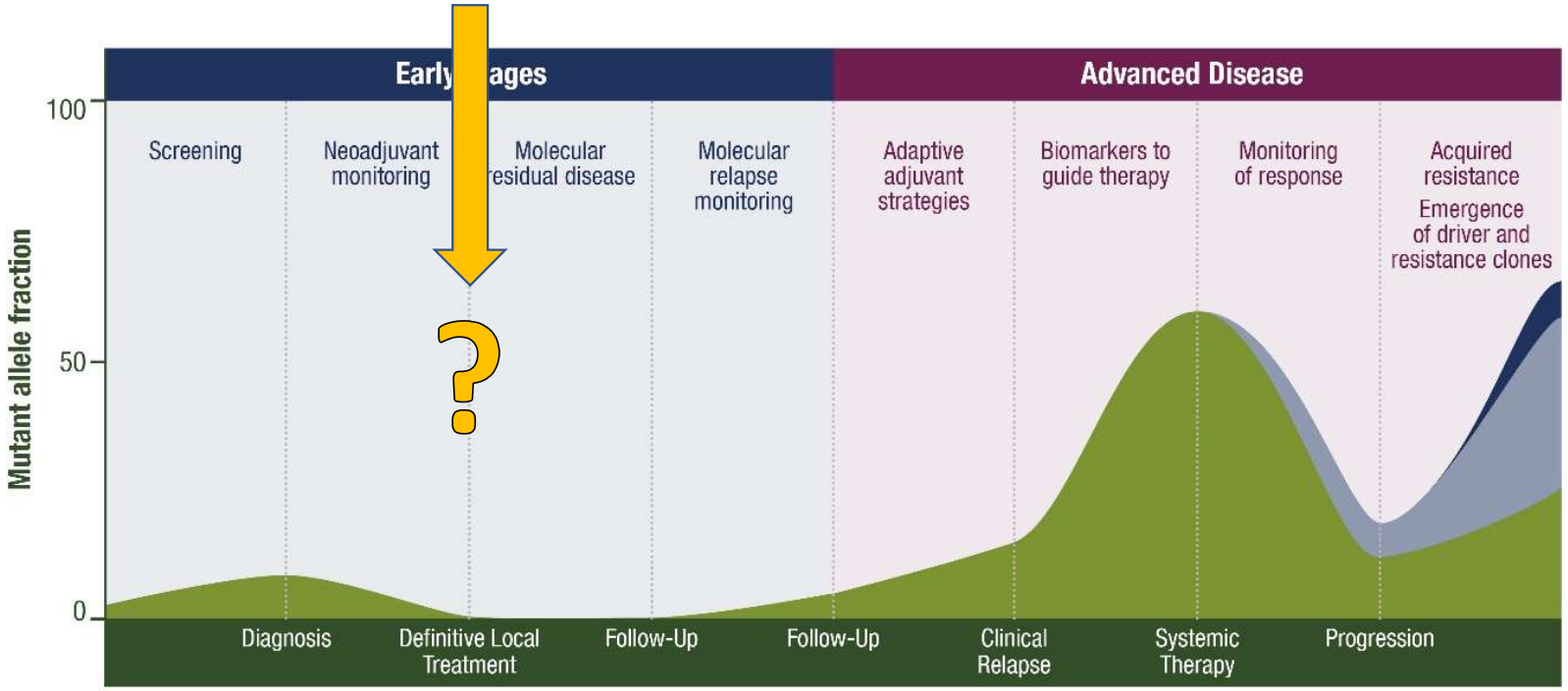
Number at risk

Observation	312	303	291	131	2
ACT	219	216	209	87	2

Treatment	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
Observation	25 out of 312	97.1% (94.5–98.5)	93.3% (89.9–95.6)	91.5% (87.6–94.2)
ACT	12 out of 219	98.6% (95.8–99.6)	95.4% (91.7–97.5)	94.9% (91.0–97.2)

