ONCOLOGÍA DE PRECISIÓN: Papel de la biopsia líquida

DIA DEL BIOQUÍMICO
15 de Junio de 2022

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Unidad Mixtra TRIAL (CIPF-FIHGUV)

CIBERONC

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DISCLOSURES

Personal finantial interests

Honoraria scientific advice- speaker: BMS, Roche, Amgen, Merck, Astra Zeneca, Takeda, Thermofisher Scientific

Institutional finantial interests

Research grants: Lilly, Astra Zeneca, Merck, Thermofisher Scientific

Non-finantial interests

Leadership role: Executive Board International Society of Liquid Biopsy

I declare no conflict of interests

1. Oncología de Precisión: biomarcadores
2. La muestra
3. La tecnología
4. Aplicaciones clínicas

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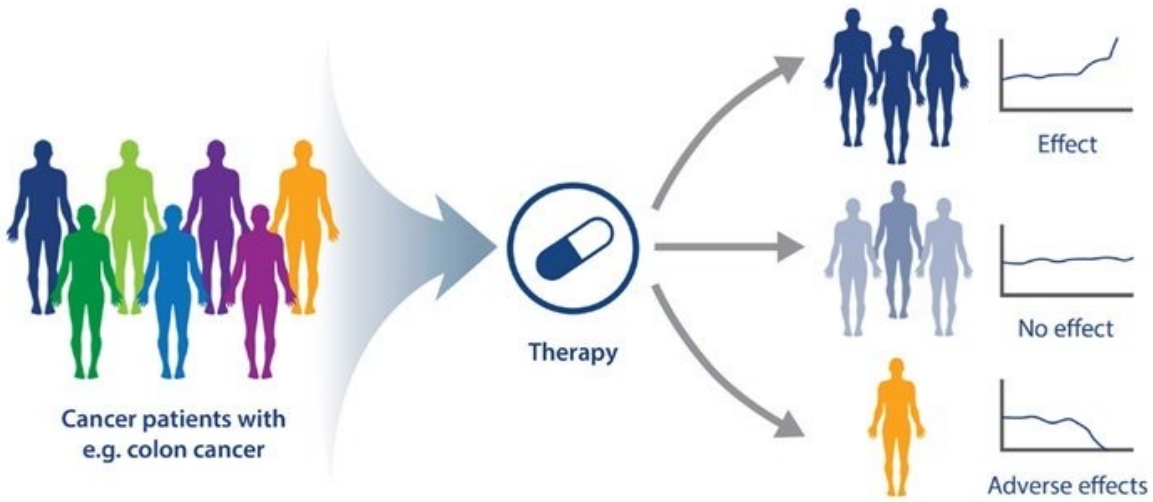
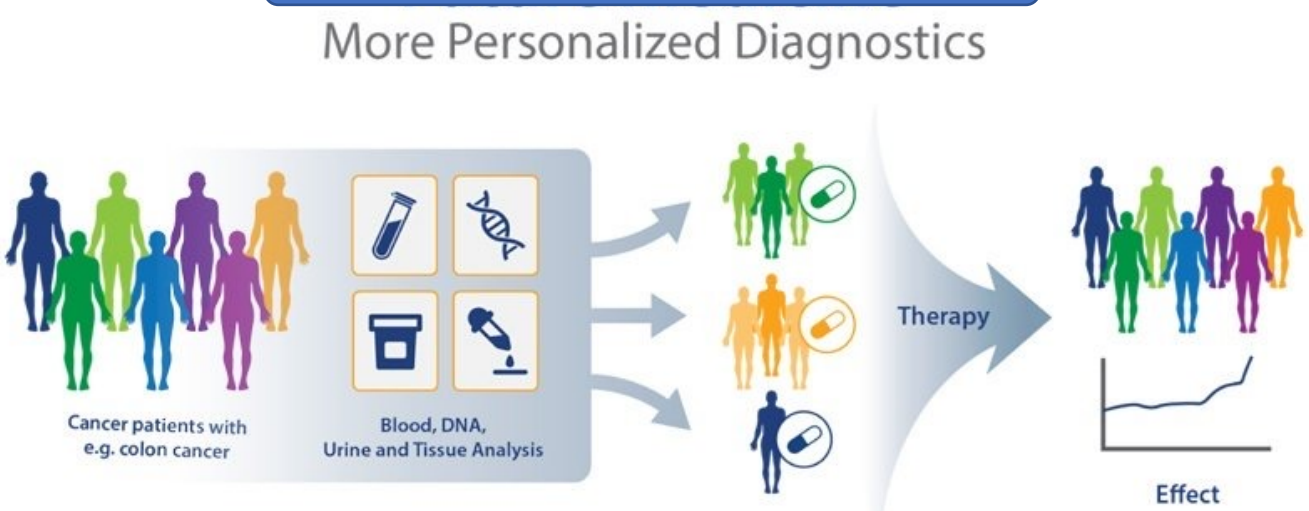
PASADO



PRESENTE



PRECISION ONCOLOGY consists of a **treatment tailored to the tumor's genomic alterations**, assuming that the identified genomic alterations are **cancer driving** and a **matched targeted therapy** is available[1,2]

Genomic testing

Biomarkers

Genomic reporting

Genomic matching

[1]. Arnedos, M., *et al.* (2014) *J Pathol.* 232:274–82; [2]. Schwartzberg, L., *et al.* (2017) *Am Soc Clin Oncol Educ Book* 37:160-9.

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BIOMARCADORES EN CÁNCER: estado del arte – terapias dirigidas

Bladder

FGFR2/3 fusions

Breast

PIK3CA mutations

ERBB2(HER2) amplification

BRCA1/2 germline and somatic mutations

ESR1 mutations

Cholangiocarcinoma

FGFR2 fusions

IDH1 mutations

Colorectal

MSI-High

RAS mutations

BRAF V600E

ERBB2(HER2) amplification

EGFR mutations

Endometrial

MSI-high

ERBB2(HER2) amplification

Gastric/Gastroesophageal

ERBB2(HER2) amplification

GIST

KIT mutations

PDGFRA mutations

BRAF mutations

NSCLC

EGFR driver mutations

ALK fusions

ROS1 fusions

BRAF V600E mutations

RET fusions

KRAS G12C

MET exon 14 skipping

EGFR/ERBB2 exon 20 insertions

Melanoma

BRAF V600E/K

Ovarian

BRCA1/2 germline and somatic mutations

Pancreatic

BRCA1/2 germline and somatic mutations

Prostate

BRCA1/2 germline and somatic mutations

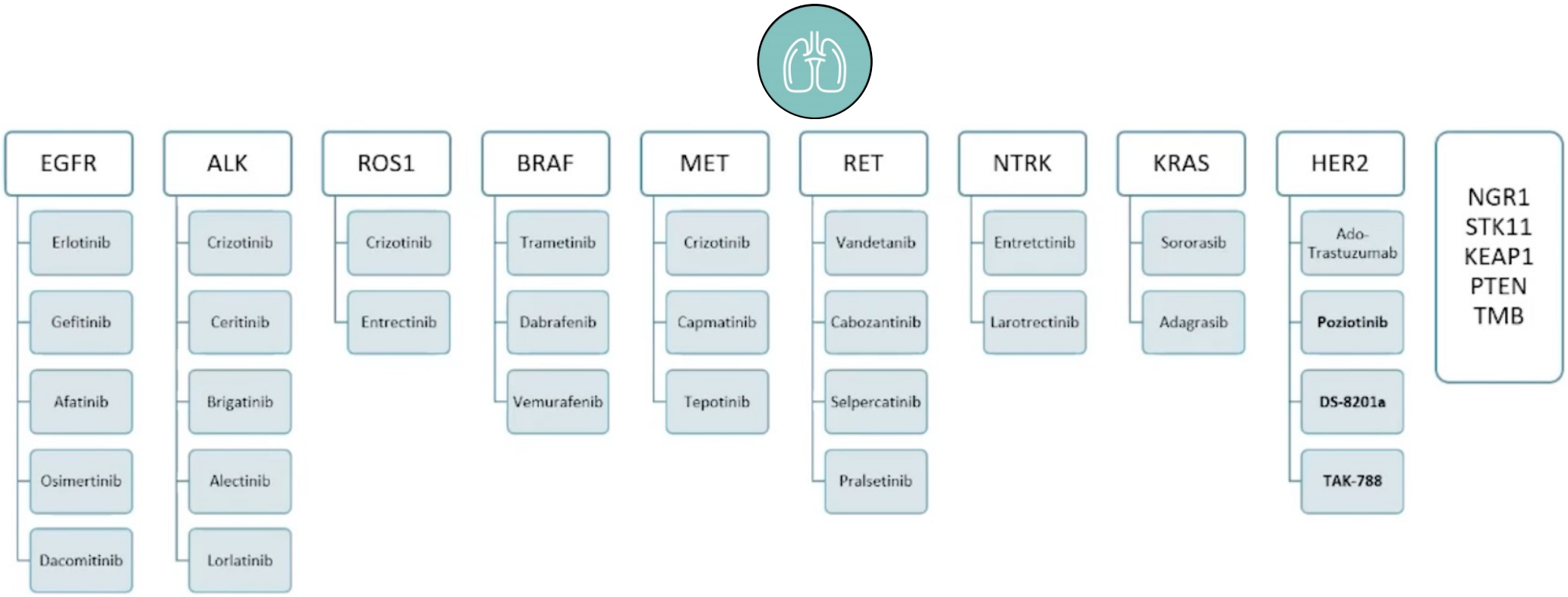
Thyroid

RET fusions

BRAF V600E

BIOMARCADORES EN ONCOLOGÍA: TERAPIAS DIRIGIDAS

Cáncer de pulmón *-> creciente número de dianas terapéuticas y de tratamientos dirigidos*

