PCP57

# Liquid biopsies in breast cancer early detection, metastatic progression and therapy success: **Opportunities and challenges for the patients, providers and payers**

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## Background

Development of metastases is a major culprit of breast cancer (BC)-related mortality. Precision oncology tries to tackle metastases by pairing cancer patients with drugs that target specific mutations in their tumors, with the aim of producing long-lasting remission, halt metastatic progression and extend survival. As opposed to solid biopsies, liquid biopsies (i.e. circulating tumor DNA - ctDNA and circulating tumor cell - CTC analysis) hold great promise for precision medicine due to their ability to provide multiple non-invasive global snapshots of the primary and metastatic tumors. Liquid biopsies are less invasive and can be repeated more frequently and therefore help clinicians screen and detect cancer early, stratify patients to the most suitable treatment more effectively, monitor in real-time treatment response and resistance mechanisms, evaluate the risk for metastatic relapse and estimate prognosis. In addition, progressive malignant disease drives the medial costs up with the highest costs associated to the management of metastatic BC. Yet, the perceived value of more frequent liquid biopsies from the payers and caregivers' perspective and to the healthcare system remains elusive.

## Objectives

We aim at evaluating the advantages and limitations of liquid biopsies in BC diagnosis and monitoring of progression from the healthcare system perspective.

## Methods

We have developed a comparative review of literature, defined methods, platforms and approaches of solid vs. liquid biopsies in early detection of BC, metastatic progression and therapy outcomes evaluation.

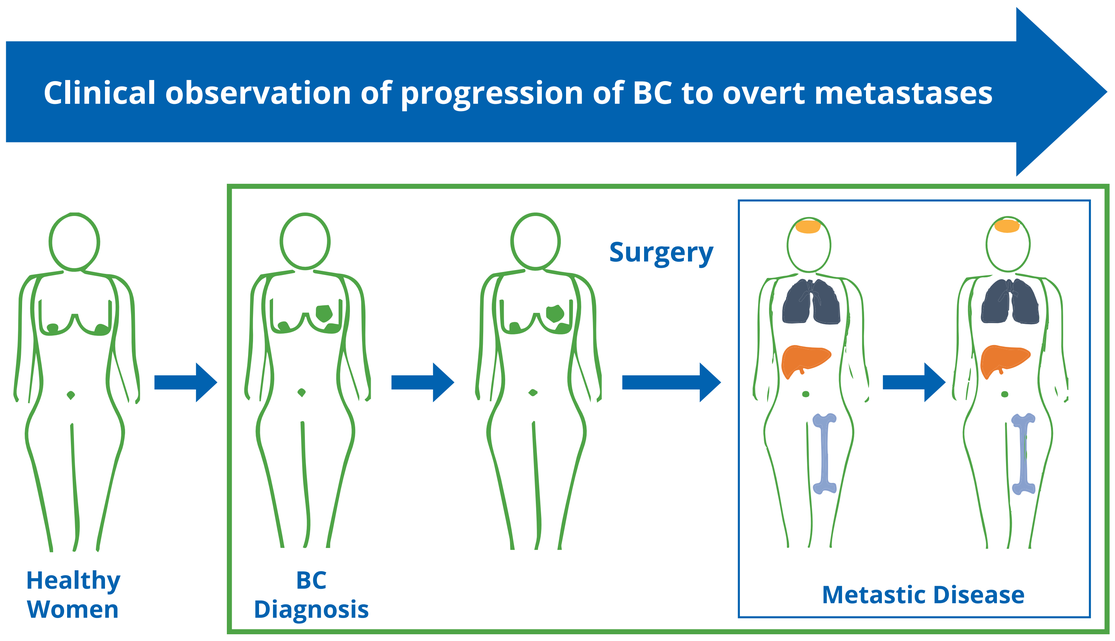
## Conclusions

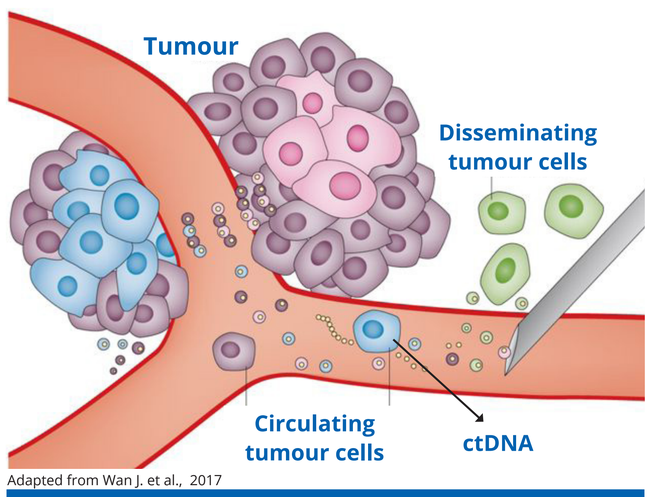
Liquid biopsies may serve as a tool to provide personalized treatment options to BC patients and simultaneously reduce over-treatment for patients who would be less likely to relapse. Thus, use of liquid biopsies may help optimize allocation of scarce economic resources and may be a cost-effective way to identify, select, and manage patients with advanced BC. Further health economic research is required to estimate impact of liquid biopsy in BC diagnosis and treatment