Kotani D et al. Nat Med 2022

MOLECULAR RESIDUAL DISEASE FOR RELAPSE PREDICTION



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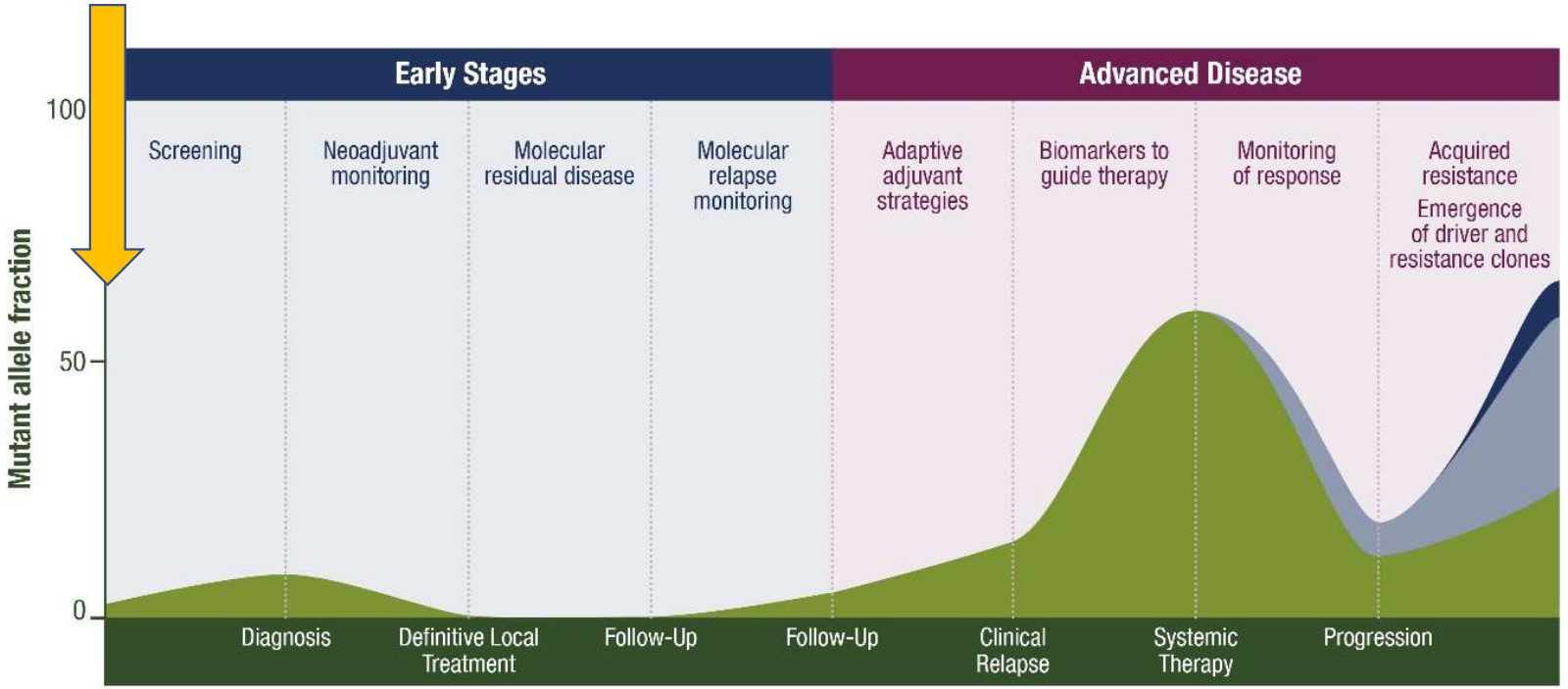
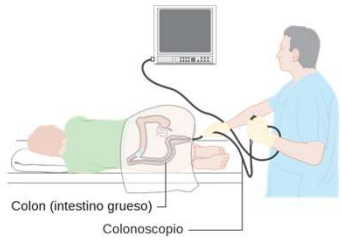
EARLY DIAGNOSIS

