Diagnostic Utility of Liquid Biopsy to Analyze Circulating Tumor DNA Via Next-Generation Sequencing

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Anna Godo Pla[1], Eva Barreda Arnau[1], Guillem Torres-Pagès[1], Maria-Dolors Estrada Sabadell[1,2], Rosa Maria Vivanco-Hidalgo[1]

[1]Agency for Health Quality and Assessment of Catalonia (AQuAS), Ministry of Health Government of Catalonia, Spain; [2]CIBER en Epidemiología y Salud Pública, CIBERESP, Spain.

/ INTRODUCTION

Recent oncology advancements in next-generation sequencing (NGS) technologies for analyzing circulating tumor DNA (ctDNA) from liquid biopsy (LB) samples have garnered significant interest due to their potential applications across various stages of the disease: cancer screening, diagnosis at early stage, profiling tumor mutations, monitoring treatment response, detecting minimal residual disease, and selecting the most appropriate treatments based on genomic alterations.

Unlike tissue biopsy, the current standard method for cancer diagnosis, LB is a minimally invasive. It allows for real-time evaluation of the tumor's genomic profile without invasive and costly procedures. The most commonly studied sample type for LB is plasma from blood.

/ OBJECTIVES

This report evaluates the potential of LB for diagnostic purpose by analyzing ctDNA via NGS in breast, lung, and colorectal cancer, aiming to assess its inclusion in the Catalan Health System (CHS) benefit package. Specific objectives are: **1**. To describe the diagnostic utility of ctDNA from LB by NGS in breast, lung and colorectal cancer, **2**. To describe the diagnostic utility of commercial ctDNA LB-based NGS panels, **3**. To identify the clinical scenarios in which LB to analyse ctDNA could be performed as the first choice in breast, lung and colorectal cancer, and **4**. To plan a budgetary impact analysis (BIA) of the inclusion of ctDNA LB-based NGS panels in breast, lung and colorectal cancer.

/ METHODS

1 Umbrella review of the diagnostic utility of ctDNA from LB by NGS in breast, lung and colorectal cancer

Systematic literature search → Literature screening and selection → Data extraction and quality assessment → Qualitative synthesis

Literature screening and selection:
- Inclusion/exclusion criteria according to PICO question
- Designs: Systematic reviews (SR) with or without Metanalysis (MA,) Health Technology Assessment (HTA) reports.
- Time period: 2019-2024

Data extraction and quality assessment: AMSTAR-2 tool

2 Narrative review of targeted commercial NGS panels

Manual search at websites and direct contact with Industry → Data extraction → Qualitative synthesis

3 Narrative review of targeted Scientific Societies (SS) recommendations and expert opinions

Manual search at websites of SS (Time period: 2019-2024) → Data extraction → Qualitative synthesis

4 Design of BIA protocol

Methodology to obtain required data → Features of the budgetary impact analysis → BIA protocol

/ RESULTS

1 Diagnostic utility of ctDNA analysis from LB by NGS vs. tissue biopsy in breast, lung and colorectal cancer

Breast cancer	
SR with MA included	Galvano et al. 2022
Use of the ctDNA LB-based NGS test	**Tumor profiling** in advanced cancer stage
Quality assessment	Very low
Diagnostic utility data vs. tissue biopsy	***PIK3CA*** Sensitivity: 0.83, Specificity: 0.98 AUC of SROC: 0.98

Lung cancer (NSCLC)	
SR with MA/HTA report included	Esagian 2020, Sebastiao et al. 2020, Ontario Health 2020
Use of the ctDNA LB-based NGS test	**Tumor profiling** in advanced cancer stage
Quality assessment	Low to Very low
Diagnostic utility of ctDNA LB-based NGS data vs. tissue biopsy	***EGFR, ALK, ROS-1, BRAF, RET, MET* exon 14** Sensitivity: 0.76, Specificity: 0.99, AUC of SROC: 0.99 ***EGFR T790M*** Sensitivity: 0.78, Specificity: 0.85 ***ALK, BRAF, ERBB2, EGFR, KRAS, MET, RET i ROS 1*** Positive Percent Agreement, PPA: 53-68% depending on the analysed gene