## Clinical Perspective: Value of liquid biopsies in the management of BC

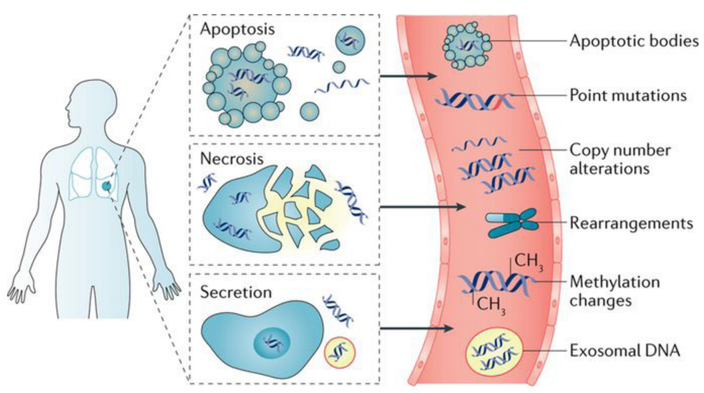
Breast cancer is a pathologic process and a complex, heterogeneous and dynamic disease involving multiple gene-environment interactions affecting numerous biological pathways with multiple variables, such as tumor entity, disease stage or tumor burden (Heitzer et al., 2017). Utilization of liquid biopsies in the management of cancer relies on the detection rate, sensitivity and specificity of methods used for ctDNA and CTC analyses. Liquid biopsies are informative regarding response to given therapies, are capable of detecting relapse with shorter lead time compared to standard measures, and reveal mechanisms of resistance in the late BC stages (Meador and Lovely, 2015). However, lower frequency and volume of aberrations, clonal expansions of non-tumorous tissues and the accumulation of cancer-associated mutations with age represent hurdles for the liquid biopsy adoption for the early breast cancer (eBC) screening (Risques and Kennedy, 2018; Klein CA, 2009). Therefore, adoption of liquid biopsy for eBC screening might result in substantial high risk of breast cancer overdiagnosis (Heitzer et al, 2017).

### Clinical observation of progression of BC to overt metastases




Adapted from Wan J. et al., 2017




Therapy: ↑ Neo-adjuvant, Adjuvant ↑

Purpose of the liquid biopsy in BC management: ↑ Screening early diagnosis; ↑ Monitoring BC progression, therapy effectiveness and failure

**Technical aspect of using liquid biopsies screening for BC**

| | Early breast cancer | | Metastatic breast cancer | |
|---|---|---|---|---|
| | **CTC** | **ctDNA** | **CTC** | **ctDNA** |
| | Low CTC frequency and lack of specific biomarkers | Low ctDNA quantity | High CTC numbers in end stage patients | Sufficient ctDNA quantity for diagnostic purposes |
| | Insufficient precision and accuracy of liquid biopsies versus solid tumor biopsy | | High number of false negative or positive cells | Need for standard methods- lack of information on metastatic site |

## Payer Perspective

### Early BC

- Despite advances in liquid biopsy technology and analysis, standard diagnostic methods such as tissue biopsy remains a "gold standard" method for BC diagnosis
- Due to technical aspects of liquid biopsies, cfDNA of non-tumor lesions, benign tumors and/or small cancers with favorable molecular features would contribute to the increased rate of BC overdiagnoses
- Introduction of liquid biopsy screening for early BC diagnosis would result in increased spending. Currently liquid biopsies lack sensitivity/specificity for the early cancer detection and confirmation of suspected positive specimens would require traditional diagnostic tools

### Testing rationale: Current and anticipated therapeutic targets

With the advent of more and more targeted therapies indicated as 1L therapy in metastatic cancers for their respective mutations, and usually priced at large premium to traditional and/or generic and/or biosimilars, payers should favor systematic mutation testing with liquid biopsies at time of diagnosis of aBC.

- **ER**→ mutation - **Her-2** → mutation, amplification - **PARP**→ BRCA1 mutation
- **Immune checkpoint inhibition** →MSI breast cancer
- **PI3KCA**→ mutation, PTEN loss - **AKT** → PIK3 hyperactivation
- **MEK**→ RAS/RAF/MEK/ERK pathway hyperactivation
- **c-MET** (HGFR) → STAT3/5, Ras/Mapk and PI3K signaling
- **HDAC**→ MLL3 mutation - **AXL**→ overexpression
- **mTOR** → PI3K hyperactivation - **CDK4/6**→ GATA3 mutation

### Advanced BC (aBC)

- Liquid biopsy is expected to capture heterogeneity and real-time status of aBC, without having to rely on archival specimens from the original primary tumor (if available and often collected prior to metastatic disease) or the need for invasive biopsy procedures at a metastatic site (when solid biopsy is feasible)
- Liquid biopsies provide oncologist information of the most suitable therapeutic option, thus overcoming potential discordance of BC predictive markers between tumor and metastases
- Liquid biopsies may be used as a valuable add-on technology to standard diagnostic methods due to the lack of information of the site of metastases

### Opportunities and Challenges of Frequent ctDNA Analysis in the Management of aBC

- Liquid biopsies could be used to monitor treatment effectiveness and timely assess benefits
- Liquid biopsies could be used to guide cancer treatment and provide the ideal scheme to precision medicine.
- Earlier diagnosis of relapsed disease would reduce high expenditures for the management of more advanced BC stages as it would enable appropriate and timely prescribing of targeted therapies.
- Identification of mutations for which targeted therapies exist but are not indicated in BC e.g. MEK, leading to off-label / off-reimbursement prescribing or ethical challenges
- Complexity around selection of the most appropriate therapeutic target for treatment of BC patients with multiple target mutations
- Economic and societal impact of broad liquid biopsy testing remain elusive

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