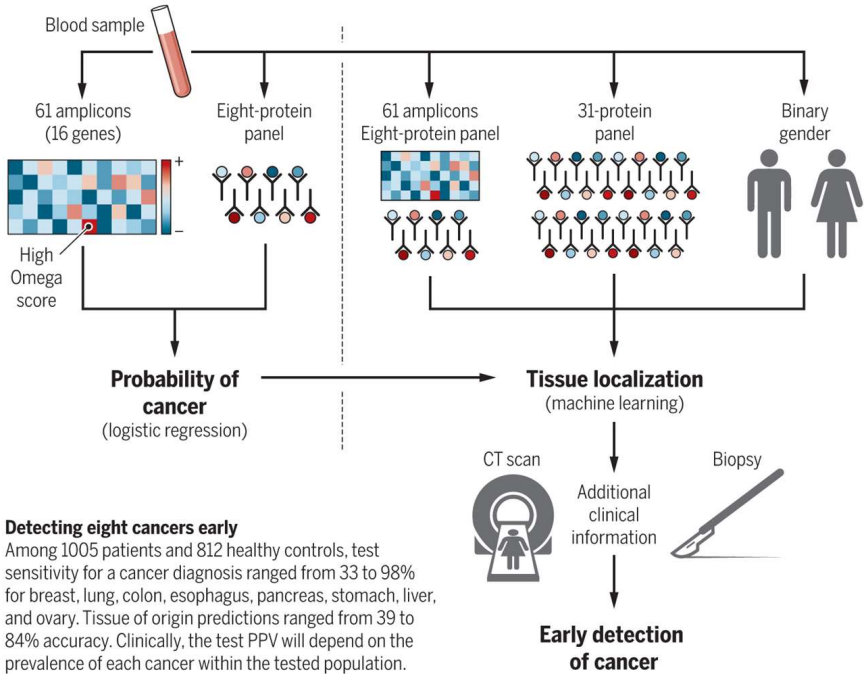


EARLY DIAGNOSIS

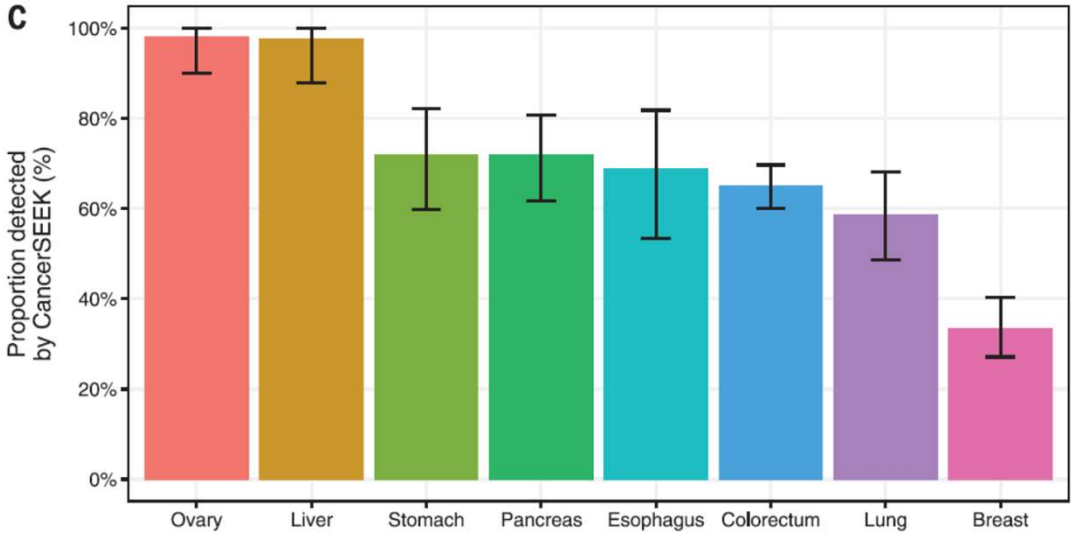
Programa de detección precoz	Población objetivo	Prueba	Intervalo entre exploraciones	Adherence
Cáncer de mama	Mujeres de 50 a 69 años	Mamografía	2 años	~80%
Cáncer de cuello de útero	Mujeres de 25 a 64 años	Citología vaginal	3-5 años	~70%
Cáncer colorrectal	Población de 50 a 69 años	Sangre oculta enheces +/- Colonoscopia	2 años	~50%