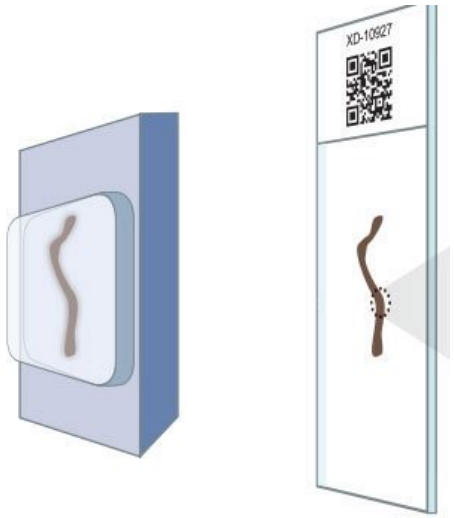


Lung cancer genotyping is a challenge

2 LA MUESTRA

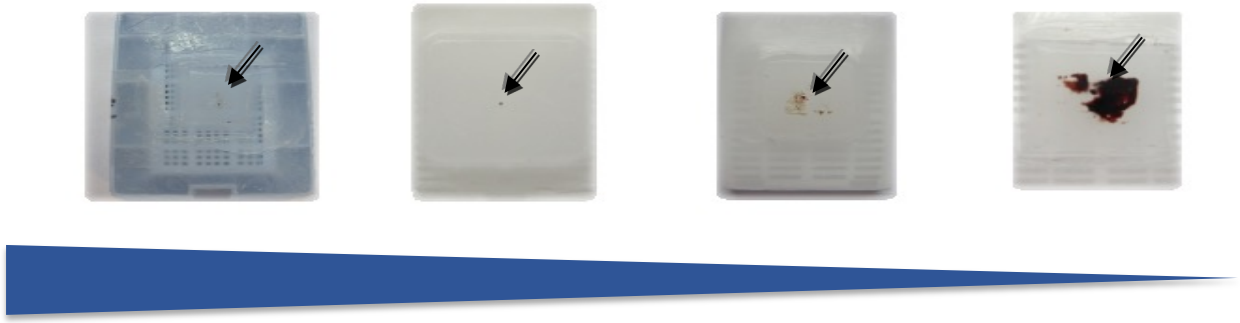
BIOMARCADORES: selección de la muestra

TEJIDO



- Es el estándar en la práctica en AP
- Información histológica completa
- Se puede analizar tumor y microambiente tumoral
- <u>Cantidad de material</u> para análisis molecular depende del tipo de tumor, estadio, abordaje para la toma de muestra, etc.
- <u>Heterogeneidad</u> plantea un problema
- Muestra invasiva / rebiopsias no siempre son posibles (-> no captura la plasticidad de los tumores)

Data from NSCLC



In real NSCLC cohort, 20- 30% of patients are NOT tested, because insufficient or NO tissue availability

~30% of tissue failure rates for tumor genotyping (NGS) in routine pathological samples

Gutierrez – Clin Lung Cancer 2017

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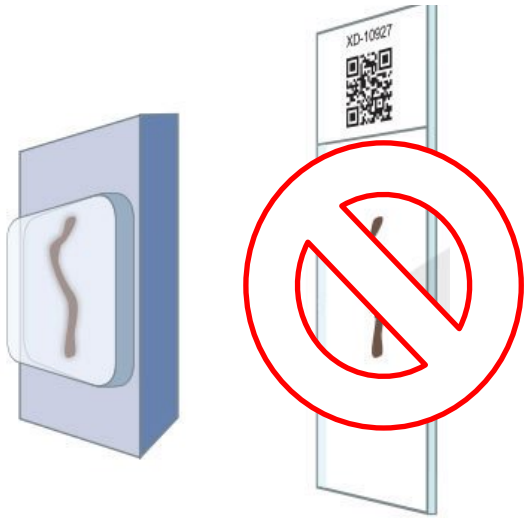
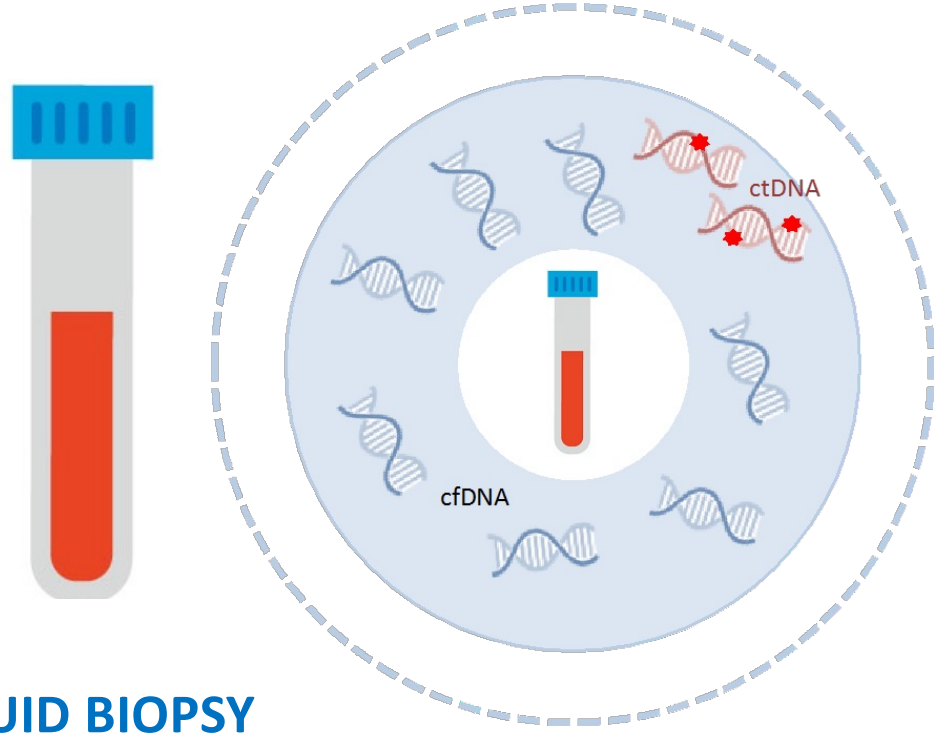
Is still possible to implement a **PRECISION ONCOLOGY** approach **in those patients w/o tissue samples** for molecular testing**??**



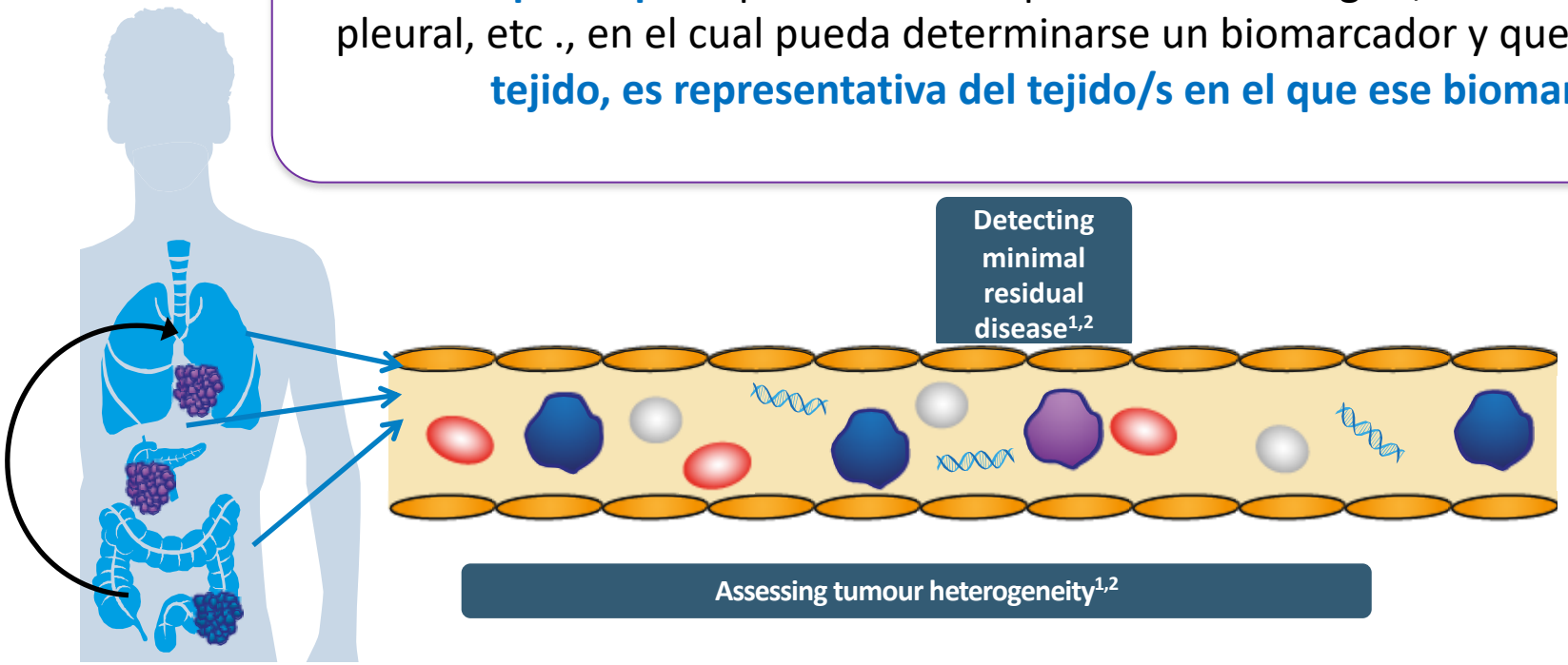
We need a
Complementary/ Alternative
option to fill this gap



