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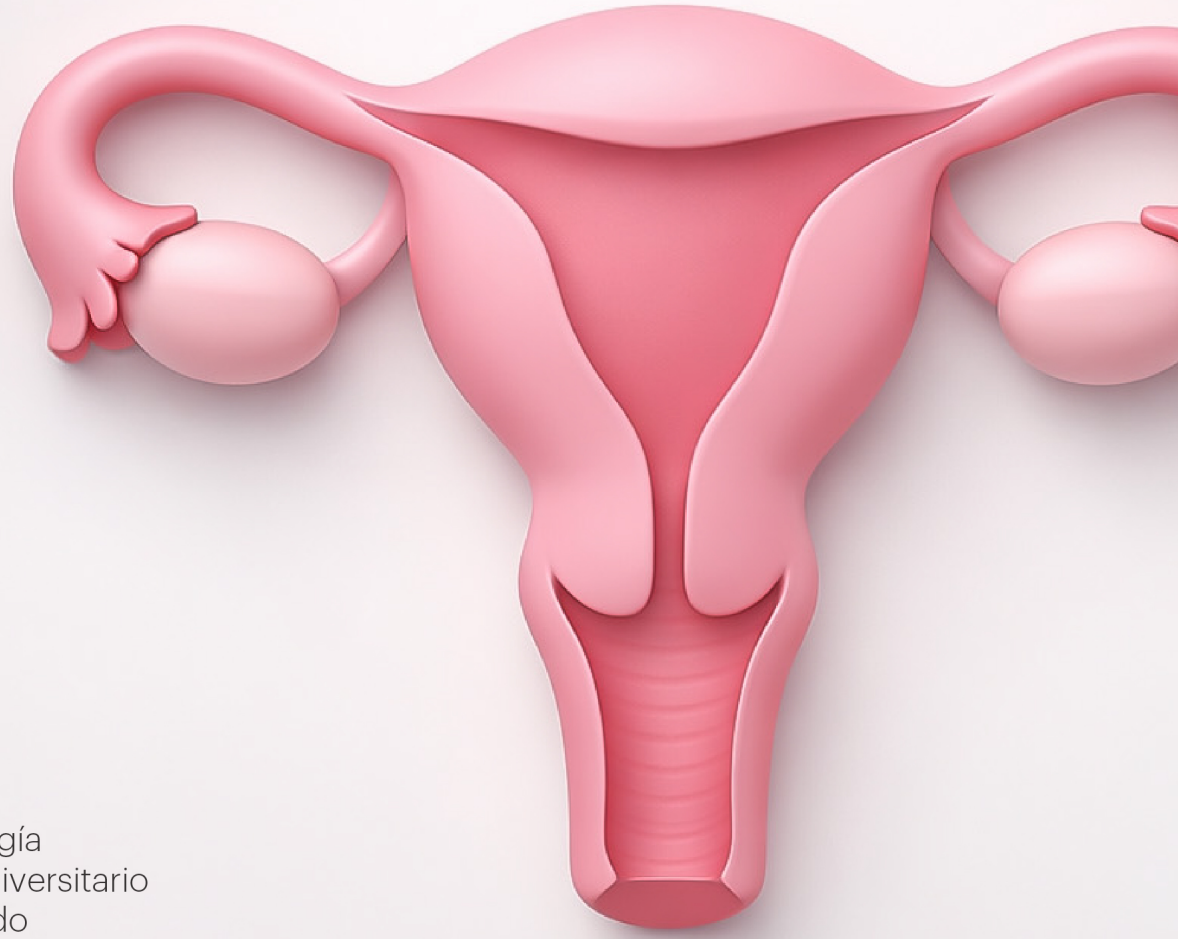
4ª Jornada de Actualización en Cáncer Ginecológico

Bilbao · 20 – 21 de mayo 2026



Utilidad del ctDNA en cáncer de ovario

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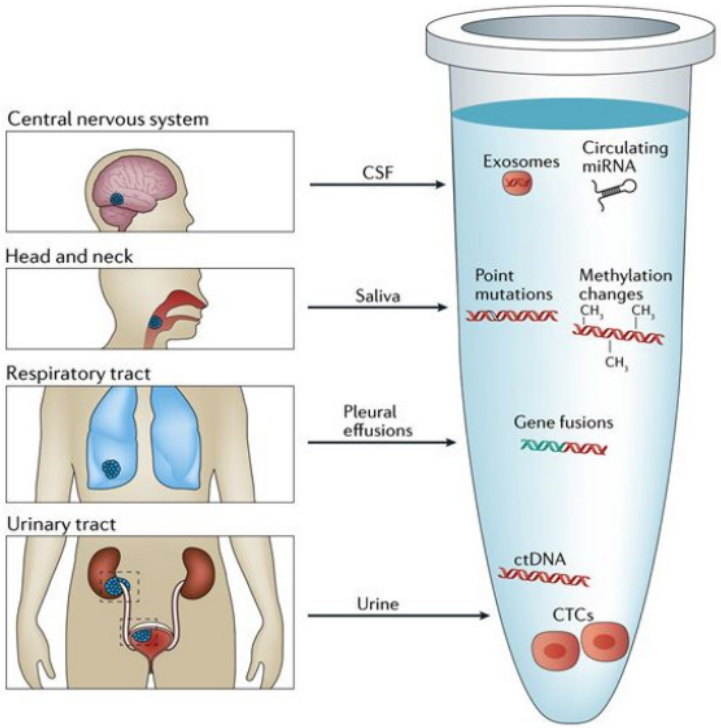
Disclosure Information

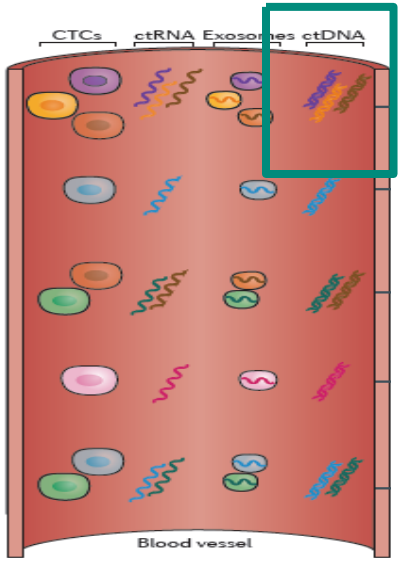
- Consultant or Advisory Role: AstraZeneca, GSK, Gemmab, MSD, BMS, Pierre Fabre, Inmunocore , Abbvie.
- Speaking: Pharmamar, AstraZeneca, MSD, GSK, BMS, Pierre Fabre,Abbvie.
- Attending scientific meetings: AstraZeneca, MSD, GSK, Pierre Fabre.

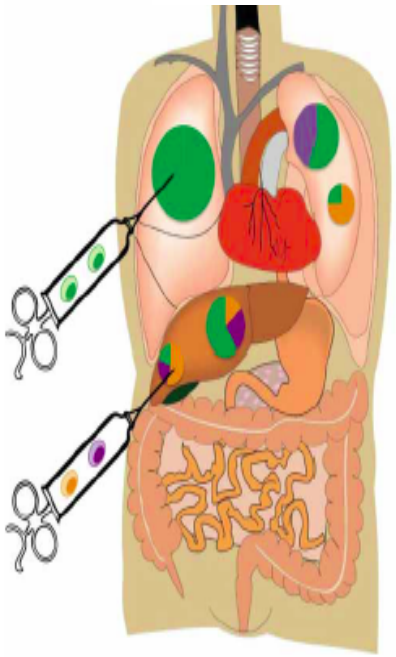
Liquid biopsy, source of tumor information

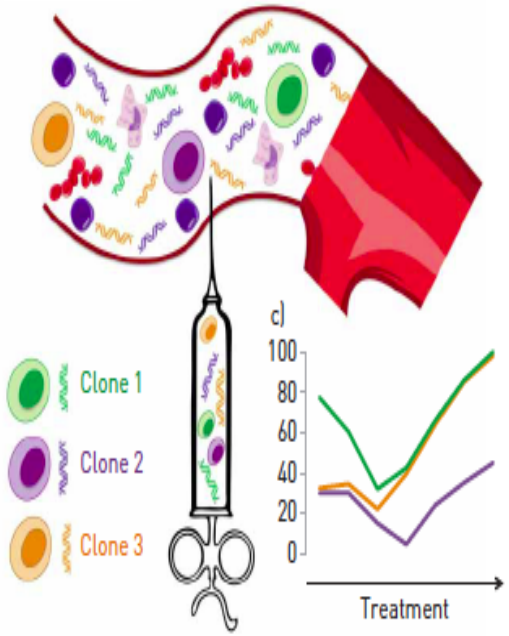
Any biological fluid contains genetic material, cell-free DNA



Peripheral blood remains the most studied liquid biopsy ctDNA assesses spatial and temporal tumor heterogeneity

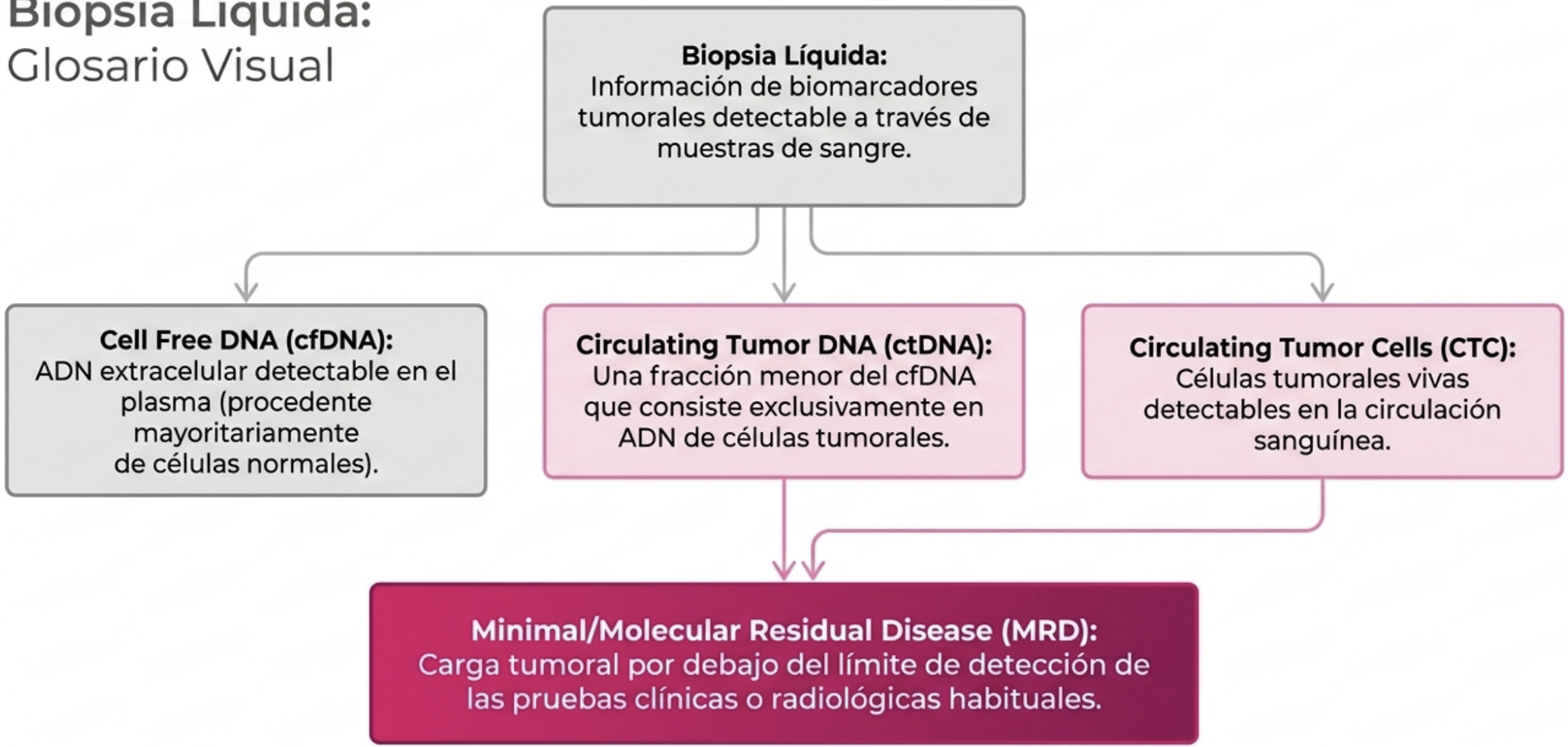






Saini et al, Diagnsotics 2018 ; Guibert et al; Eur Resp Rev 2020; Siravegna et al Nature Rev Clin Oncol 2017; Cargnin et al, JTO 2017