EARLY DIAGNOSIS



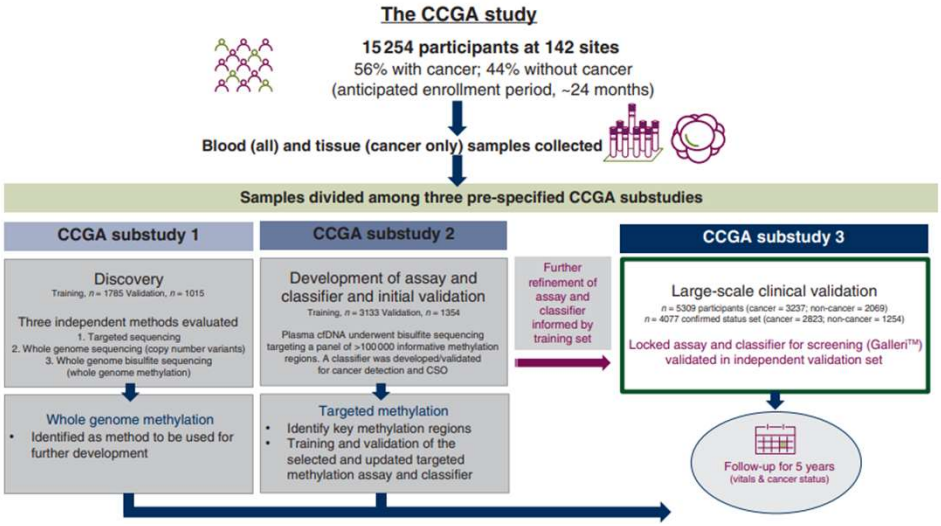
Detecting eight cancers early
Among 1005 patients and 812 healthy controls, test sensitivity for a cancer diagnosis ranged from 33 to 98% for breast, lung, colon, esophagus, pancreas, stomach, liver, and ovary. Tissue of origin predictions ranged from 39 to 84% accuracy. Clinically, the test PPV will depend on the prevalence of each cancer within the tested population.



Cohen JD et al. Science 2018

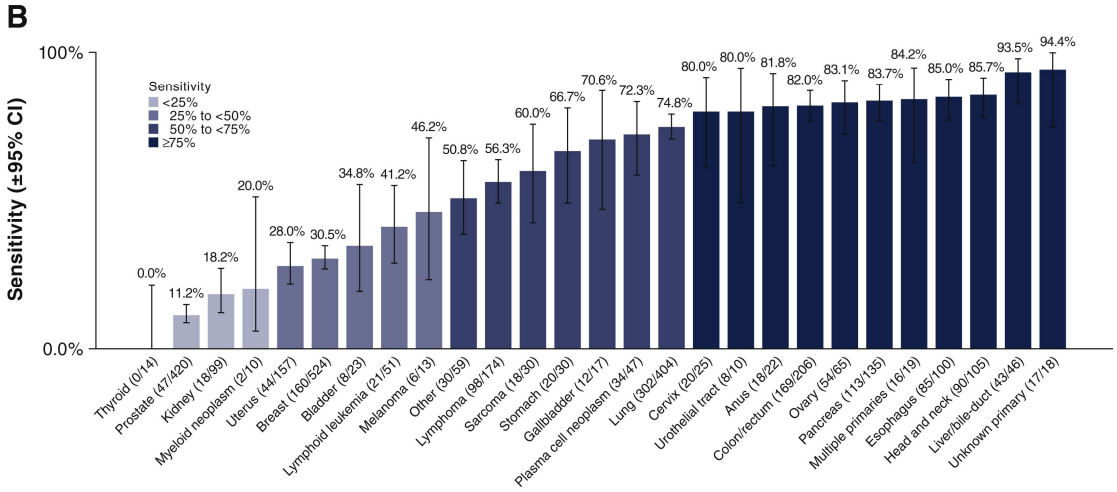
EARLY DIAGNOSIS

GRAIL



	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.