LIQUID BIOPSY

Jantus-Lewintre E, WCLC 2019

Una **biopsia líquida** puede ser cualquier fluido biológico, como la sangre, orina, ascitis, líquido pleural, etc ., en el cual pueda determinarse un biomarcador y que al **igual que en una biopsia de tejido, es representativa del tejido/s en el que ese biomarcador se ha producido**



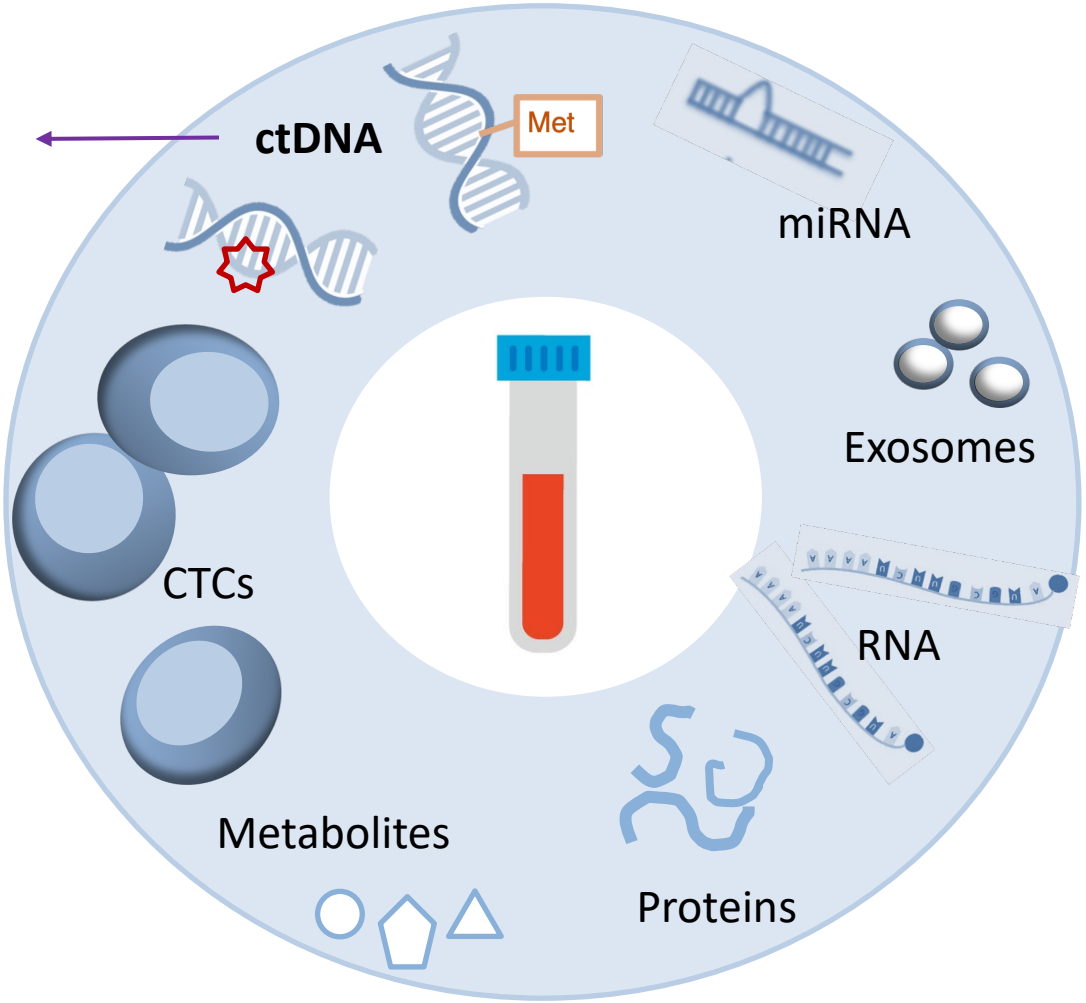
Please note: clinical utility data may not be available for all applications described above.

Primary tumour cell Metastatic tumour cell

Diaz LA, Bardelli A. J Clin Oncol 2014;32:579–86; Haber DA, Velculescu VE. Cancer Discov 2014;4:650–61.

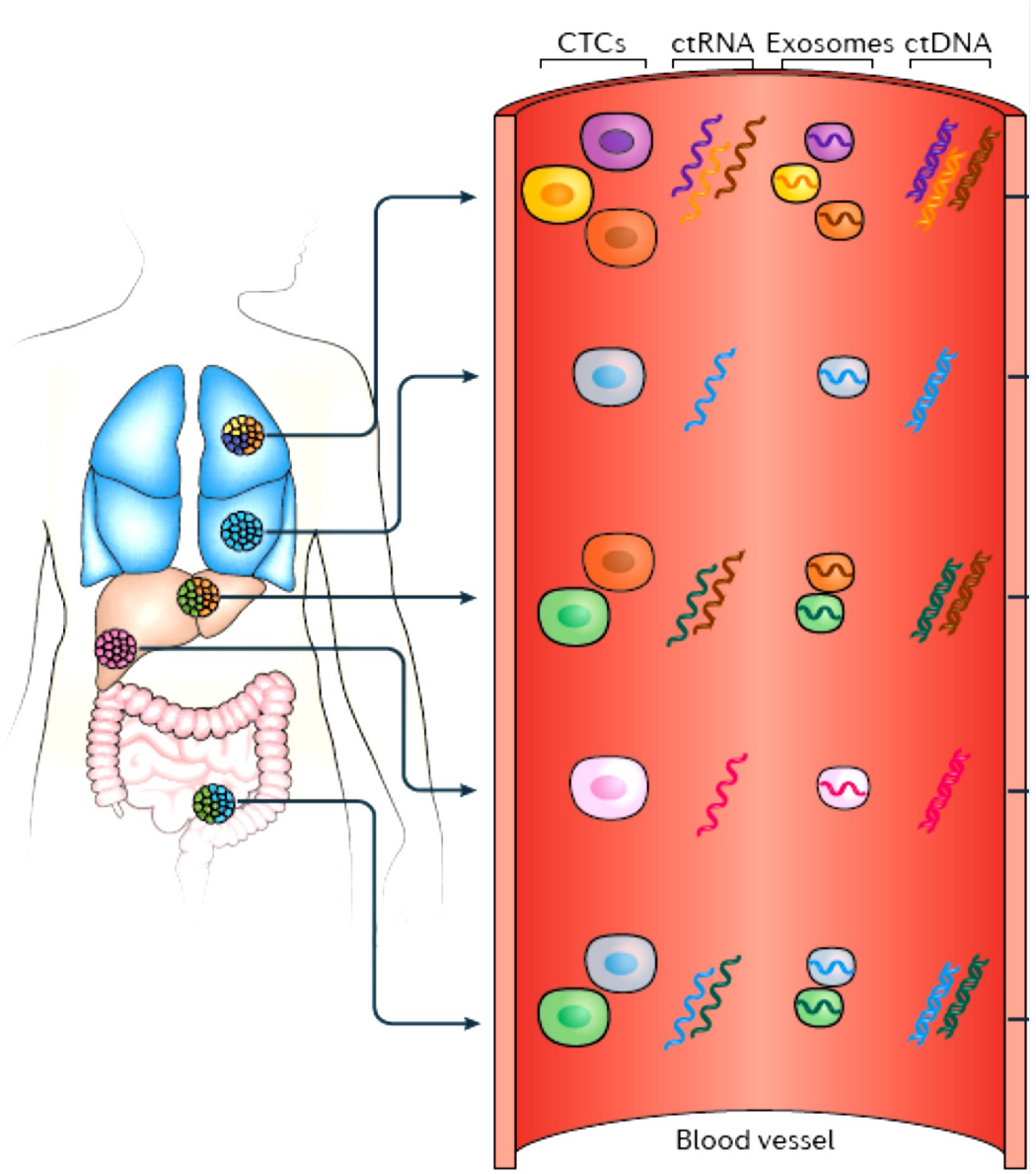
¿Qué entendemos por Biopsia Líquida? -> **SANGRE**