El Ecosistema de la Biopsia Líquida: Glosario Visual



Liquid biopsy in Ovarian Cancer:ctDNA

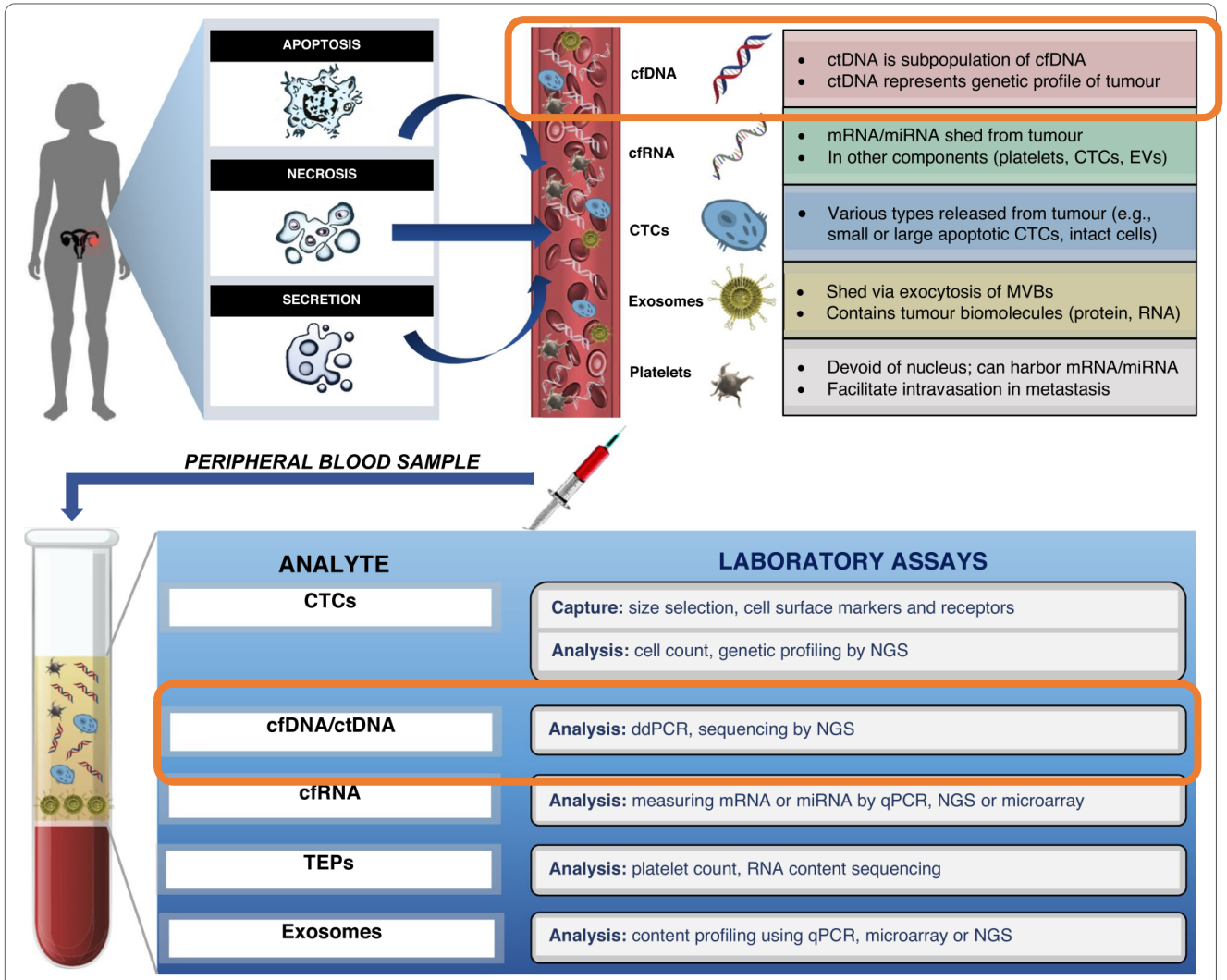


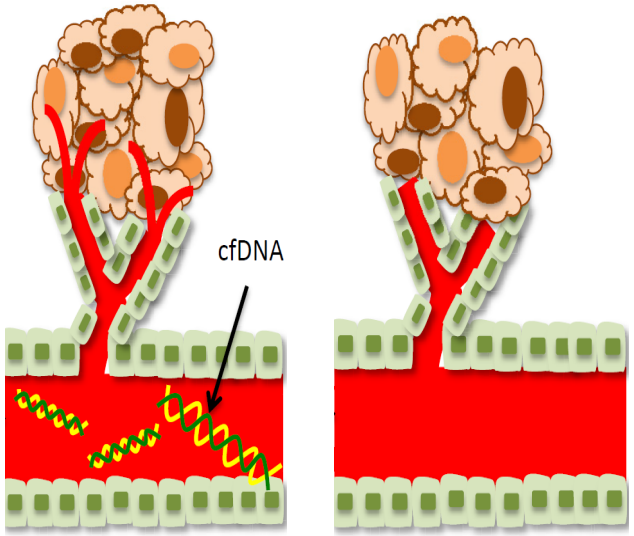
Fig. 2 Overview of the liquid biopsy process, from hypothesized mechanisms of tumour release of liquid biopsy components, to laboratory analysis techniques. Tumour biomarkers are first released and enter the circulation via one of three main mechanisms: apoptosis, necrosis, or secretion. Liquid biopsy involves the collection and analysis of five distinctive tumour components from peripheral blood samples: cell-free nucleic acids (cfDNA/ctDNA, cfRNA), CTCs, exosomes and tumour educated platelets. Tumour components in peripheral blood samples are then captured and analyzed using their corresponding laboratory assays. cfDNA: circulating free DNA, ctDNA: circulating tumour DNA, cfRNA: cell-free RNA, CTCs: circulating tumour cells, TEPs: tumour educated platelets, NGS: next generation sequencing, qPCR: quantitative polymerase chain reaction

Zhu et al. Molecular Cancer (2022) 21:114

- Las células tumorales liberan/desprenden ctDNA al torrente sanguíneo mediante apoptosis, necrosis y secreción.
- El ctDNA puede diferenciarse por su menor longitud en comparación con el ADN libre circulante (cfDNA), que procede de células normales.
- La fracción tumoral de ctDNA mide el porcentaje de ctDNA en relación con el ADN total presente en sangre (ctDNA + cfDNA). El ctDNA está presente en pequeñas cantidades (0,1–10% del ADN circulante total).
- La detección de ctDNA requiere métodos de detección altamente sensibles, generalmente secuenciación de nueva generación (NGS).
- No todos los tipos tumorales liberan suficiente ctDNA como para ser detectado. En tumores con alta liberación (“high shedding”), el ctDNA puede servir como herramienta para:
  - diagnóstico del cáncer,
  - monitorización,
  - pronóstico,
  - y detección de mutaciones

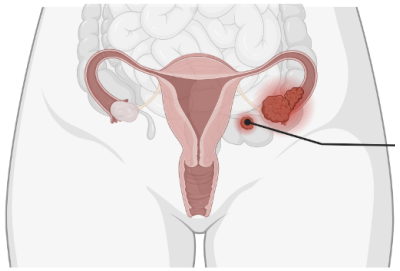
Factors that may influence sensitivity and specificity of ctDNA detection

Shedding vs. Non-shedding



- ctDNA accounts for 0.4% (median) of cfDNA
- cfDNA exists as very short fragments of DNA (150-200 base pairs)
- There is a correlation between Disease burden and amount of tumour derived DNA (ctDNA) in the blood
- The higher disease stage, the greater the chance to detect ctDNA

Stage

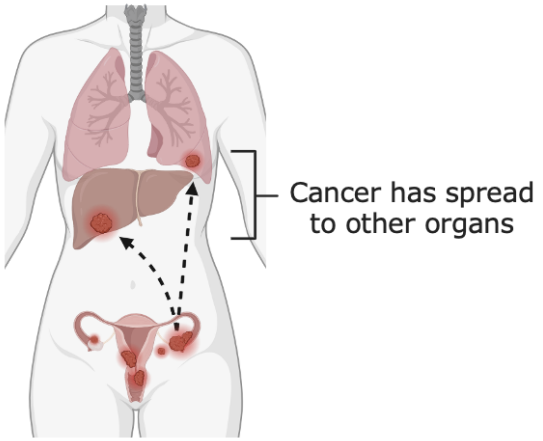


Requires more sensitivity than tissue analysis

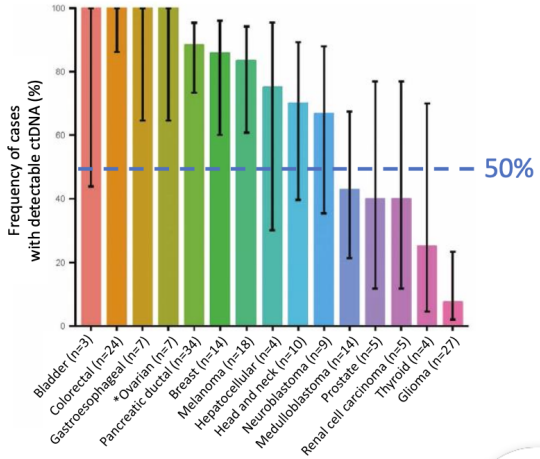
◆ Circulating tumor derived (ct)DNA is ≤0.5% (can vary) of total cell free (cf)DNA versus ≥10% in tissue

◆ Short half-life (~2 hours)

Inter-metastatic heterogeneity



Tumor type

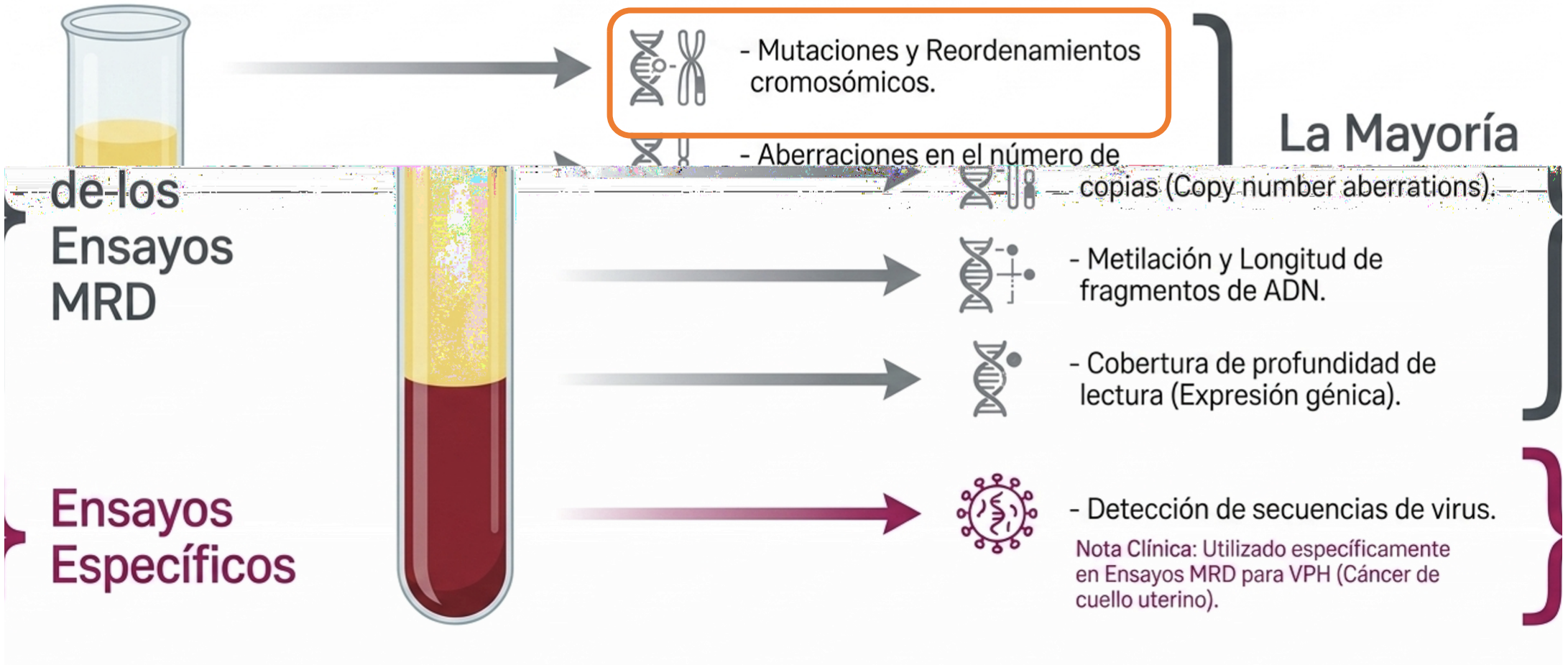


Biological and pathological factors affecting ctDNA levels:

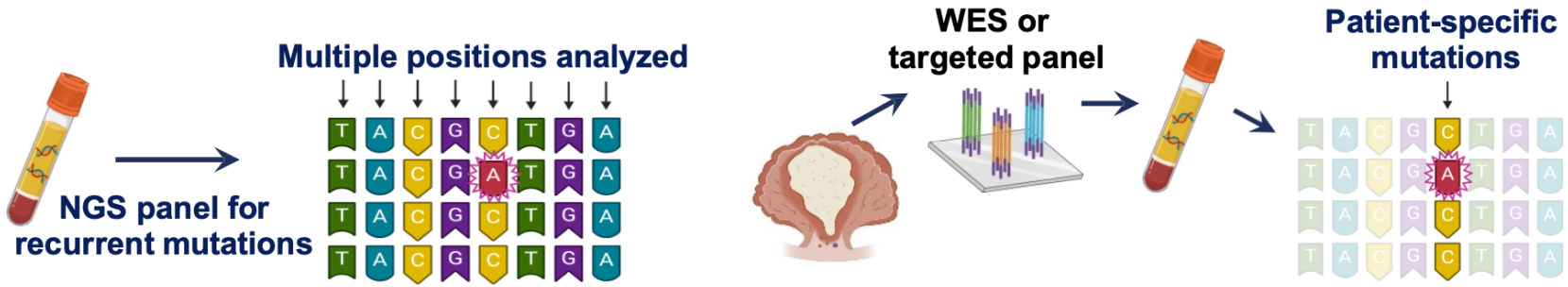
- Tumor burden
- Anatomical site of the tumor Histology
- Proliferation index
- Necrosis
- Type of biological fluid

Sacher AG, et al. J Thorac Oncol 2017; *Jamal-Hanjani et al. CCR 2015;* Bettegowda et al, Sci Trans Med 2014. Adapted from Bettegowda, et al. 2014 & Dang and Park, 2022.

Arquitectura del ctDNA: ¿Qué Estamos Midiendo Exactamente?



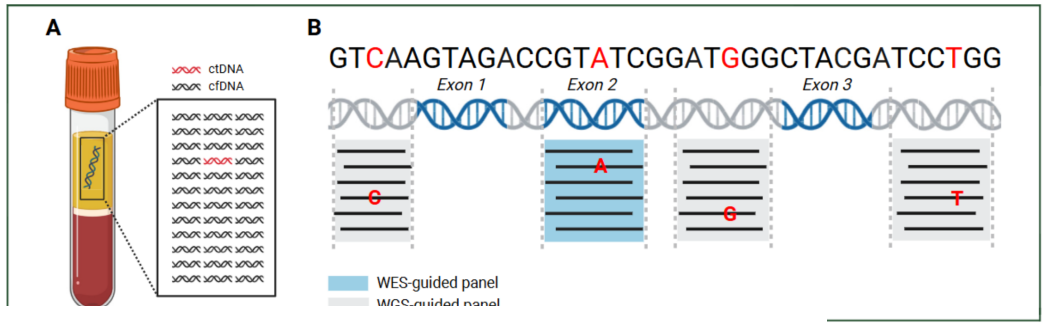
ctDNA Analysis: Tumor-Naïve vs Tumor-Informed Approach



	Tumor-Naïve	Tumor-Informed
Method	Detect mutations de novo from plasma (same panel for all patients)	Identify mutations in tumor tissue ➔ track mutations in plasma (personalized panel)
Key Advantage	Does not require tumor tissue	**Higher Sensitivity**
Key Disadvantage	Lower sensitivity	Requires tumor tissue
Applications	Non-invasive genotyping (metastatic) Detect emerging resistant mutations Cancer screening	**Minimal residual disease detection** Surveillance – monitor recurrence Response monitoring

Técnicas de detección de ctDNA

Tumor Informed (Bespoke) ctDNA Assays: WES vs. WGS



	Tumor-naïve	Tumor-informed (WES)	Tumor-informed (WGS)
Variant source	Targeted NGS panel of cancer-associated genes	Top somatic variants from whole exome sequencing	WGS-derived patient-specific variants
Variants tracked	~10-100 genes	16 variants	Up to 1,800 variants
Limit of detection (tumor fraction)	0.1-1%	0.01-0.02%	< 0.01%
Tissue requirement	None	Tumor + matched normal	Tumor + matched normal

Utilidad de la biopsia líquida en cáncer de ovario

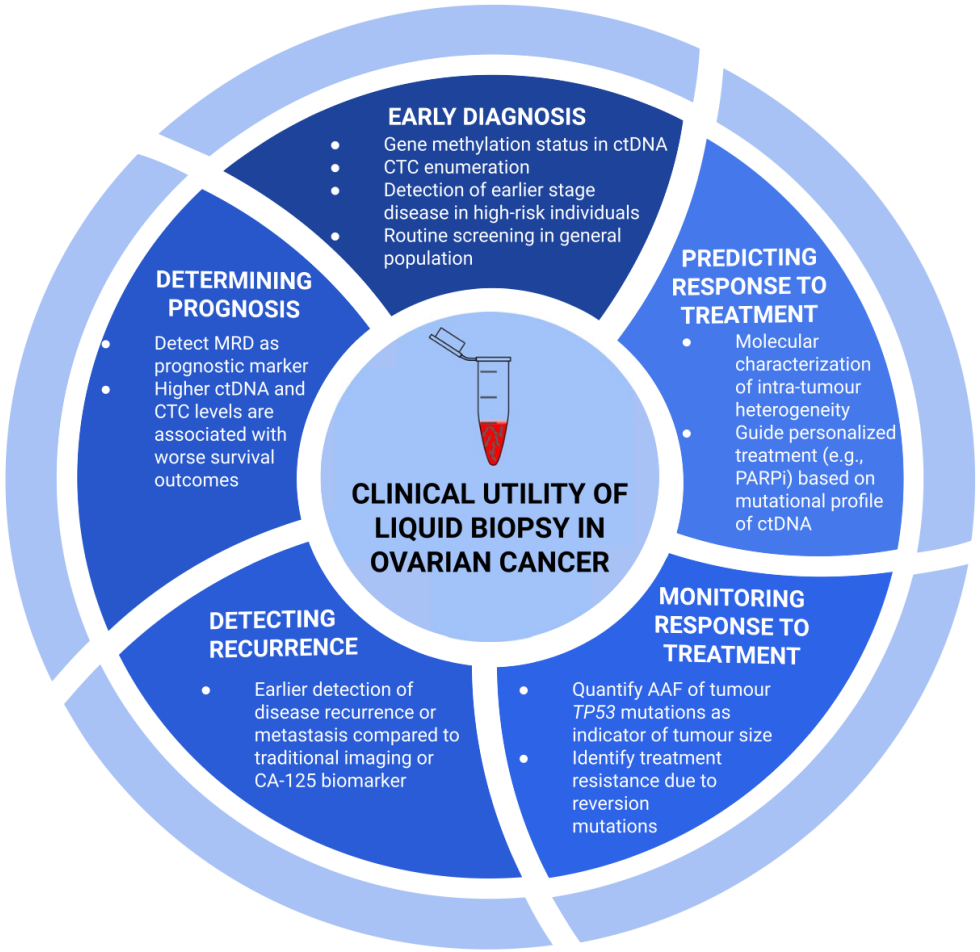


Fig. 3 Overview of the five major clinical applications of liquid biopsy in ovarian cancer. Earlier in the disease course, sample analysis for ovarian cancer biomarkers can allow earlier diagnosis. Following primary debulking surgery, liquid biopsy can detect minimal residual disease as a prognostic indicator and allow for earlier detection of recurrent disease. During treatment, liquid biopsy may enhance longitudinal monitoring with its non-invasive approach that enables serial sampling. Additionally, liquid biopsy offers the advantage of capturing the entire tumour genome, which can help identify novel genetic markers for targeted therapies and detect treatment resistance. ctDNA: circulating tumour DNA, MRD: minimal residual disease; AAF: alternative allele frequency

ctDNA en cáncer de ovario: aplicaciones clínicas,ventajas y limitaciones

Liquid Biopsy Component	Circulating Tumour Cells (CTCs)	Circulating Tumour DNA (ctDNA)	Cell-Free RNA (cfRNA)	Tumour Educated Platelets (TEPs)	Exosomes
Main Clinical Application	Diagnosis and prognosis	Diagnosis, prognosis, predicting response to treatment, monitoring response to treatment and detection of recurrence	Diagnosis and prognosis	Diagnosis	Diagnosis, prognosis, and prediction of response to treatment
Advantages	• Earlier detection of recurrence or metastasis • Predicting recurrence • Accessible source of tumour RNA/DNA/proteins • Detecting CTCs originating from both primary tumour and metastatic sites • Non-invasive	• Higher available concentrations in bloodstream • Availability of laboratory techniques for analysis (e.g., NGS, ddPCR) • Higher stability compared to other liquid biopsy components • Capturing tumour heterogeneity • Available in a variety of body fluids • Non-invasive	• Providing information on tumour's genetic expression profile • Monitoring tumour expression changes over time • Non-invasive	• Potential use for earlier diagnosis • Routinely available clinical tests for quantification (e.g., CBC) • Non-invasive	• Genomic contents protected from degradation • Accessible and variable source of tumour components • Available in a variety of body fluids • More abundant • Non-invasive
Limitations	• Low plasma counts • Difficulty differentiating CTCs from other cells in bloodstream	• Low concentration (ctDNA:cfDNA ratio) in early stages make detection difficult • Difficulty differentiating ctDNA from cfDNA	• More difficulty with isolation compared to cfDNA • Unstable molecule • No reliable methods for reproducible and practical application in clinical setting	• Limited research • Lack of reliable methods for reproducible and practical application in clinical setting	• Lack of standardized isolation methods • Lack of reliable methods for clinical application
Future Directions	• Improving methods for detection (e.g., low EpCAM expression settings) • Higher quality studies with larger sample sizes for determining prognostic applications	• Improving methods for enrichment of ctDNA • Optimizing sensitivity for analysis techniques for detection at low allele frequencies • Further studies with larger sample sizes	• Optimal combination of RNA candidates using machine learning methods • Improving methods for stabilizing cfRNA and extraction of cfRNA from plasma • Further studies with larger sample sizes	• More evidence on the diagnostic sensitivity and specificity in different cancers • More standardized methods for analyzing platelet content • Further studies with larger sample sizes	• More evidence on the diagnostic sensitivity and specificity in different cancers • More standardized methods for extraction of exosomes • Further studies with larger sample sizes

Fig. 4 Comparison of five liquid biopsy components and the main advantages, disadvantages, and future directions of their clinical application in ovarian cancer management

- ✓ **Non-invasive**
- ✓ **Reflects tumour heterogeneity**
- ✓ **Real-time monitoring is feasible**