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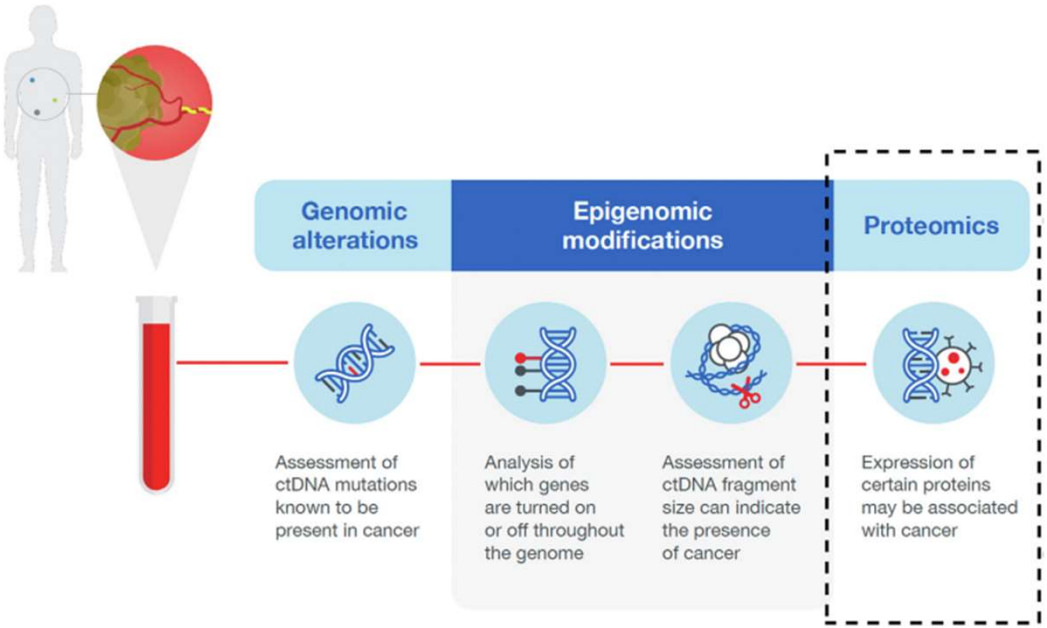
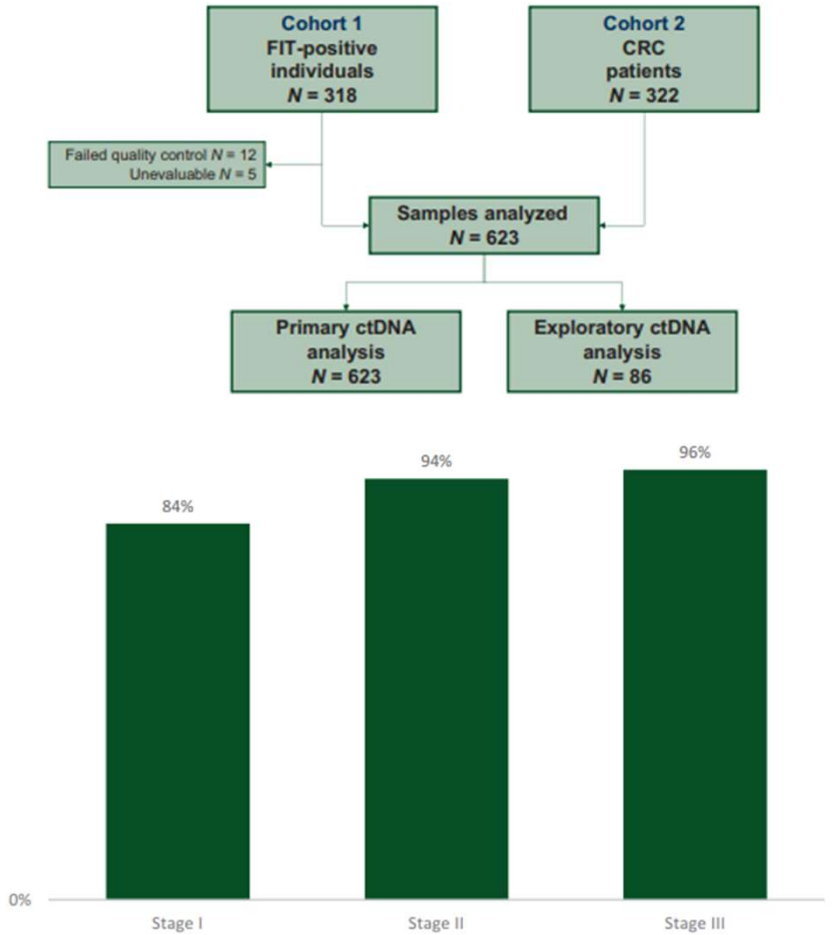
Klein et al. Ann Oncol 2021