ctDNA
SNV
Indel
CNV
Metilación

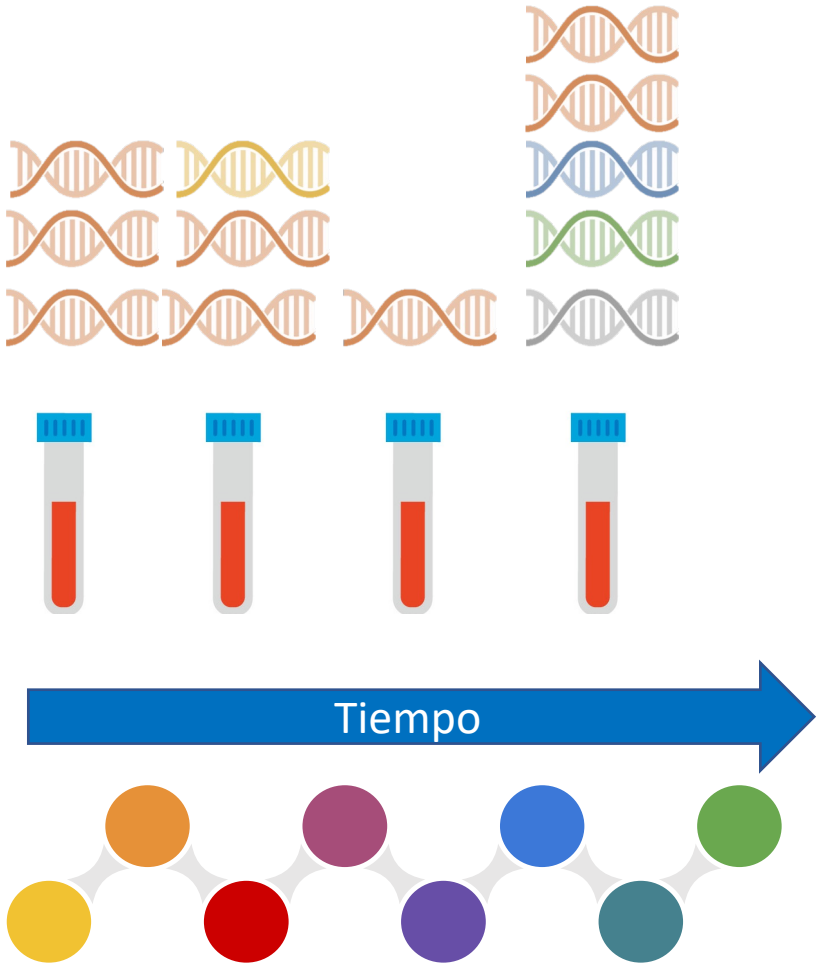


Jantus-Lewintre, E, WCLC 2019

Heterogeneidad

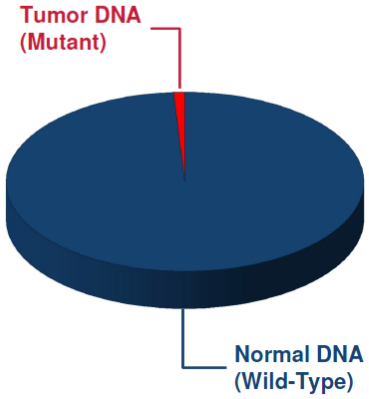


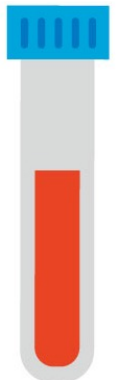
Plasticidad



Siravegna et al , Nat Rev Clin Oncol , 2017

PERO…. La sensibilidad es importante





VENTAJAS

- Mínimamente invasiva/ menor morbilidad
- Simple de obtener/ resultados más rápidos
- Se puede repetir-> monitorización en tiempo real
- Recapitula mejor la heterogeneidad tumoral

LIMITACIONES

- No todos los pacientes tienen ctDNA
- Resultados negativos deben confirmarse en tejido

3

Tecnologías para análisis de Biopsia Líquida.

BIOMARCADORES: tecnologías disponibles

Análisis de biomarcadores de forma individual

Análisis de multigénico (NGS)

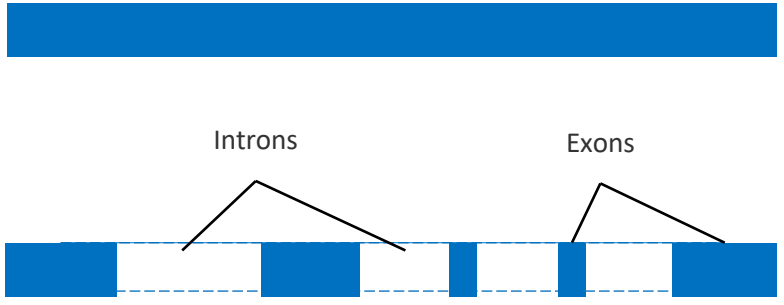
Tecnologías para el análisis de biomarcadores: NGS

Detection cut-off

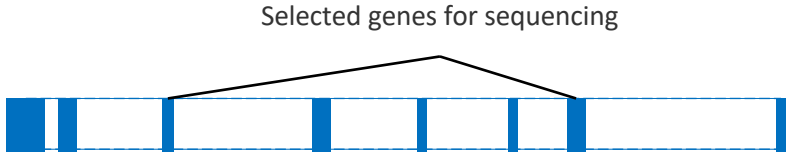
INCREASING DEPTH OF COVERAGE

Patient genome

WGS
(whole genome)



WES
(exons only)



Gene panel (selected genes)

INCREASING BREADTH OF COVERAGE

Sample quality requirement
Genome Coverage. Analysis complexity

amplicones

captura

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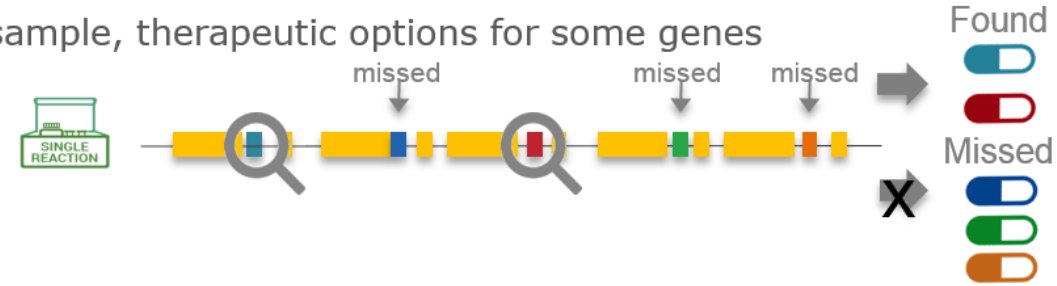
Tecnologías para el análisis de biomarcadores: NGS

Hot-Spot Testing

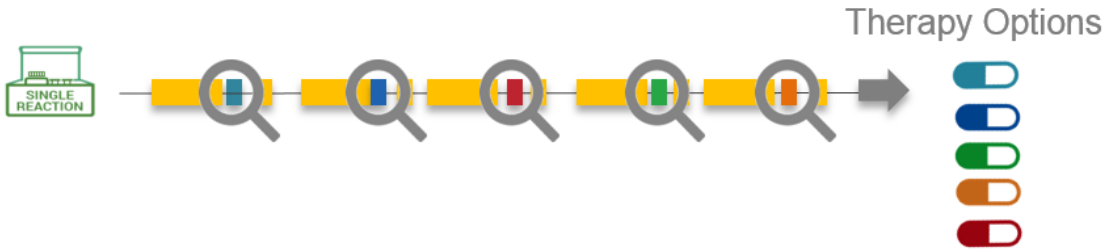
1 sample, therapeutic options for some genes



10-30% actionability

Comprehensive Genomic Profiling

1 samples, therapeutic options for many genes



25-55% actionability

Lyle J et al, Clin Oncol 2016; Johnston KM et al, Curr Oncol 2020; Ozdemir MAP 2020.

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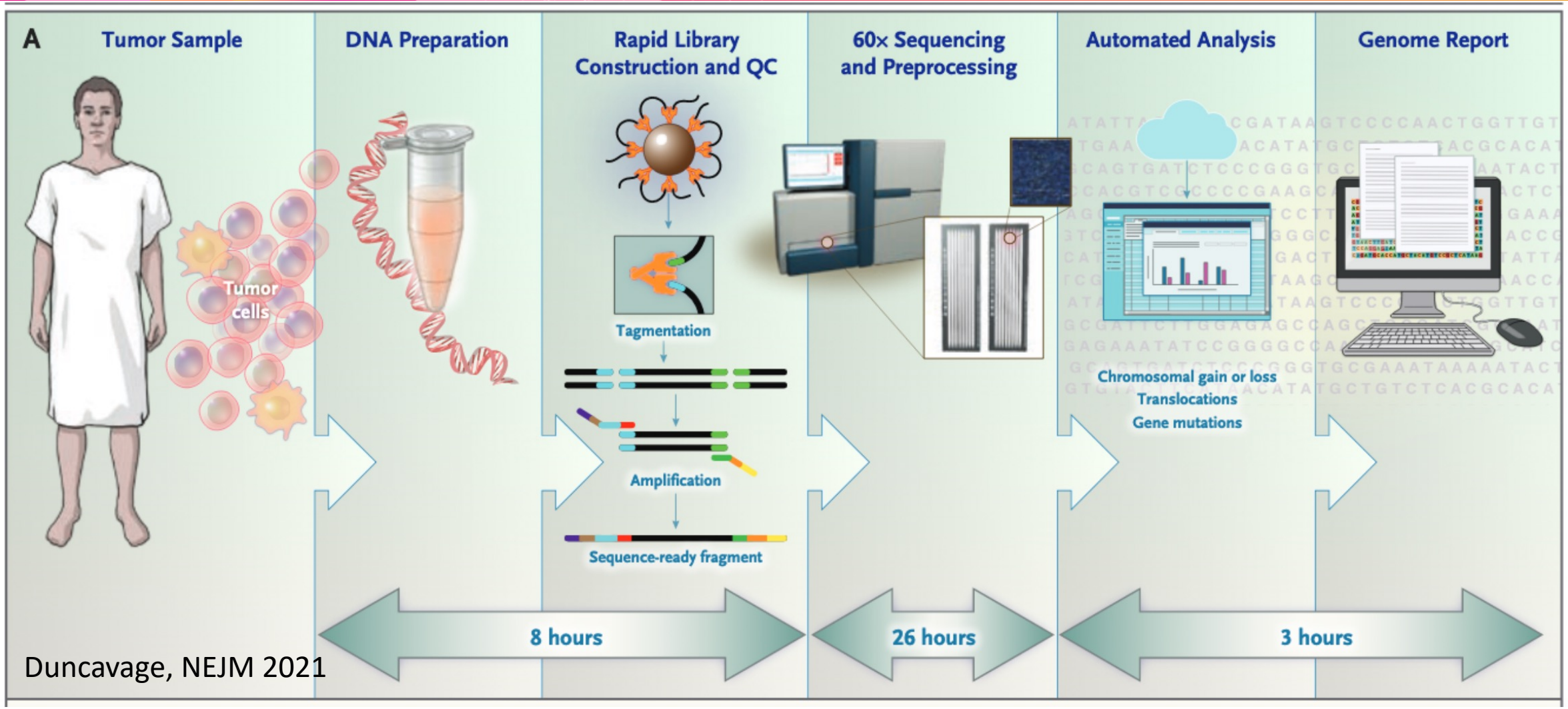
Tecnologías para el análisis de biomarcadores: NGS