- ✗ Lack of standardization
- ✗ Need for sensitive techniques

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

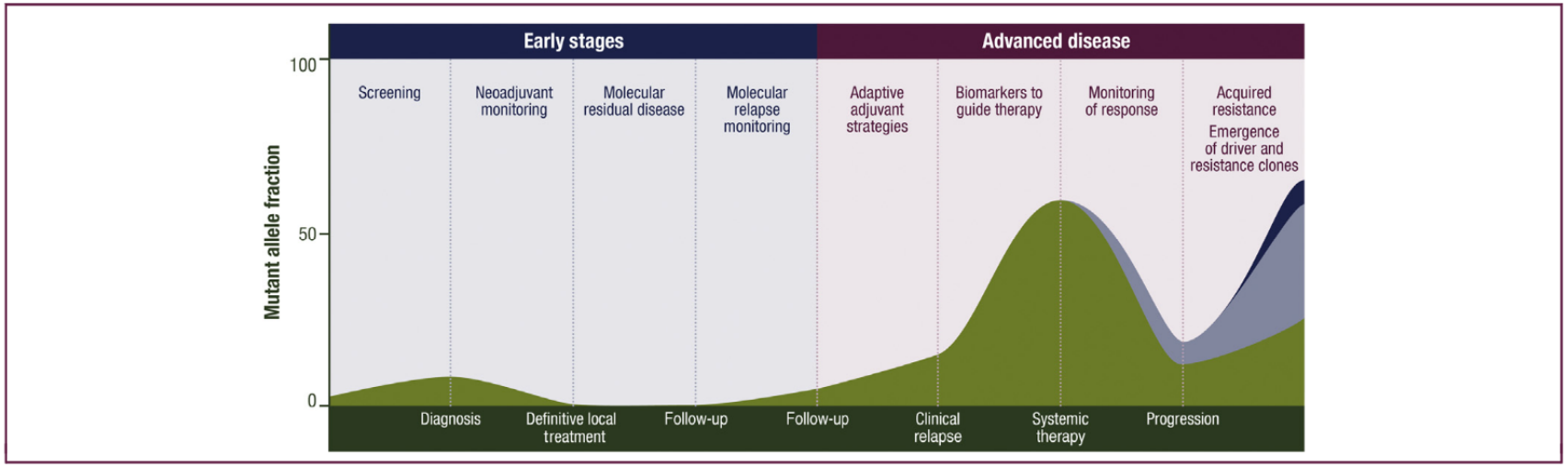
ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

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

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

https://doi.org/10.1016/j.annonc.2022.05.520



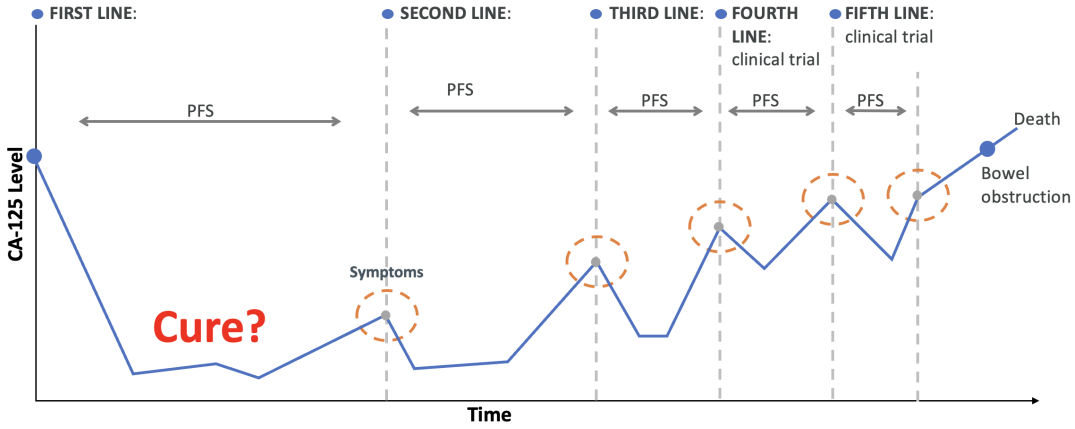
print & web 4C/FPO

Figure 1. Clinical applications of ctDNA assays for patients with cancer and expected DNA levels in different phases of the disease.
ctDNA, circulating tumour DNA.

Advanced cancer ctDNA dynamics for cancer monitoring

In ovarian cancer, pretreatment ctDNA levels and the extent of ctDNA decrease after chemotherapy initiation were significantly associated with time to progression, and were more informative than CA 125 levels

¿Puede ser útil el ctDNA en Cáncer de ovario?



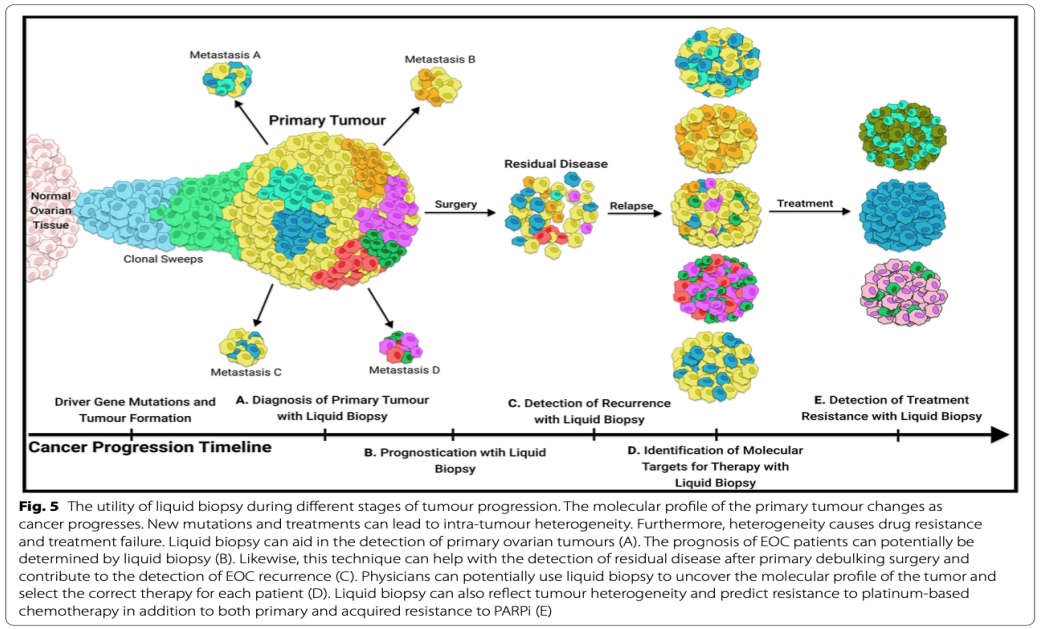
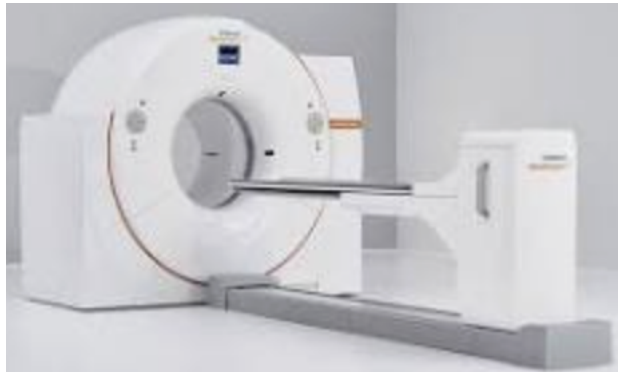


Fig. 5 The utility of liquid biopsy during different stages of tumour progression. The molecular profile of the primary tumour changes as cancer progresses. New mutations and treatments can lead to intra-tumour heterogeneity. Furthermore, heterogeneity causes drug resistance and treatment failure. Liquid biopsy can aid in the detection of primary ovarian tumours (A). The prognosis of EOC patients can potentially be determined by liquid biopsy (B). Likewise, this technique can help with the detection of residual disease after primary debulking surgery and contribute to the detection of EOC recurrence (C). Physicians can potentially use liquid biopsy to uncover the molecular profile of the tumor and select the correct therapy for each patient (D). Liquid biopsy can also reflect tumour heterogeneity and predict resistance to platinum-based chemotherapy in addition to both primary and acquired resistance to PARPi (E)

¿Qué herramientas tenemos en práctica clínica para diagnostico precoz, monitorizar respuesta a tratamiento y detectar recaídas?

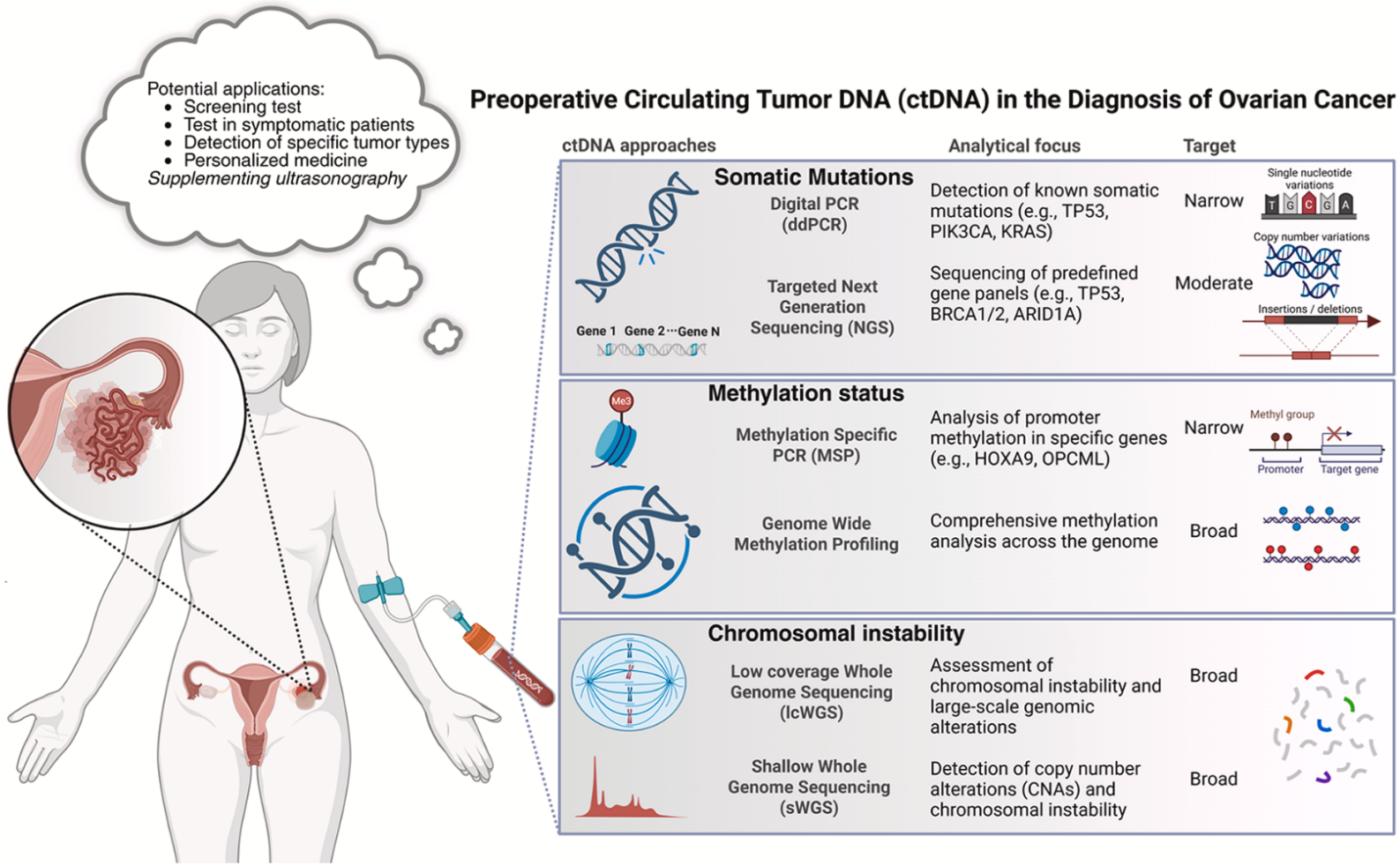
	CA-125
Naturaleza del Biomarcador	Proteína genérica del epitelio.
Sensibilidad a la Recurrencia Temprana	Baja (A menudo se eleva solo en progresión macroscópica).
Rendimiento bajo PARPi	Pobre (Alta tasa de falsos negativos).
Capacidad Predictiva	Reactiva.