EARLY DIAGNOSIS





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Bessa X et al. Ann Oncol 2023

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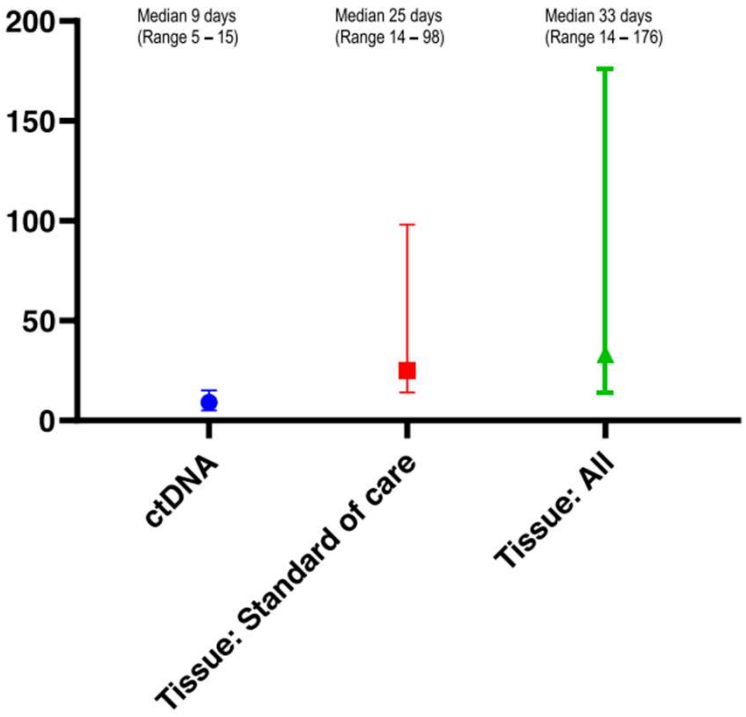