Duncavage, NEJM 2021

Biopsia Líquida -> selección de la metodología adecuada

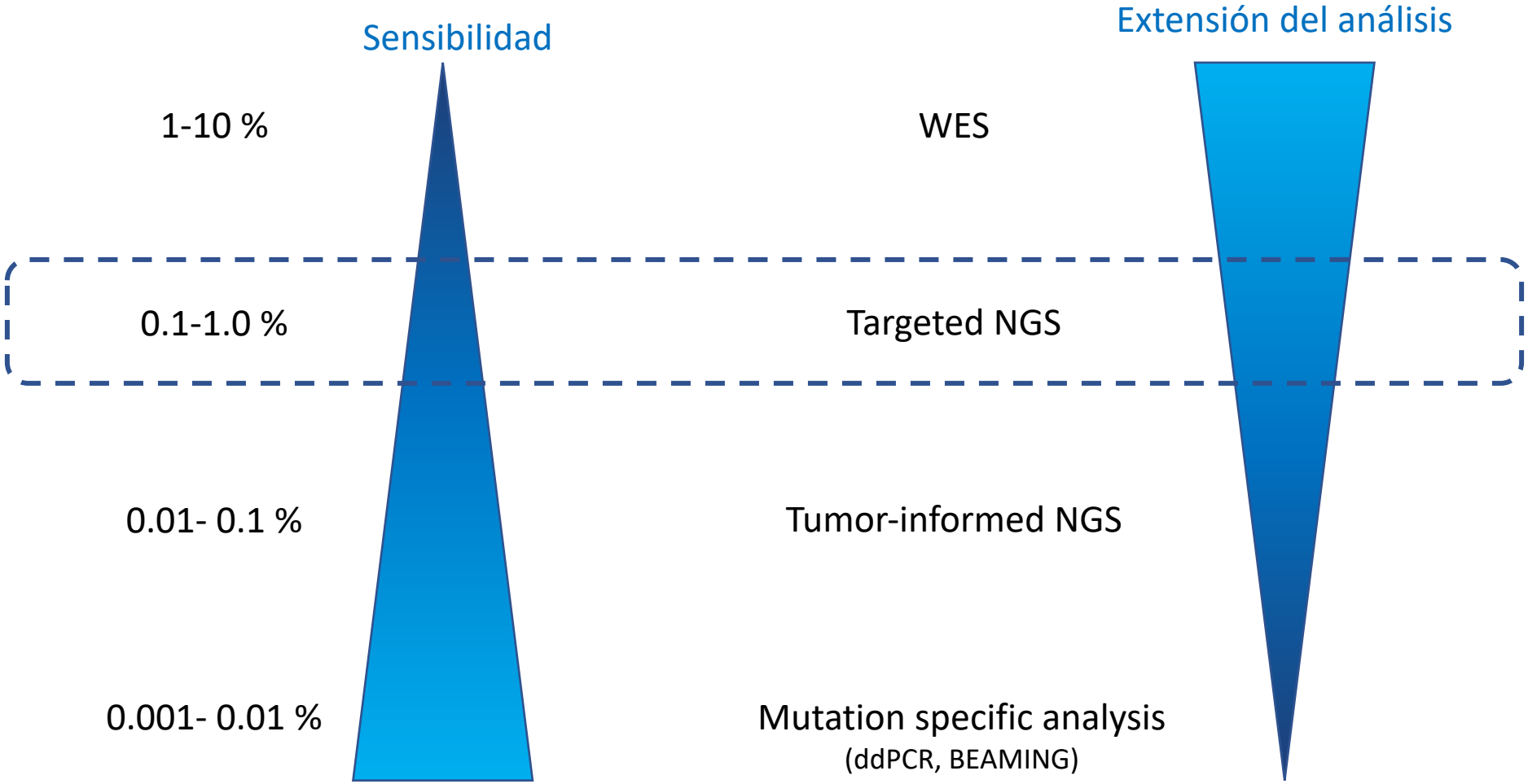


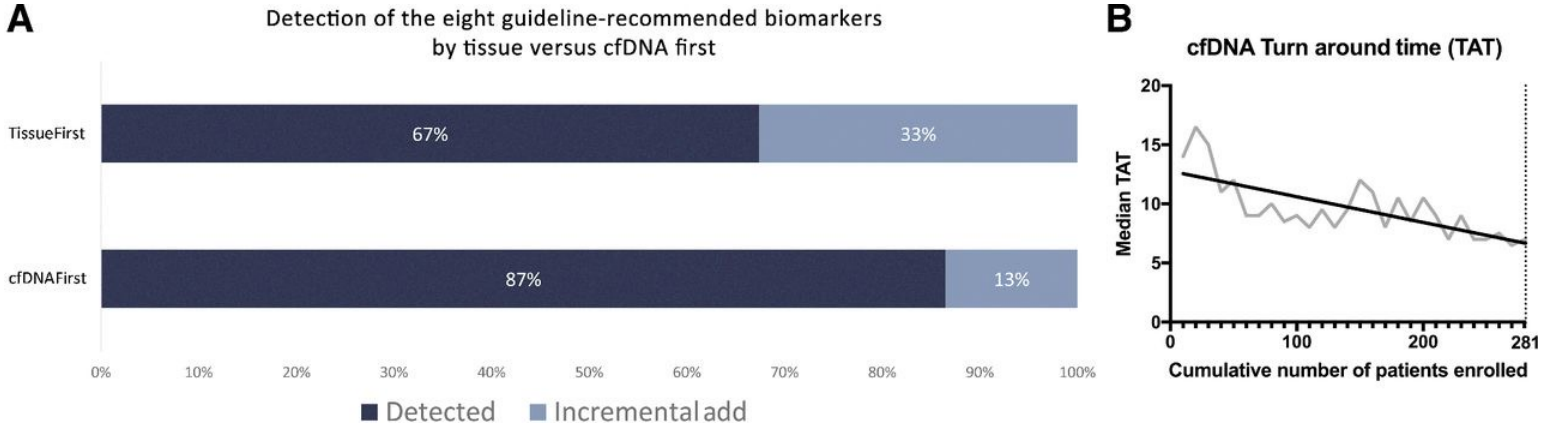
Table 1. Comparison of different ctDNA testing methodologies.

	Technologies		
	Allele-specific PCR	Emulsion PCR	Capture-Based Targeted NGS
Advantages	Fast results and easy to understand FDA approved kits Low cost of reagents Less labourious	Fast results easy to understand High sensitivity and specificity Low cost of reagents Absolute quantification	High-throughput of multigenetic detection (CNV, exonic mutations, etc) High specificity and sensitivity
Disadvantages	Detection of a small number of alterations Lower sensitivity Qualitative and semi-quantitative tests, not for absolute quantification of the mutation	Detection of a small number of alterations Specialized instruments necessary	Consumables and reagents more expensive Most time-consuming Specialized instruments necessary
Limit of detection	0.1–1%	0.001–0.1%	0.01–2%
Examples	Therascreen(Qiagen); Cobas (Roche)	BEAMing (Sysmex Inostic); dPCR (Thermofisher)	Oncomine Ion Torrent (Thermo Fisher); FoundationOne (Foundation Medicine); Guardant360 (Guardant)
References	[17–20]	[21–25]	[26–28]

CNV: copy number variation; NGS: next-generation sequencing. BEAMing: Beads, Emulsion, Amplification, and Magnetics; ddPCR: digital polymerase chain reaction.

Torres S , Jantus et al; Expert Rev Mol Diagnostics 2020

NILE



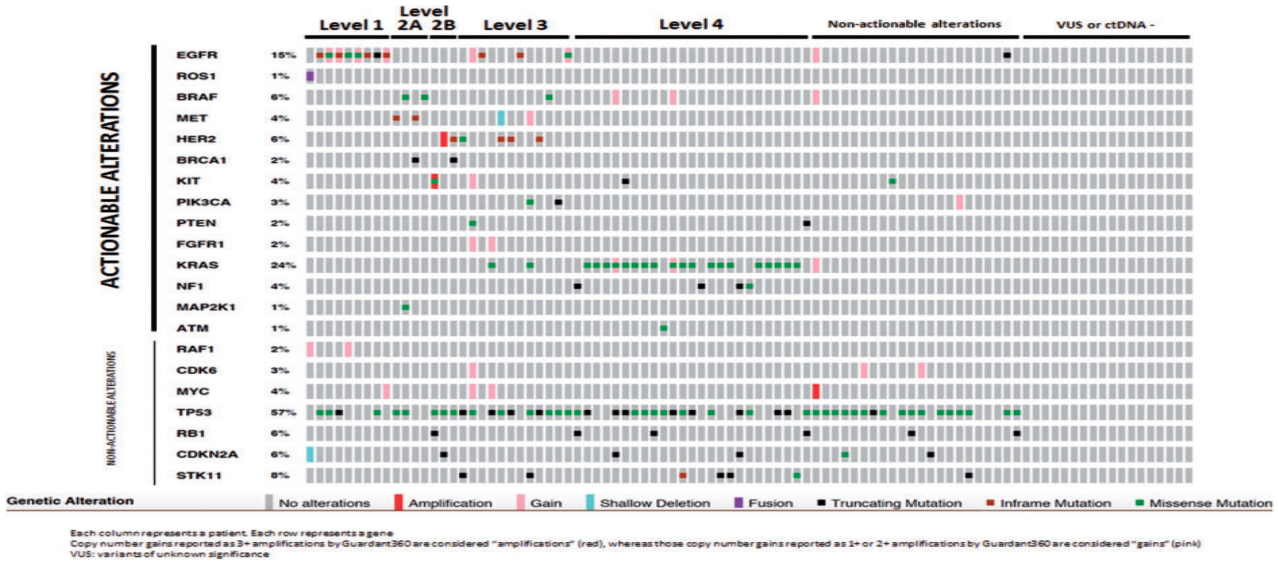
BFASt

Blood First Assay Screening Trial (BFAST) in Treatment-Naive Advanced or Metastatic NSCLC: Initial Results of the Phase 2 *ALK*-Positive Cohort