Las herramientas actuales para disgnóstico inicial, detectar recaídas, monitorizar la respuesta al tratamiento, como las pruebas de imagen y el CA-125, a menudo son inconsistentes con los hallazgos clínicos y los resultados de las pacientes.



Adated Ledermann. Ann Oncol. 2013;24 (suppl 6): vi24. Tjokrowidjaja, A, jCO, 2024

Utilidad de ctDNA: diagnóstico precoz del cáncer de ovario

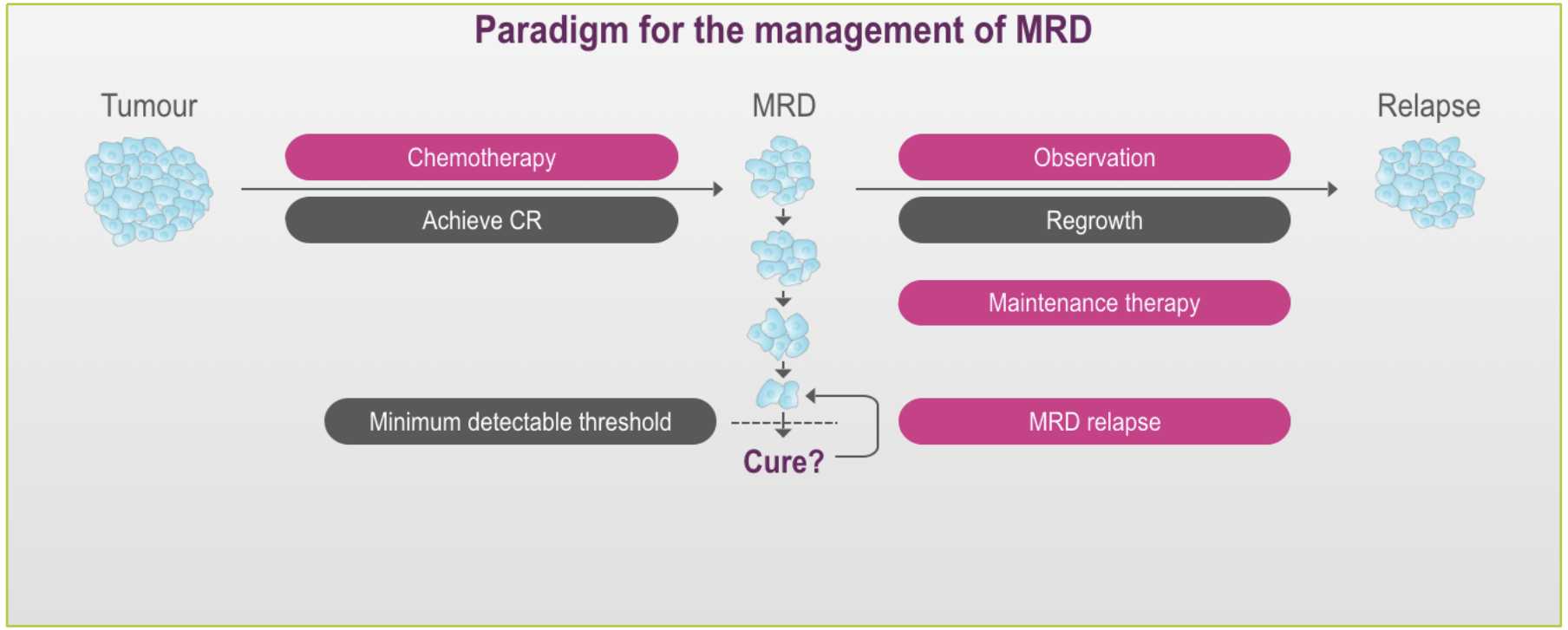


ctDNA is emerging as a highly promising diagnostic biomarker for ovarian cancer. Most studies have focused on the analysis of promoter methylation profiles of various tumor suppressor genes, identifying a strategy that has shown great potential, particularly for the early detection.However or the clinical implementation of liquid biopsy through ctDNA analysis, continued research is necessary to identify the most effective approach for a tumor as highly heterogeneous as ovarian cancer

Figure 3 Preoperative circulating tumor DNA in the diagnosis of ovarian cancer. Schematic overview of circulating tumor DNA-based approaches and their potential clinical applications. CAN, copy number alteration; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; lcWGS, low-coverage whole genome sequencing; MSP, methylation-specific polymerase chain reaction; NGS, next-generation sequencing; sWGS; shallow whole genome sequencing.

Importancia de la MRD en el Cáncer de ovario avanzado

Maintenance therapy with PARPis have brought forward a paradigm shift, altering the natural course of disease in ovarian cancer by extending PFS



Goals of maintenance therapy

1. Prolong benefit following surgery and chemotherapy
2. Improve survival (PFS and hopefully OS)
3. Manageable toxicity and no negative effects on QoL

CR, complete response; MRD, minimal residual disease
Luskin MR, et al. Nat Rev Cancer 2018;18:255–263. Domenica Lorusso.ESMO 2022

“The essential is invisible to the eyes”

El Principito. Antoine de Saint Exupery

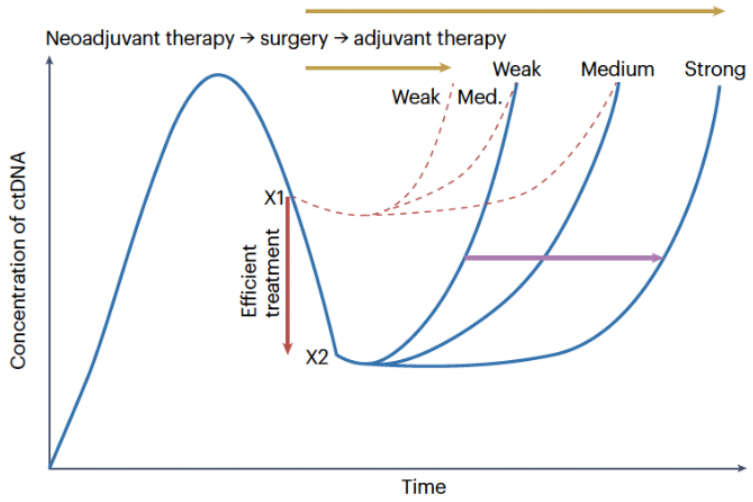
Utilidad de ctDNA: detectar recurrencias

Aplicaciones clínicas del ctDNA en la MRD

Clinical applications – Minimal Residual Disease (MRD)

- *Identifying small traces of residual cancer post-treatment*
- *Detecting relapse earlier than imaging, especially at early stages*

- **Role in recurrence prediction**: ctDNA positivity post-surgery predicts relapse risk.
- **Potential for therapy escalation or de-escalation**: Personalizing adjuvant therapy based on MRD status.

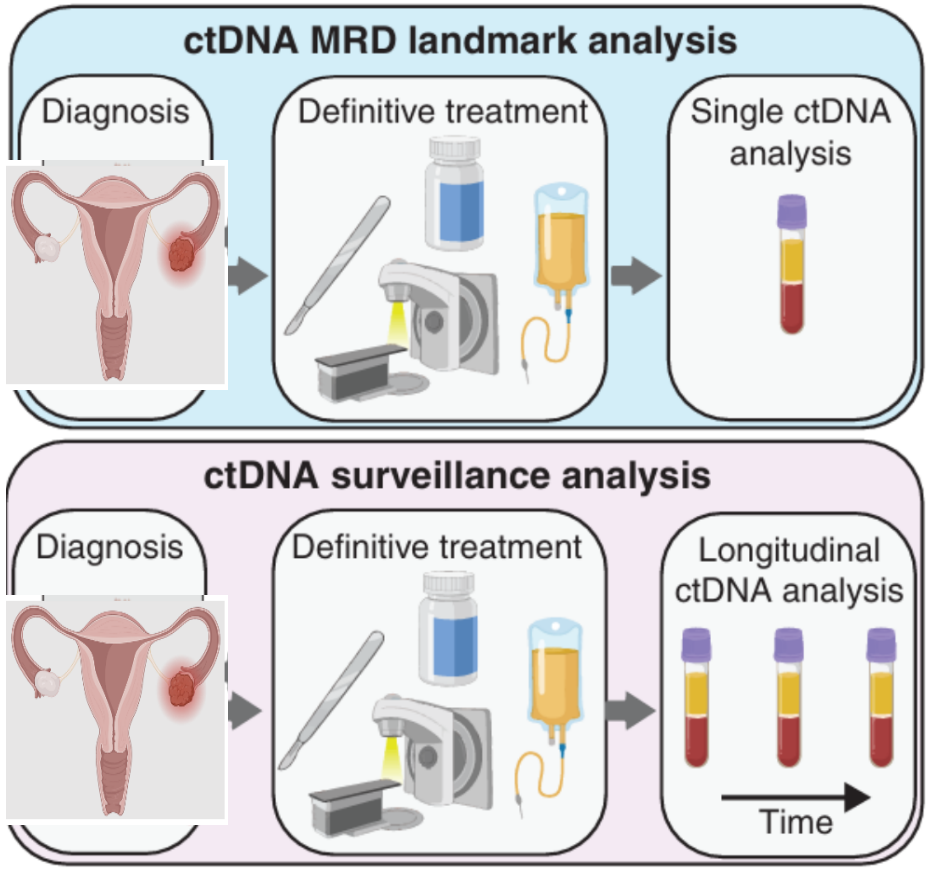


Evolution of MRD patients with solid tumors

nature REVIEWS CLINICAL ONCOLOGY

Pantel & Alix-Panabières, Nat Rev Clin Oncol 2024

Estrategias de evaluación de ctDNA: landmark vs longuitudinal



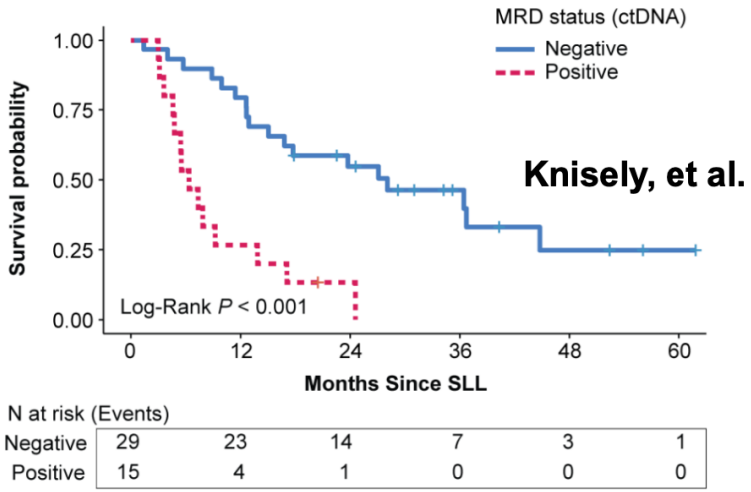
Feature	Landmark Assessment	Longitudinal Assessment
Primary Purpose	Early MRD detection at a fixed time point	Continuous monitoring for recurrence and early relapse detection
Sensitivity	Moderate	Higher due to repeated sampling
Specificity	High when positive	High but may detect transient fluctuations
Logistics	Simpler	Requires repeated draws
Limitations	Timing-dependent, may miss late MRD	More complex interpretation, potential noise

Utilidad de ctDNA: determinar pronóstico

Tumor-informed ctDNA status is highly prognostic

SGO ANNUAL MEETING ON WOMEN'S CANCER
SAN JUAN, PR
APRIL 10-13, 2026

Post treatment ctDNA PFS

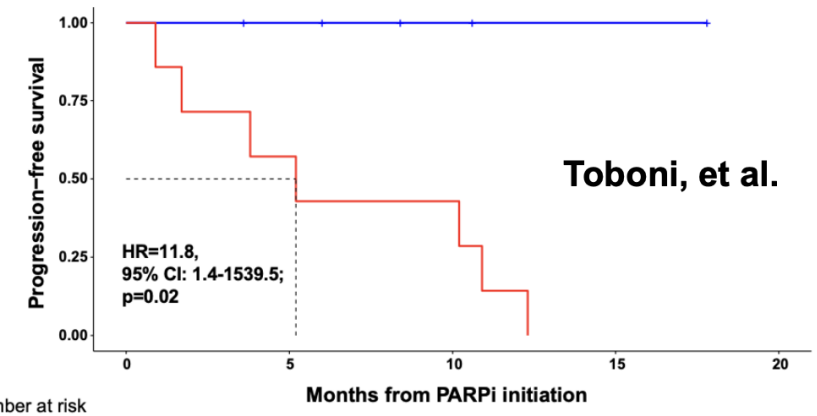


N at risk (Events)

Negative	29	23	14	7	3	1
Positive	15	4	1	0	0	0

ctDNA negativity in NACT OVCA patients was associated with prolonged PFS, while positivity identified early progression in post-ACT samples.