NHS England - ctDNA Transformation Pilot

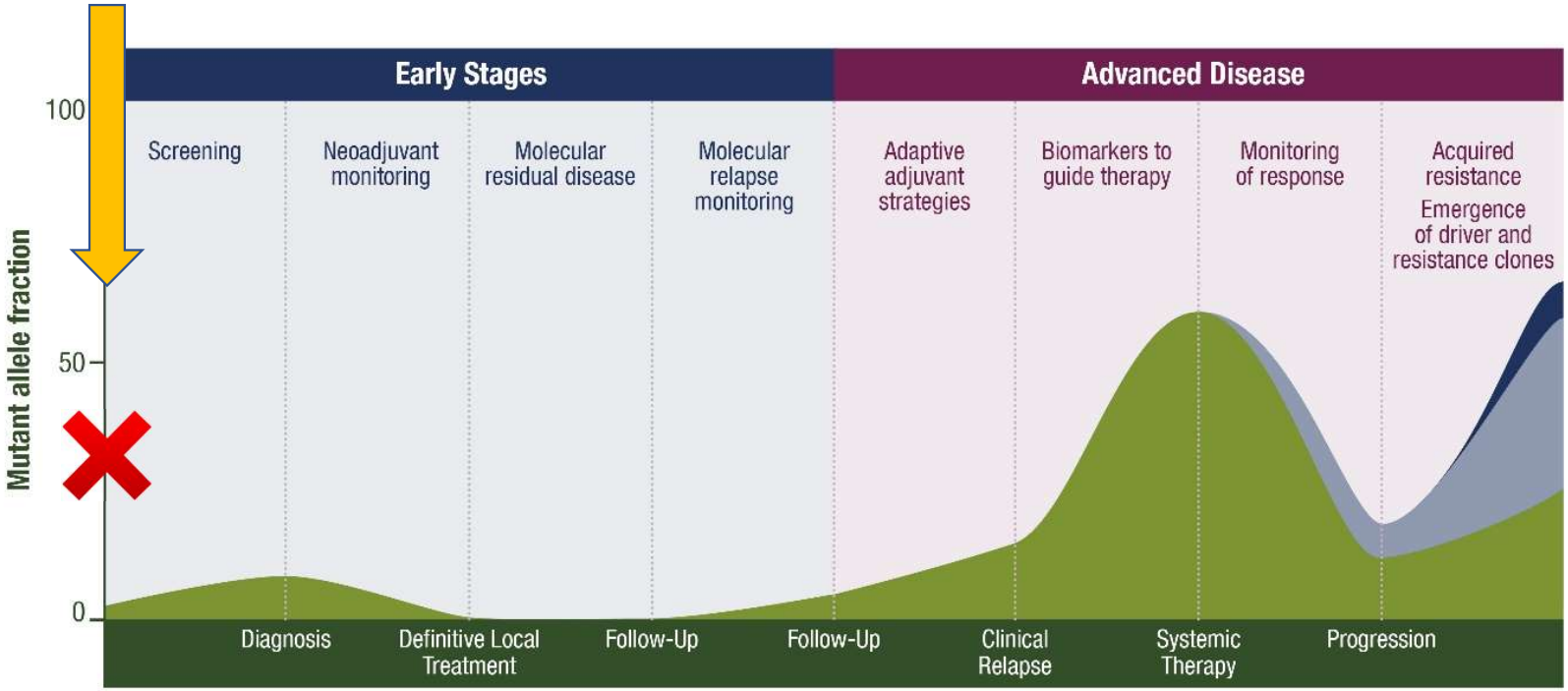
Working with validated liquid biopsy providers, 700 suspected advanced NSCLC patients undergo ctDNA NGS testing.

Outcomes

- 450 samples processed.
- Malignancy confirmed in 92%, with low 'no ctDNA detected' rates of 8.0% of all reported samples.
- Average overall detection rate for actionable mutations with targeted therapies was 21.5%.
- Testing NSCLC patients at radiological suspicion – easy to implement across all settings, from large teaching hospitals to smaller district general hospitals.
- Blood draw to sample report averaged 9 days. Shortening time to diagnosis

Cui W et al. Lung Cancer 2022; Johnson P. NHS Genomic Summit 2023

EARLY DIAGNOSIS



CONCLUSIONS

1. **ctDNA assays can be routinely used to select treatments in the advanced setting provided limitations are understood**
   - Optimal for SNVs
   - Relatively limited for CNV, fusions, splicing variants
   - **Reflex tissue testing if ctDNA negative testing but alteration clinically important**

2. **ctDNA dynamics in the advanced setting for early on-treatment decisions have shown clinical validity but we need large-scale homogeneous studies to claim clinical utility**
   - Very difficult task since it is highly dependent on clinical context, assay, methodology….

3. **ctDNA testing for MRD pending full clinical utility confirmation to adopt in routine clinics**
   - Although **clinical utility can probably be claimed for stage II-III CRC to guide adjuvant CT** (next guidelines versions should incorporate this)
   - Large interventional studies ongoing for other malignancies

4. **ctDNA for early diagnosis looks promising and assay sensitivity is reaching acceptable levels to move to next-stage studies in truly healthy individuals**

¡GRACIAS!

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