Zugazagoitia et al

FDA APPROVED

GUARDANT360 CDx



Leighl, N.B. et al . Clin. Cancer Res. 2019, 25, 4691–4700; Rolfo, C.et al. Crit. Rev. Oncol. Hematol. 2020, 151, 102978; Zugazagoitia et al, Ann Oncol 2019, 30 :290-296; Dziadziuszko R,. et al J Thorac Oncol. 2021,16: 2040–2050

a		Tissue SOC result		
		Mutation detected	No mutation detected	Total
Plasma BEAMing result	Mutation detected	113	8	121
	No mutation detected	18	97	115
	Total	131	105	236
		Overall percent agreement = 89.0%		
		Positive percent agreement = 86.3%		
		Negative percent agreement = 92.4%		

b		Tissue SOC + Tissue BEAming result		
		Mutation detected	No mutation detected	Total
Plasma BEAMing result	Mutation detected	115	6	121
	No mutation detected	13	102	115
	Total	128	108	236
		Overall percent agreement = 92.0%		
		Positive percent agreement = 89.8%		
		Negative percent agreement = 94.4%		

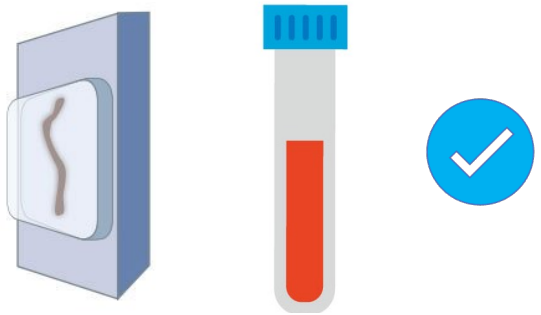
Fig. 1 Concordance between plasma and tissue results obtained by SOC (**a**) or SOC + BEAMing (**b**). SOC standard of care

BJC British Journal of Cancer www.nature.com/bjc

ARTICLE
Clinical Study

Prospective multicenter real-world *RAS* mutation comparison between OncoBEAM-based liquid biopsy and tissue analysis in metastatic colorectal cancer

Jesús García-Foncillas[1], Josep Tabernero[2,3], Elena Élez[2,3], Enrique Aranda[4], Manuel Benavides[5], Carlos Camps[6,7], Eloisa Jantus-Lewintre[8,9], Rafael López[10], Laura Muinelo-Romay[10], Clara Montagut[11], Antonio Antón[12], Guillermo López[13], Eduardo Díaz-Rubio[14], Federico Rojo[15] and Ana Vivancos[16]



Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review

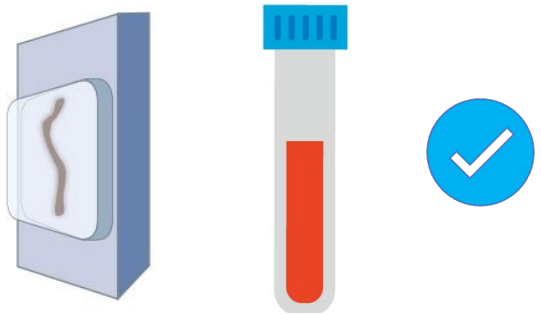
J. García-Foncillas[1*], E. Alba[2], E. Aranda[3], E. Díaz-Rubio[4], R. López-López[5], J. Tabernero[6] & A. Vivancos[7]

Garcia-Foncillas et al, British J Cancer, 2017.
García-Foncillas et al, Ann Oncol 2017

NGS en BIOPSIA LÍQUIDA: concordancia con tejido, utilidad clínica

Cell-free DNA NGS			
	Tissue Reference		
G360	**Positive**	**WT**	**Total**
Positive	159	38	197
Not Det.	28	8.685	8.713
TOTAL	187	8.723	8.910

- **Sensitivity:** 85%
- **Specificity:** 99,6%
- **Accuracy:** 99,3%



Analytical and clinical validation of a digital sequencing panel for quantitative, highly accurate evaluation of cell-free circulating tumor DNA.
Lanman RB, Mortimer SA, Zill OA, et al

- >700 patients with positive and negative concordance **>99%** for all 4 target genomic alterations (ALK, EGFR, ROS1 y BRAF V600E).

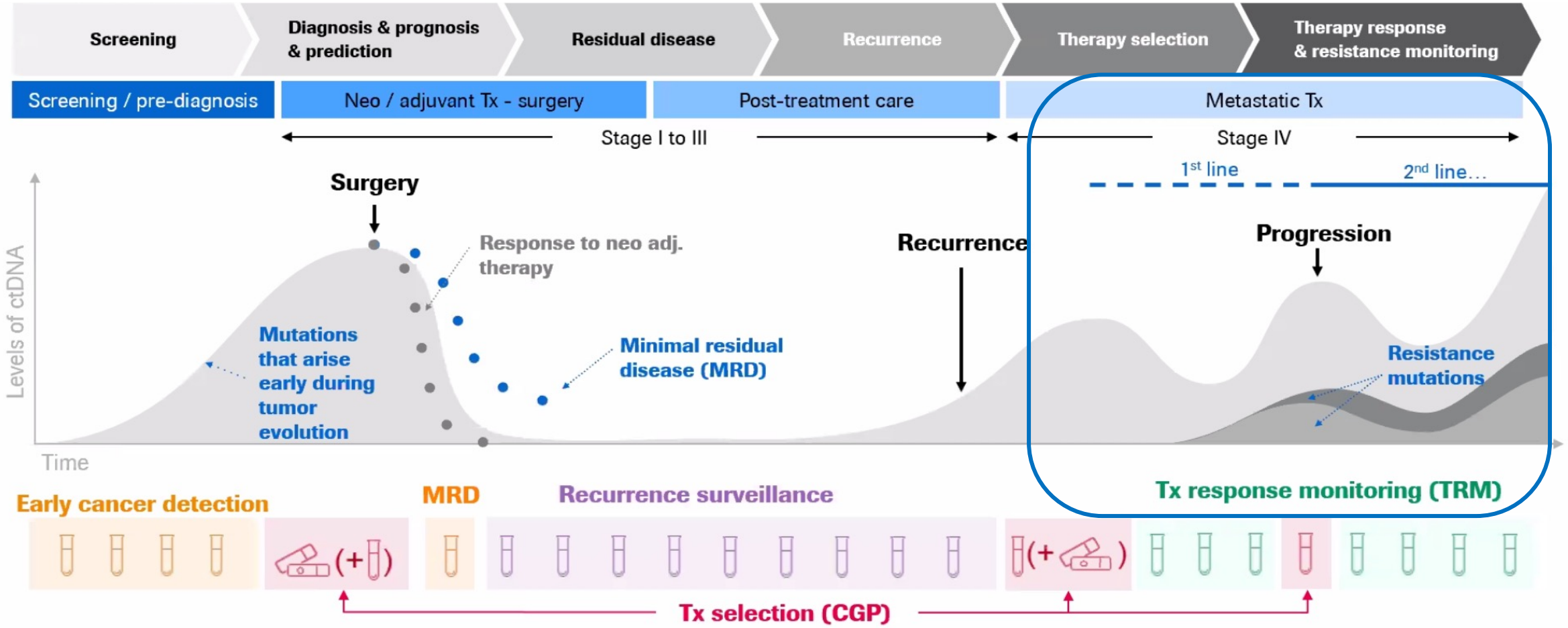
Clinical utility of plasma-based digital next-generation sequencing in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping
Zugazagoitia J, Jantus-Lewintre, et al.

Lanman RB, et al. PLoS One. 2015;16:10.