Pre-PARPi ctDNA PFS



Number at risk

ctDNA Negative	5	4	2	1	0
ctDNA Positive	7	4	3	0	0

ctDNA negativity in OVCA patients on PARPi was associated with prolonged PFS.

1. Toboni MD, Gyn Onc 2026.
2.Knisely A, Clin Cancer Res 2025.

Utilidad de ctDNA: monitorizar respuesta y recurrencia al tratamiento

Clinical Performance of a ctDNA Genome Assay to Predict Treatment Response in Patients with Advanced-Stage Ovarian Cancer Receiving Neoadjuvant Chemotherapy

Emily E. O'Brien, MD
University of Alabama at Birmingham
Division of Gynecologic Oncology
O'Neal Comprehensive Cancer Center

Objective
To investigate the utility of ctDNA levels both at baseline and throughout therapy for treatment response and recurrence monitoring in advanced-stage ovarian cancer patients who received NACT

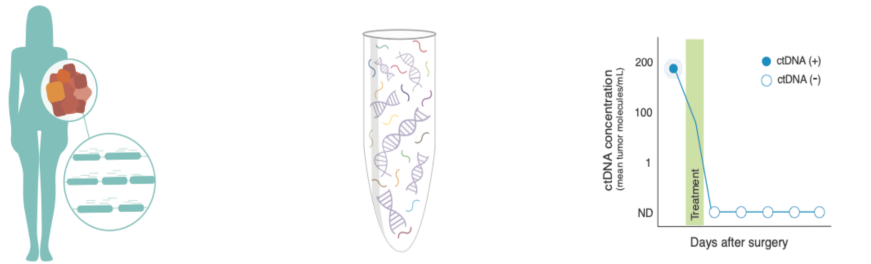
Study Design

Tissue and plasma samples from newly diagnosed, advanced ovarian cancer patients managed with neoadjuvant chemotherapy (NACT) were prospectively banked.

Longitudinal blood samples were collected across four timepoints:

Pre-NACT → Post-NACT Pre-IDS → Post-IDS Pre-ACT → Post-ACT

ctDNA assay creation and analysis



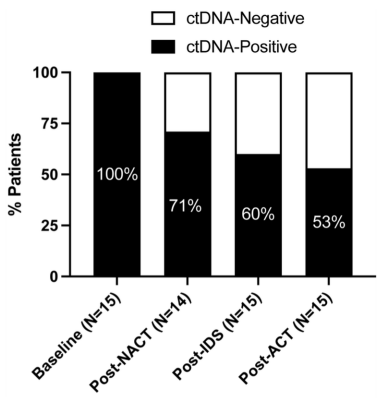
Matched tumor and normal blood samples collected → Whole genome sequencing used to create ctDNA assays → Assay used to detect ctDNA at distinct time points

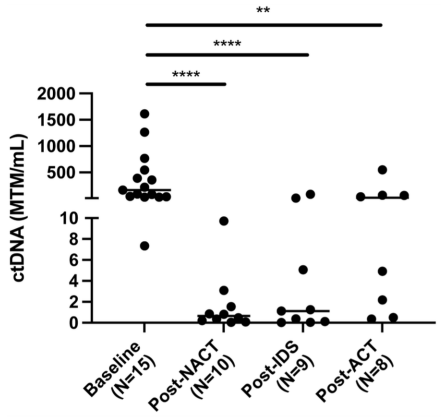
Utilidad de ctDNA: monitorizar respuesta y recurrencia al tratamiento

Patient Demographics (N=15)

Variable	Patient N (%)
Median age (years)	65 (46-86)
Race	
White	9 (60%)
African American	6 (40%)
Stage at Diagnosis	
III	11 (73%)
IV	4 (27%)
Debulking Status	
Optimal	15 (100%)
Suboptimal	0 (0%)
Disease Recurrence	
Yes	6 (40%)
No	9 (60%)
Platinum Status at Recurrence	
Sensitive	1 (17%)
Resistant	4 (66%)
Refractory	1 (17%)

ctDNA detection rates and MTM/mL





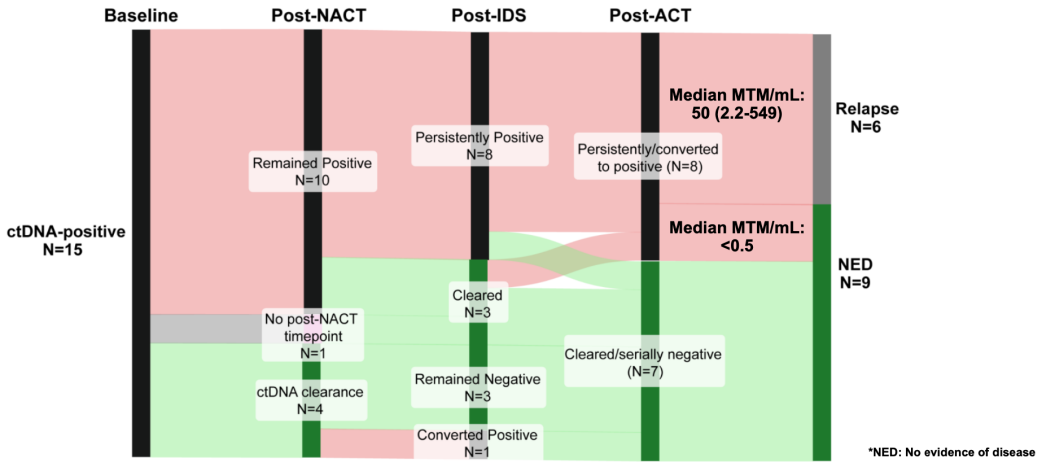
Median MTM/mL

Baseline ~ 165
Post-NACT ~ 0.6
Post-IDS ~ 1.1
Post-ACT ~ 20.7

- Baseline ctDNA detection rate was 100%
- Post-ACT ctDNA positivity rate was 53%

- Baseline ctDNA median MTM/mL was 165
- Post-NACT ctDNA detection median MTM/mL was 0.6

Longitudinal ctDNA dynamics across treatment timepoints



All recurrences had a ctDNA-positive result prior to radiographic finding; while ctDNA negativity correlated with 0% recurrence rate. (median follow up: 17.3 months from end of ACT)

Utilidad de ctDNA: monitorizar respuesta y recurrencia al tratamiento

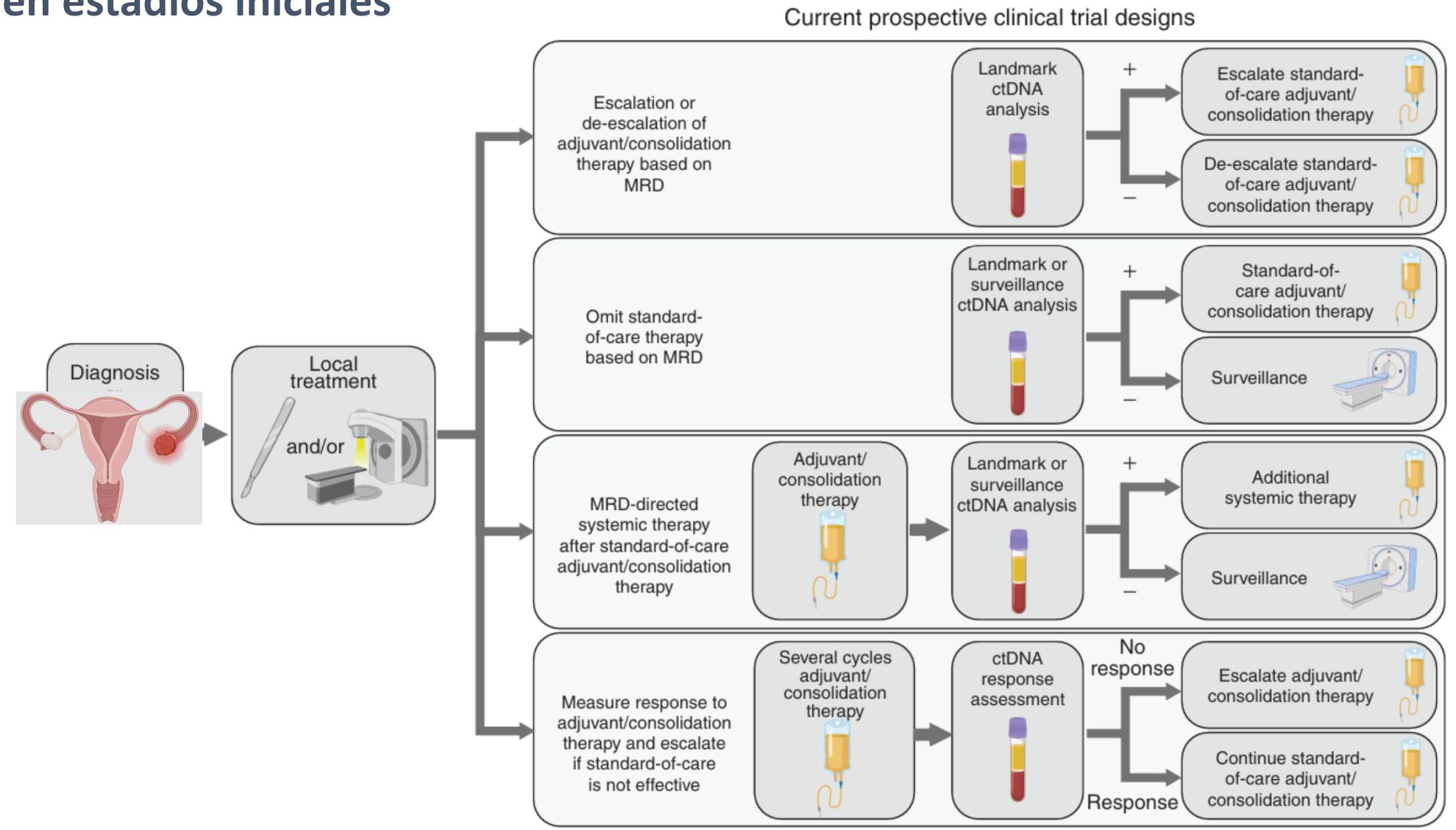
Evaluación de ctDNA en Cáncer de ovario: herramienta para predecir recurrencia y eficacia