Colorectal cancer	
SR with MA included	Galvano et al. 2019, Ye et al. 2021
Use of the ctDNA LB-based NGS test	Tumor profiling in advanced cancer stage
Quality assessment	Very low
Diagnostic utility of ctDNA LB-based NGS data vs. tissue biopsy	***RAS*** Sensitivity: 0.75, Specificity: 0.91, AUC of SROC: 0.81 ***KRAS*** Sensitivity: 0.65, Specificity: 0.88, AUC of SROC: 0.86

2 Commercial NGS panels

ctDNA LB-based NGS panels reviewed: FoundationOne Liquid CDx, Oncomine™ Lung cfDNA Assay Oncomine™ Colon cfDNA Assay, Oncomine™ Lung Cell-Free Total Nucleic Acid Assay, Oncomine™ Pan-Cancer Cell-Free Assay, Oncomine™ Precision Assay, Oncomine™ Precision Assay GX (Ion Torrent, Guardant 360, AVENIO ctDNA Panel Targeted Kit, AVENIO ctDNA Expanded Kit, AVENIO ctDNA Surveillance Kit, TruSight Oncology 500 ctDNA	
None of the reviewed panels have an intended use for cancer screening or early stage diagnosis	
NGS test with CE mark	FoundationOne Liquid CDx (Roche), Guardant 360 CDx (Guardant Health). Intended use: Tumor mutation profiling for treatment selection
Mutations detection	Oncomine™ Lung cfDNA Assay and Oncomine™ Colon cfDNA Assay: only single nucleotide variants (SNV) and indels. Other panels: also copy number variations (CNV) and gene fusions.
Diagnostic utility data	Heterogeneity between tests in diagnostic utility data. Sensitivity (7 panels): 89.2-99.9%; Specificity (4 panels): 99.6-99.9%; Positive Predictive Value (PPV) (7 panels): 99-100%; Negative PV (NPV) (2 panels): 94-100%; PPA (2 panels): 98-100%; Negative percent agreement (NPA) (2 panels): 93.9-100%; Overall Predictive value (1 panel): 93.4%

3 SS recommendations and expert opinions about LB in breast, lung and colorectal cancer

SS reviewed: SEOM (Sociedad Española de Oncología Médica), ESMO (European Society of Medical Oncology), ASCO (American Society of Clinical Oncology)	
Cancer screening or early diagnosis	Not recommended
Tumor profiling	Recommended Analysis of ctDNA from LB in advanced disease for cancer genotyping and guide treatment decisions. The use of BL as the first choice is only recommended in specific cases, such as not having tissue samples or when urgent therapeutic decisions need to be made. In the specific case of breast cancer, it is recommended to analyze ESR1 in an advanced state to the progression of hormonal therapy, preferably through the determination of ctDNA.

4 Budgetary impact analysis protocol

BIA features	
Data obtention	Narrative review
Objective	To estimate the monetary units that should be disbursed by the CHS
Perspective	Healthcare payer
Population	Patients likely to be diagnosed or already diagnosed with lung, breast or colorectal cancer of any age and any stage of the disease.
Temporal horizon	1 year
Comparison scenarios	Different scenarios based on different % expansion of LB use vs. tissue biopsy. A complementary or alternative use of the LB use will also be considered. Results will be differentiated according to the use of LB in diagnostic/screening or tumor profiling.

/ CONCLUSIONS

- Existing evidence of LB to analyse ctDNA via NGS from **SR with MA** is limited to the **molecular profile application and for certain target genes**.
- Most NGS panels allow the detection of **SNV, indels, CNV, and fusions**.
- SS recommendations suggest that **LB may be complementary to tissue biopsy**.
- The BIA will help decision-makers understand the potential costs and economic benefits in different scenarios, facilitating **better resource management.**

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Author's email: annagodo@gencat.cat | rvivanco@gencat.cat
Agency for Health Quality and Assessment of Catalonia (AQuAS).
Aragó 330-332. 08009 Barcelona | http://aquas.gencat.cat

@AQuAScat

https://es.linkedin.com/company/aquas-salut