Zugazagoitia J, et al. Ann Oncol. 2019; 30(2):290-296

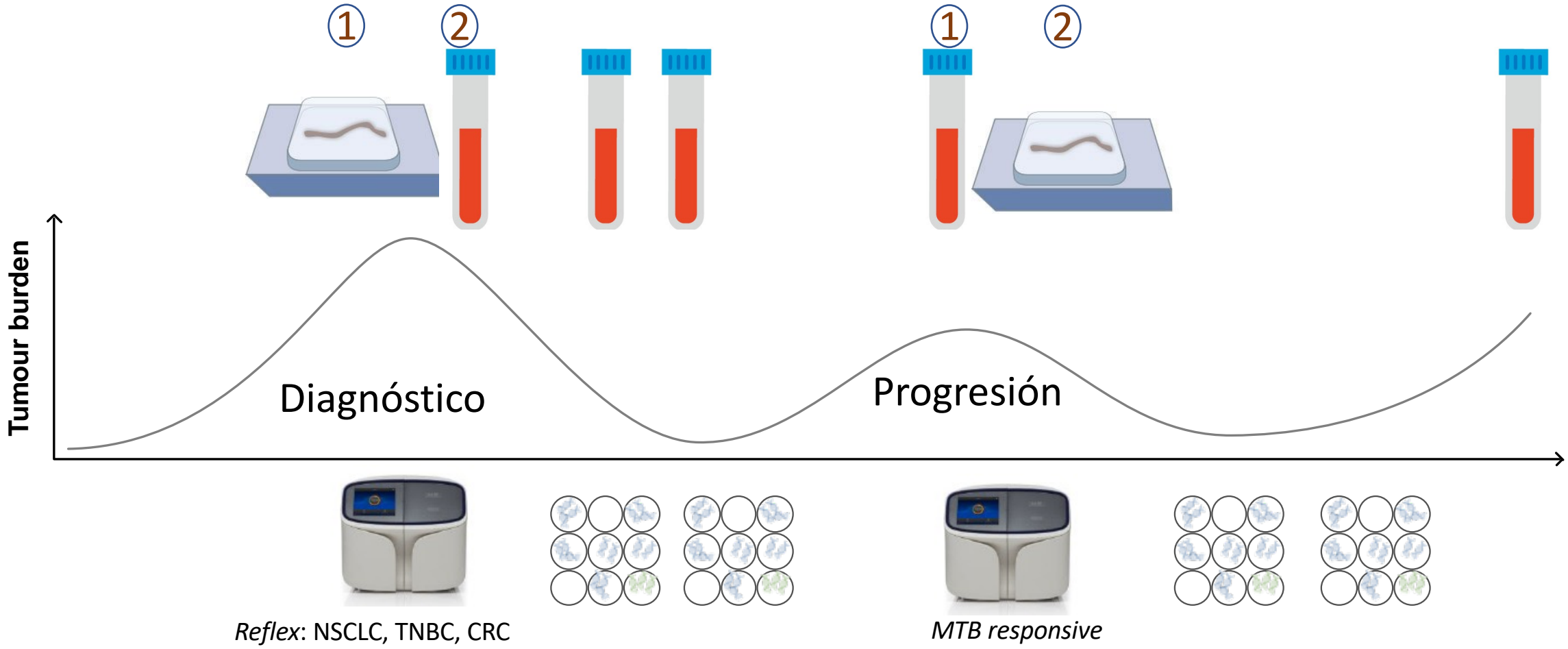
4 Aplicaciones clínicas

Biopsia Líquida-> ¿en qué momento?

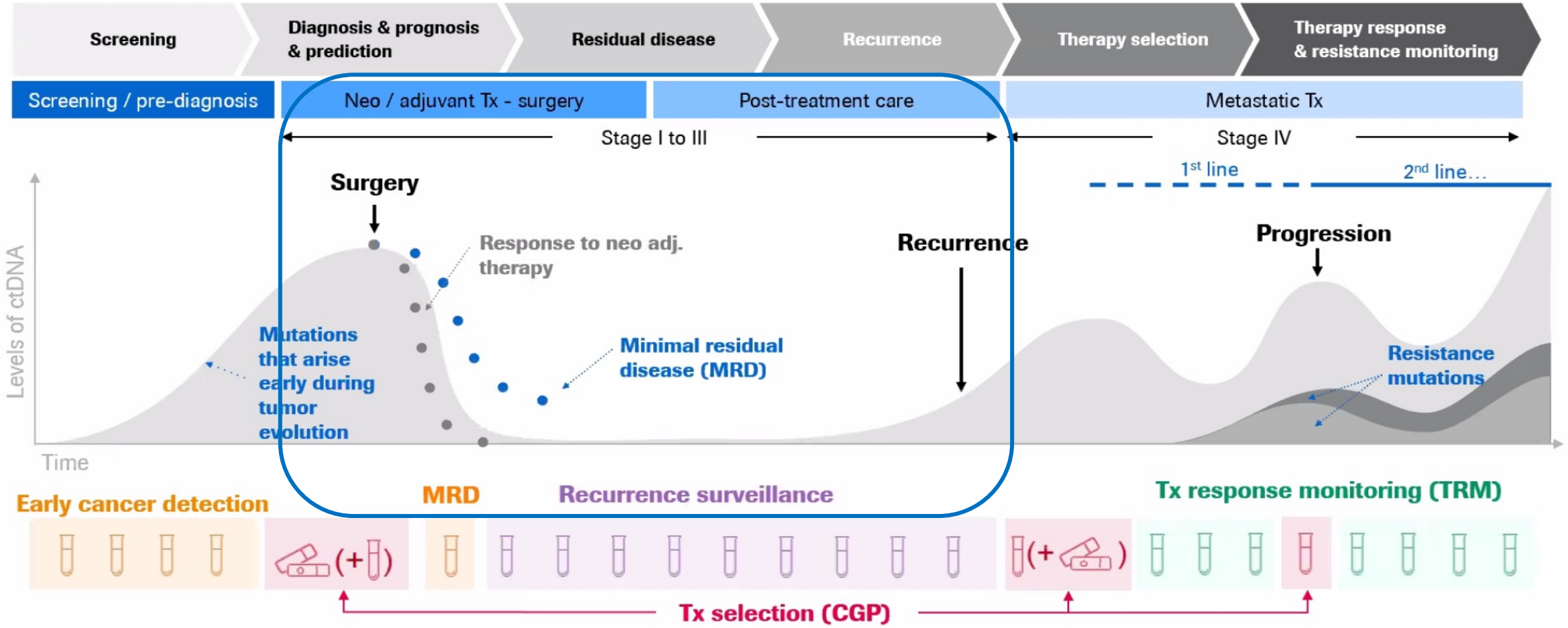


CGP: comprehensive genomic profiling; ctDNA: circulating tumour DNA; MRD: minimal residual disease; TRM: treatment response monitoring; Tx: treatment.
Adapted from Wan, J.C.M., et al. (2017) *Nat Rev Cancer* 17:223-38.

NUESTRA ESTRATEGIA



Biopsia Líquida-> ¿en qué momento?

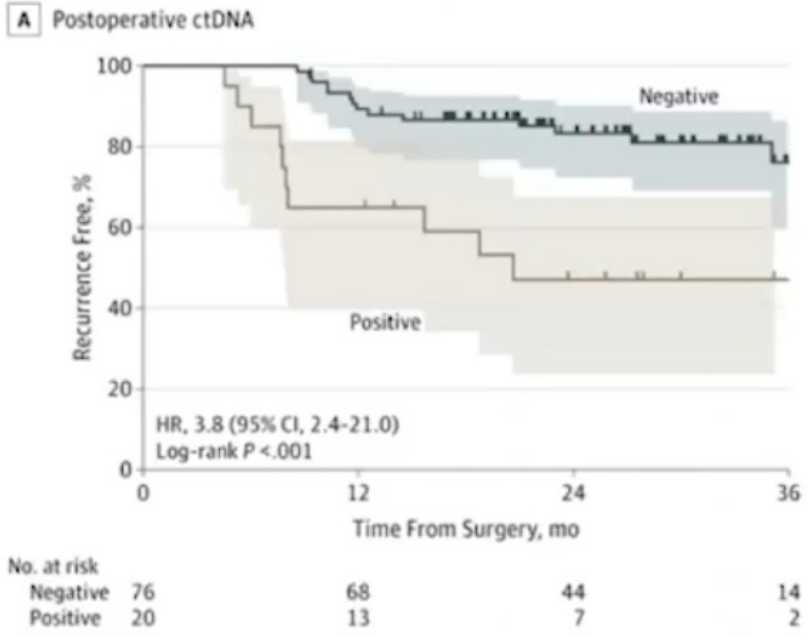


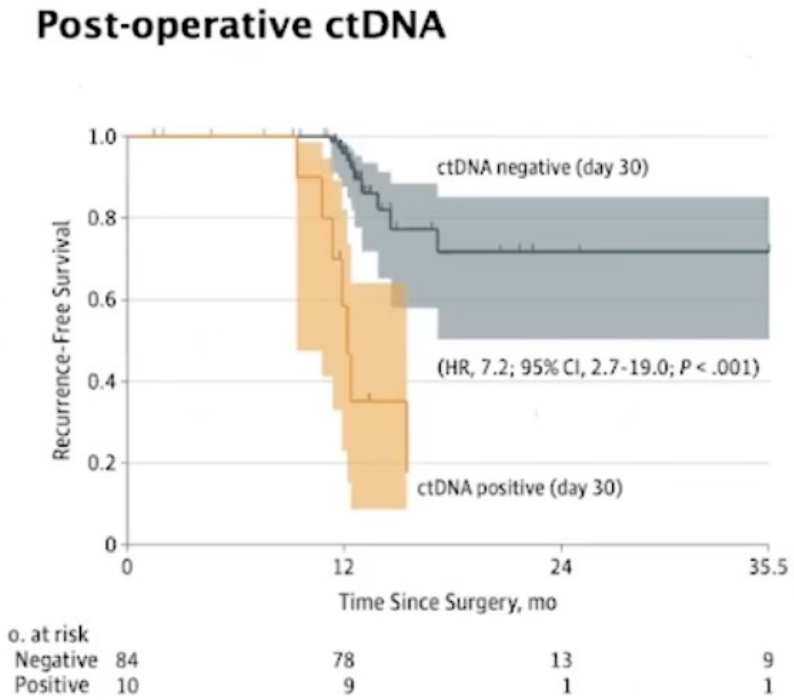
CGP: comprehensive genomic profiling; ctDNA: circulating tumour DNA; MRD: minimal residual disease; TRM: treatment response monitoring; Tx: treatment.
Adapted from Wan, J.C.M., et al. (2017) *Nat Rev Cancer* 17:223-38.