APRIL 10-13, 2026

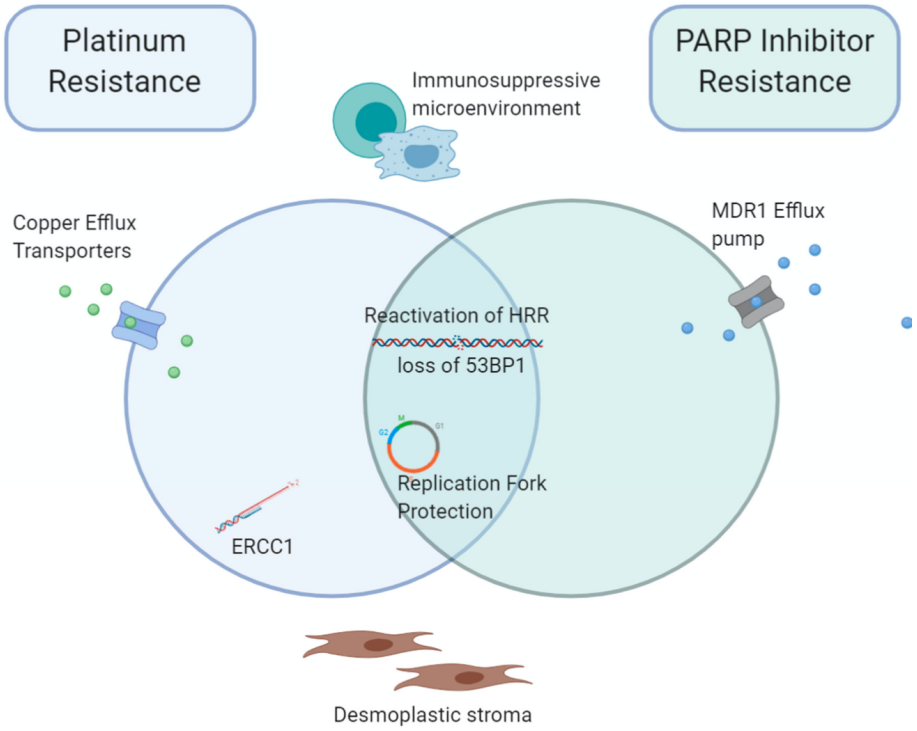
Study	Setting	Assay	Headline MRD / monitoring signal
Hou 2022	69 Pre-op, postop, surveillance subsets	Tumor-informed panel ctDNA (Signatera)	Detected all 7 relapses in the serial surveillance subset (HR 17); ~10-month average lead over imaging; CA-125 elevation not predictive
Zhang 2024	51 epithelial ovarian cancer after PDS and ACT	ctDNA MRD assay of 1021 sequenced genes	Post-surgery MRD independently associated with relapse-free survival (HR 3.4); all post-ACT + MRD relapsed, outperformed CA 125
Kallio 2024	63 EOC patients undergoing upfront treatment; serial plasma	Tumor guided plasma ctDNA (479-1,856 variants)	Positive last on-treatment sample - shorter progression interval (HR 5.6) and OS (8.2); ctDNA anticipated progression with median lead time 5.9 months.
Glueck 2025	27 advanced ovarian cancer postop after PDS	Personalized tumor-informed dPCR based on WGS	Day-10 postop ctDNA was higher with residual disease (367.38 vs 0.92 copies/mL) and moved in the expected direction with incomplete vs complete resection.
Knisely 2025	Complete clinical response with second-look laparoscopy	Tumor-informed ctDNA	ctDNA positivity separated PFS (6.4 vs 28.1 months), but ctDNA detected only 11 of 22 surgically MRD-positive patients.
Paracchini 2026	172 OVCA post PDS, post chemo, post maintenance bev (MITO16a/MaNGO-OV2)	Multimodal ctDNA WGS based tumor fraction	Early postop tumor fraction detectable in 97% outperformed residual tumor (captures MRD); fragmentomics independently stratified PFS/OS risk
Toboni 2026	53 ovarian cancer patients on PARPi maintenance after response to platinum	Personalized tumor-informed Signatera	Pre-PARPi ctDNA 58% (7/12); early persistent or converted + on PARPi marked shorter PFS; no ctDNA-negative patient recurred at last follow-up; ctDNA outperformed CA-125 / BRCA-HR status.

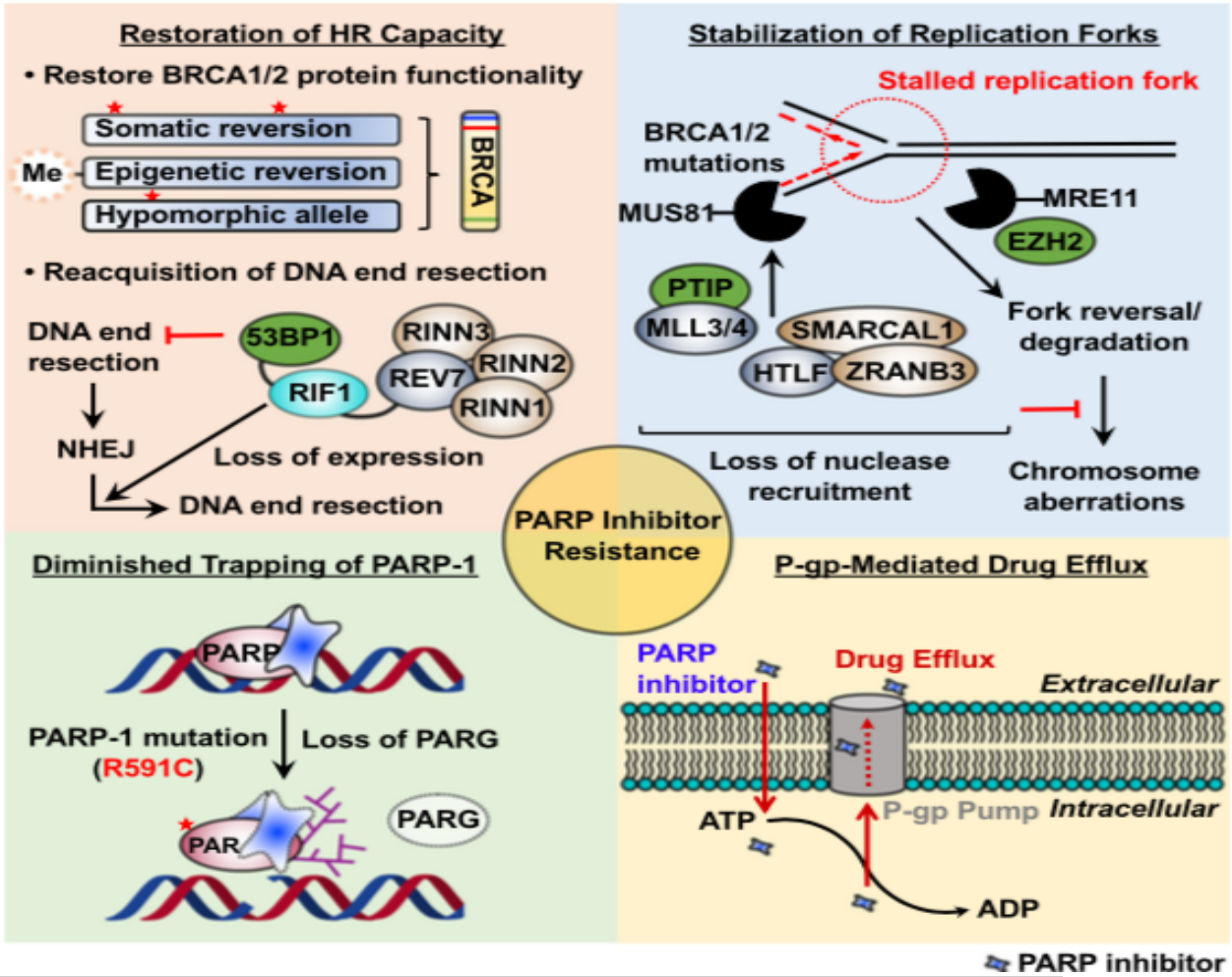
Gynecol Oncol 2022, BMC Cancer 2024, Life Sciences Alliance 2024, Cancers (Basel) 2025, Clin Cancer Res 2025, J Gynecol Oncol 2019, Biomol 2020, Sci Rep 2023, ESMO Open 2026, Gynecol Oncol 2026. Presented by Rebecca A. Brooks, MD.SGO2026

Futuro.. Incorporación del análisis de ctDNA en el diseño de los ensayos clínicos en estadios iniciales



Mecanismos de resistencia a iPARP y platino





Los principales mecanismos descritos hasta la fecha se relacionan con la restauración de la reparación de la recombinación homóloga y la estabilización de las horquillas de replicación.

Kim et al. Experimental & Molecular Medicine (2021) 53:42–51. Lee EK, Matulonis UA.. Cancers (Basel). 2020 Jul 25;12(8):2054 McMullen M, et al. Cancers 2020

Utilidad de ctDNA: Predecir /monitorizar respuesta al tratamiento

Mutaciones de reversión de BRCA en ctDNA: predicción de resistencias primarias y adquiridas a iPARP.

Múltiples mutaciones de reversión pueden presentarse en un paciente individual.

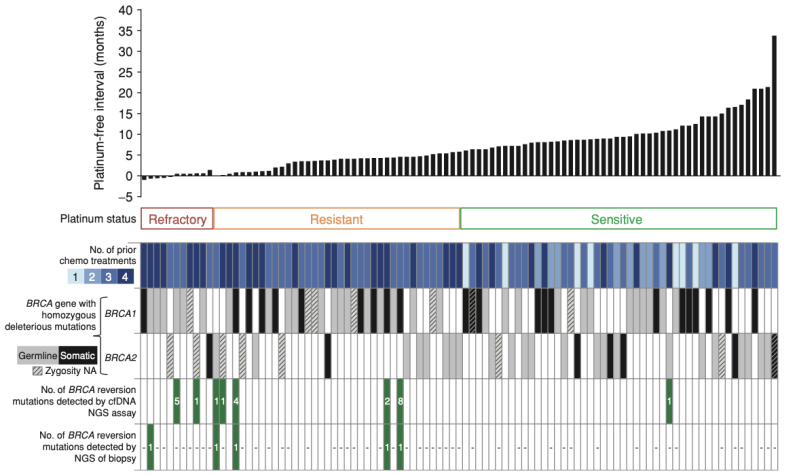
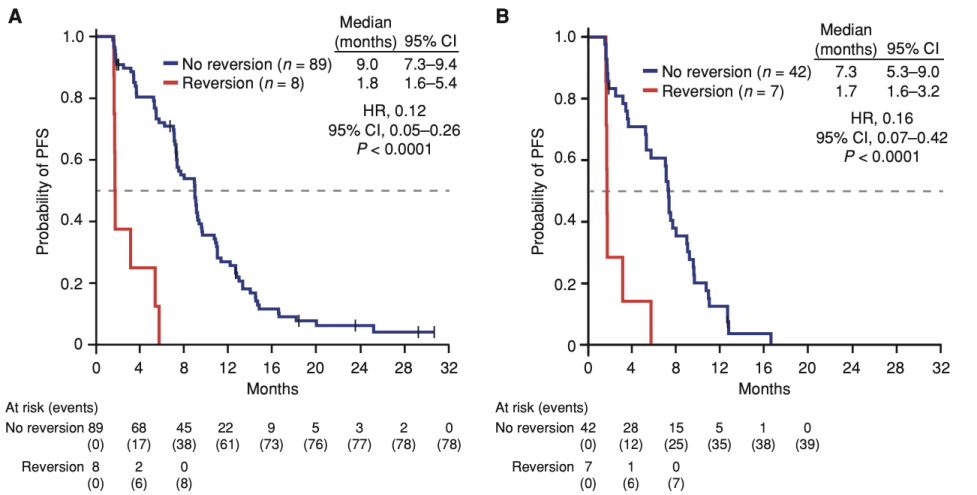


Figure 1. Detection of *BRCA* reversion mutations in pretreatment cfDNA and tumor biopsy. The platinum-free interval and platinum status is based on the patient's most recent platinum-based treatment. The primary deleterious *BRCA* mutations are categorized based on their germline or somatic origin. All tumors with evaluable zygosity of the *BRCA* mutation were found to be homozygous; tumors with indeterminate zygosity are indicated with hatching. The number of *BRCA* reversion mutations detected by each assay is indicated; an empty cell denotes that no reversion mutation was detected. A dash within a cell denotes a pretreatment tumor biopsy sample was not available for sequencing.

BRCA Reversion Mutations and Resistance to PARP Inhibitor RESEARCH BRIEF



ABSTRACT

A key resistance mechanism to platinum-based chemotherapies and PARP inhibitors in *BRCA*-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function. To estimate the prevalence of *BRCA* reversion mutations in high-grade ovarian carcinoma (HGOC), we performed targeted next-generation sequencing of circulating cell-free DNA (cfDNA) extracted from pretreatment and postprogression plasma in patients with deleterious germline or somatic *BRCA* mutations treated with the PARP inhibitor rucaparib. *BRCA* reversion mutations were identified in pretreatment cfDNA from 18% (2/11) of platinum-refractory and 13% (5/38) of platinum-resistant cancers, compared with 2% (1/48) of platinum-sensitive cancers ($P = 0.049$). Patients without *BRCA* reversion mutations detected in pretreatment cfDNA had significantly longer rucaparib progression-free survival than those with reversion mutations (median, 9.0 vs. 1.8 months; HR, 0.12; $P < 0.0001$). To study acquired resistance, we sequenced 78 postprogression cfDNA, identifying eight additional patients with *BRCA* reversion mutations not found in pretreatment cfDNA.