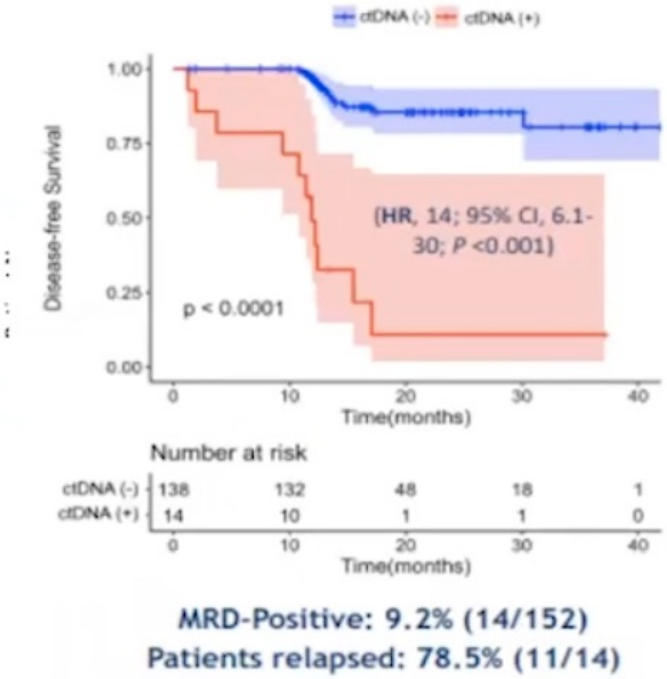
BL-> Aplicaciones en CRC -> post cirugía

Detección de **MRD** -> riesgo de recaída

RFS







Tie et al, JAMA Oncol 2019

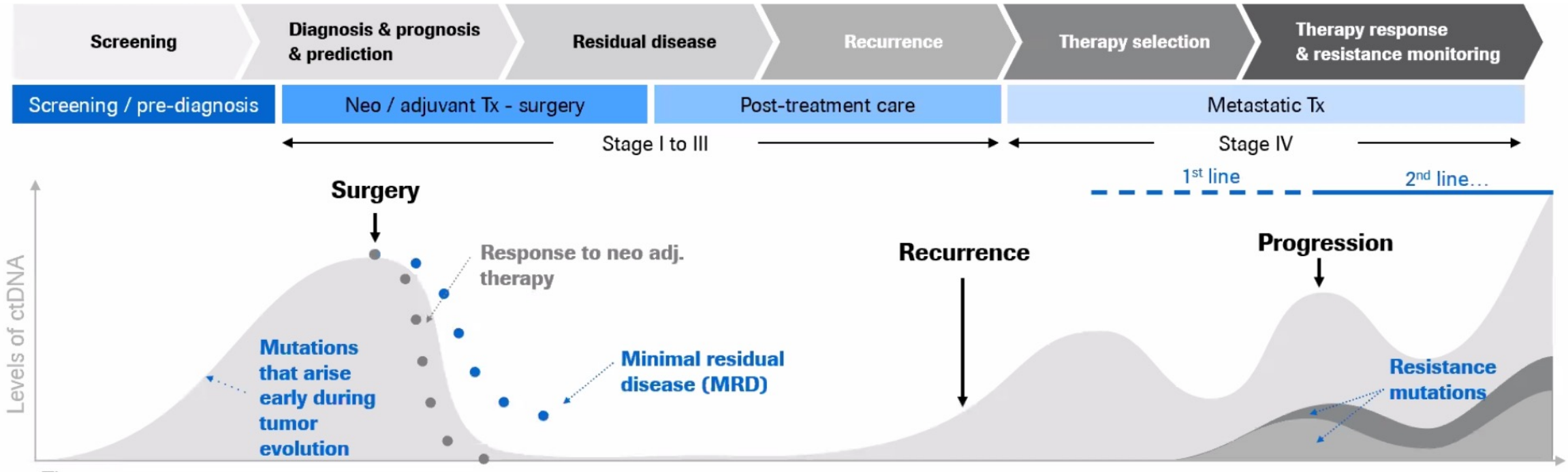
Tumor informed

Reinert et al, JAMA Oncol 2019

Tumor informed

Tarazona et al, ASCO 2019

Tumor informed

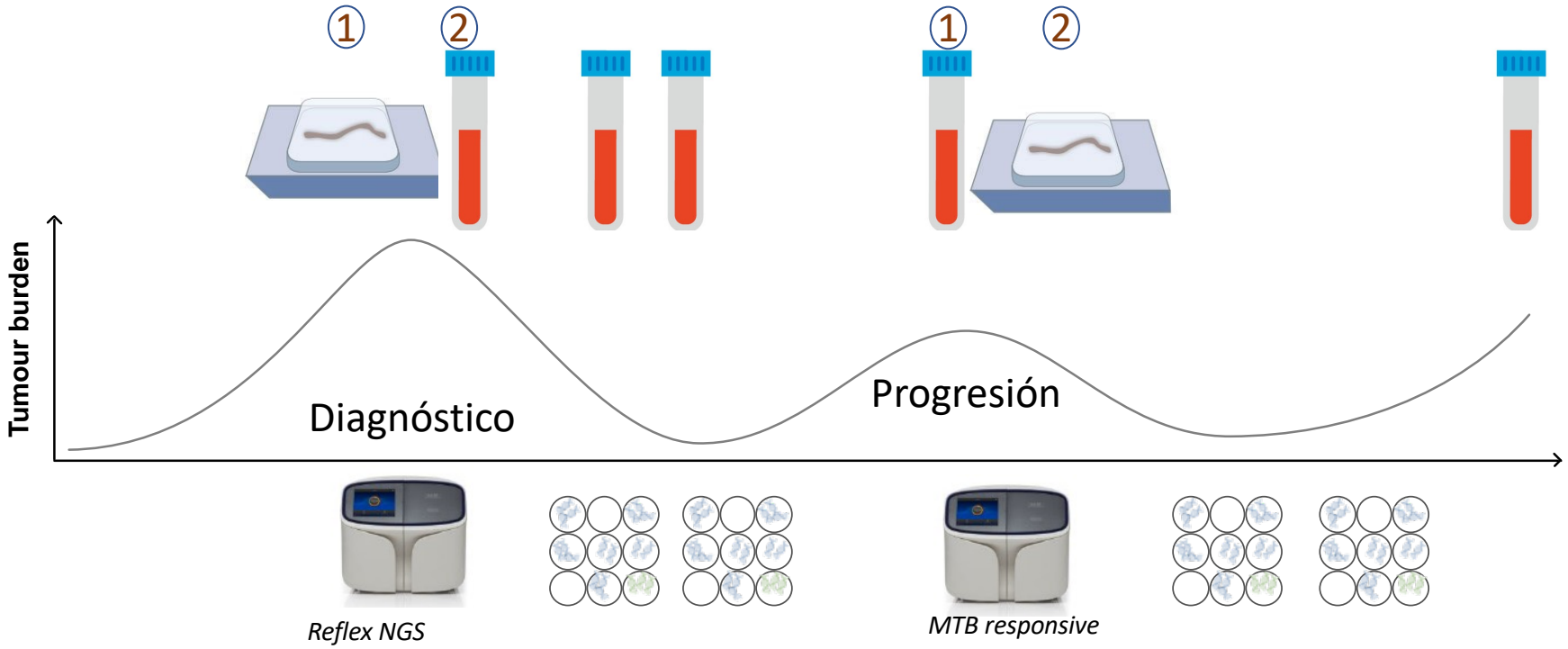


"ONGOING"->ENORME
IMPACTO EN EL TRATAMIENTO

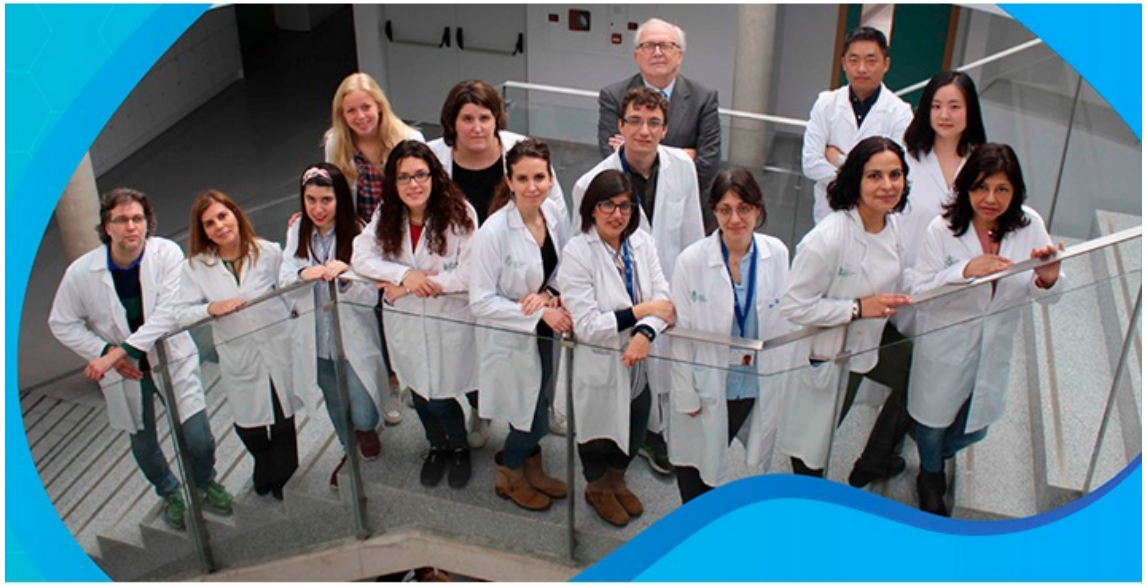
EN **PRACTICA CLINICA**

La BIOPSIA LÍQUIDA cambiará la forma en que el cáncer es DETECTADO, MONITORIZADO Y TRATADO en forma personalizada

Solo cuestión de tiempo



https://oncologiamolecularvalencia.com/



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Centro de Investigación Biomédica en Red
Cáncer

UNIVERSIDAD POLITECNICA DE VALENCIA

SAVE THE DATE

20 – 22 October, 2022

Miami, Florida

ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

4TH ANNUAL CONGRESS

Liquid Biopsy

20 – 22 October 2022 | Miami, Florida

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