SIGNIFICANCE: *BRCA* reversion mutations are detected in cfDNA from platinum-resistant or platinum-refractory HGOC and are associated with decreased clinical benefit from rucaparib treatment. Sequencing of cfDNA can detect multiple *BRCA* reversion mutations, highlighting the ability to capture multiclonal heterogeneity.

LIBINI (GEICO 155-T)

LIquid BIopsy for predicting NIraparib benefit in 1st line

Samples and storage

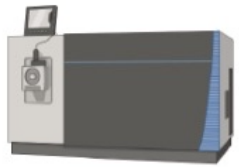
Plasma

FFPE
(baseline)

Biobanco Universidad de Navarra

Sample schedule

PROTEOMICS

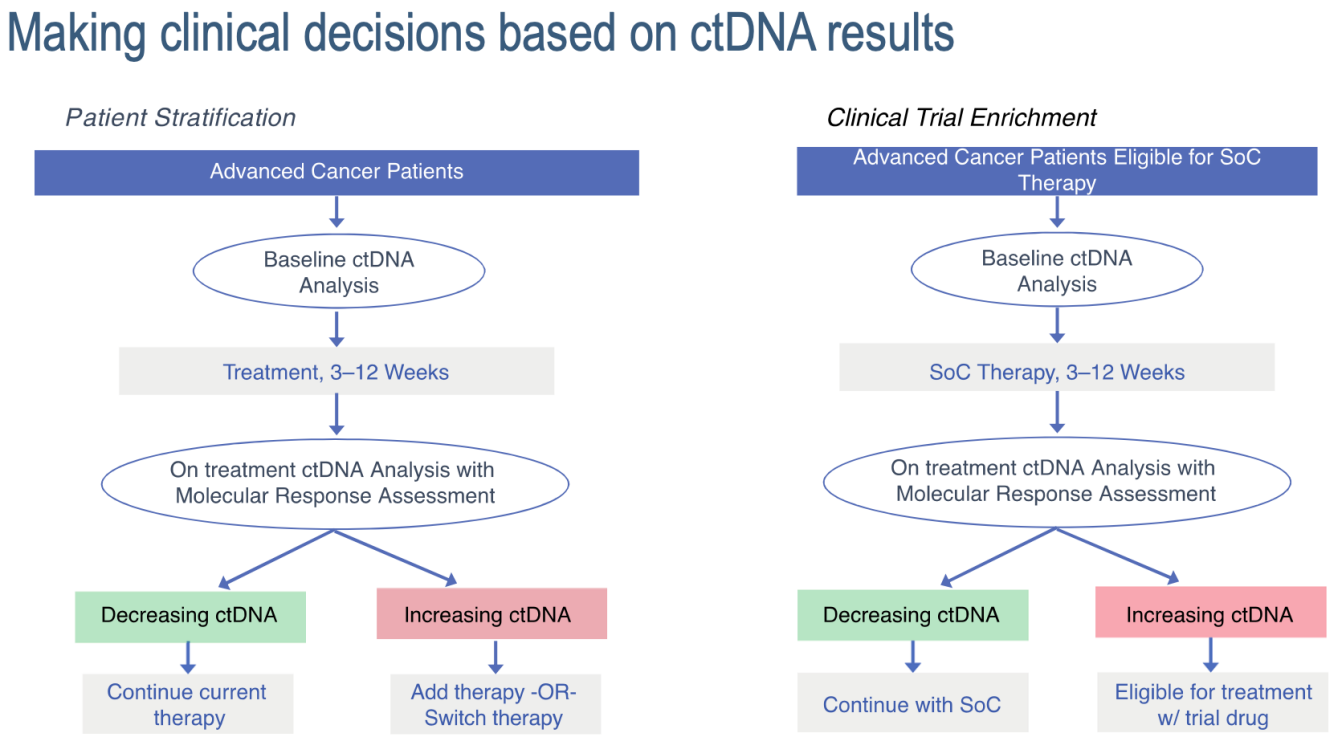


Mass spectrometry

SECRETOME

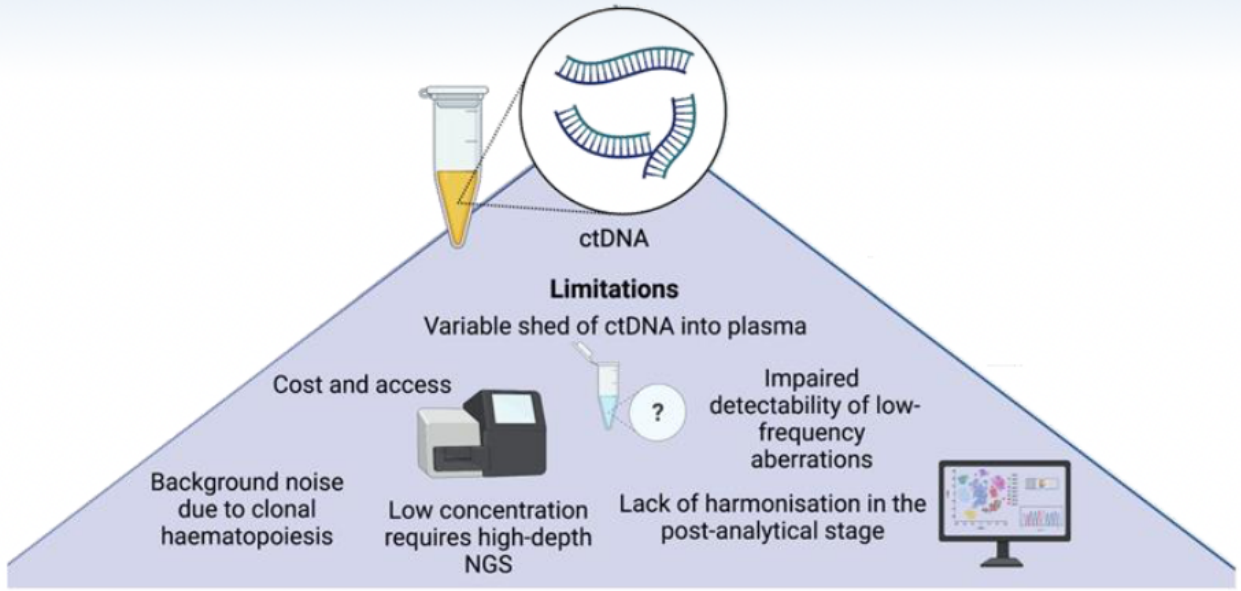
ctDNA

Futuro.. Incorporación del análisis de ctDNA en el diseño de los ensayos clínicos en estadios avanzados



Thompson et al. Br J Ca. 2023

Pitfalls and Challenges



Technical challenges

- Sensitivity of detection method – due to low abundance
- False Positive/Negatives – non-tumor-derived cfDNA mutations
- Standardization of (pre)-analytical protocols → **ELBS**

Biological limitations

- Low ctDNA levels in Early-Stage Cancers & MRC
- Tumor Heterogeneity and ctDNA shedding

Cost and Accessibility

- High cost – Sequencing technologies and assays can be expensive
- Limited accessibility

EUROPEAN LIQUID BIOPSY SOCIETY
RESEARCH FOR CLINICAL IMPLEMENTATION

Future Directions

➢ Future improvements in sequencing technologies - aim to enhance the sensitivity and specificity of ctDNA detection

✓ Ultra-sensitive next-generation sequencing (NGS)

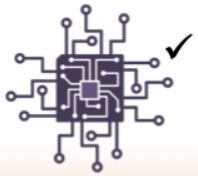
✓ Whole-genome sequencing (WGS),

✓ Single-molecule sequencing

➢ Exploration of ctDNA biological roles beyond a biomarker

➢ Integration with AI and multi-omics approaches

✓ Integrating AI with ctDNA analysis facilitates the interpretation of complex genomic data.



✓ Machine learning algorithms can identify patterns and predict treatment responses, thereby personalizing cancer therapy

Take home message in 2026

Lo que el ctDNA puede hacer ahora

- ✓ Identificar pacientes de alto riesgo después de la cirugía o terapia de primera línea.
- ✓ Detectar la recurrencia molecular antes que la confirmación estándar en algunos pacientes.
- ✓ Complementar el CA-125 y las imágenes cuando las decisiones de vigilancia son inciertas.
- ✓ Monitorear potencialmente el riesgo molecular durante el mantenimiento con PARPi (Toboni 2026).

Lo que el ctDNA aún no puede hacer

- × Reemplazar las imágenes o la evaluación clínica como estrategia de vigilancia única.
- × Descartar enfermedad peritoneal microscópica con una sola muestra de plasma.
- × Justificar la intensificación o desintensificación rutinaria del tratamiento fuera de protocolos basados en evidencia.
- × Aplicarse por igual en todas las histologías ováricas con la misma confianza.

El desarrollo de ensayos posoperatorios más sensibles, la aplicación de enfoques multimodales de fracción tumoral / fragmentómica, y la incorporación de estudios de mantenimiento guiados por ctDNA o intervenciones basadas en EMR son los pasos lógicos a seguir.

CONCLUSIONES
ctDNA en cáncer de ovario

> *"The essential is invisible to the eyes"*

1. El ctDNA es una herramienta prometedora
para avanzar hacia una monitorización más dinámica y personalizada del cáncer de ovario.

2. Supera las limitaciones actuales
Frente al CA-125 y la imagen, el ctDNA ofrece una evaluación en tiempo real de la carga tumoral, la respuesta al tratamiento y la evolución clonal.

3. Monitorización longitudinal = información clave
- Identificar precozmente resistencia.
- Detectar recaídas moleculares antes de la progresión clínica.
- Mejorar la estratificación pronóstica.

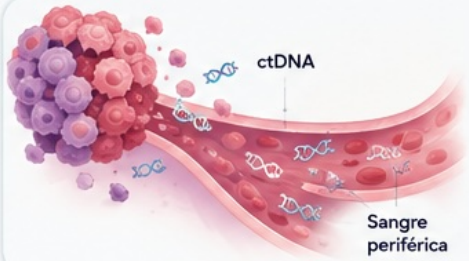
4. El ctDNA y la MRD: el escenario con mayor potencial
- Detectar enfermedad mínima residual.
- Guiar decisiones en mantenimiento.
- Vehículo hacia estrategias de escalada/desescalada terapéutica.

5. Comprender la resistencia para anticiparnos
- El ctDNA permite detectar mecanismos de resistencia, como las mutaciones de reversión BRCA y la restauración de la recombinación homóloga.
- Información clave para orientar decisiones futuras.

6. Retos importantes por superar
- Sensibilidad en tumores con bajo shedding.
- Estandarización de plataformas y puntos de corte.
- Validación prospectiva.
- Demostración de utilidad clínica real.

7. ¿Dónde estamos hoy?
El ctDNA tiene gran validez biológica y pronóstica, pero aún necesitamos estudios prospectivos que demuestren que actuar sobre esta información mejora los resultados clínicos.

8. Hacia una nueva oncología
Estamos pasando de una oncología basada en la anatomía a una oncología **dinámica, molecular y evolutiva.**



MENSAJE FINAL

> El ctDNA no solo nos permite observar el tumor; **nos permite seguir su evolución en tiempo real y comprender cómo cambia bajo presión terapéutica.**

DETECTAR antes → **MONITORIZAR** en tiempo real → **COMPRENDER** la evolución del tumor → **DECIDIR** mejor para cada paciente

HACIA UNA ONCOLOGÍA VERDADERAMENTE PERSONALIZADA

Mucho camino por recorrer, pero el futuro es prometedor.
El ctDNA puede convertirse en un cambio de paradigma en el manejo del cáncer de ovario.

Muchas Gracias

4ª Jornada de Actualización en Cáncer Ginecológico

Bilbao · 20 – 21 de mayo 2026