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Expanding screening through the use of liquid biopsy for early cancer detection

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Screening programs have helped reduce cancer-specific mortality by detecting cancer at earlier stages. Developing increasingly sensitive, organ-specific liquid biopsy assays to evaluate tumor-derived analytes could pave the way for non-invasive early cancer diagnosis in population screening programs.

Current population-based early detection programs for asymptomatic individuals, such as screening mammography for breast cancer (BC), often use a one-size-fits-all approach that may not effectively address the needs of specific populations. This is the case for pregnant and post-partum women, who are usually not included in routine BC screening programs, making it extremely rare to detect lesions through imaging without any physical signs. Moreover, the physiological changes in the mammary gland during pregnancy and lactation can complicate standard radiologic examinations and are believed to contribute to the aggressive behavior often associated with pregnancy-related breast cancer (PrBC) compared to non-pregnancy-related tumors. This can potentially lead to delays in diagnosis[1] and worse outcomes. On the other hand, high-risk groups, such as carriers of germline mutations in genes associated with hereditary syndromes (e.g., *BRCA1/2*, *RAD51*, *PALB2*, *TP53*), are generally offered specialized surveillance programs due to their increased risk of developing neoplasms[2]. In recent years, significant efforts have been made to develop multifactorial prediction algorithms capable of risk stratification, aiming to design tailored interventions for early detection.

Liquid biopsy (LB) refers to the non-invasive sampling and analysis of biomarkers in body fluids and has become an important tool in precision oncology, offering a novel approach to diagnose and manage cancer. LB can be used to detect the presence of tumor cells and specific alterations within them. This application can allow for dynamic monitoring of disease course and the identification of target mutations to guide treatment decisions.

Several analytes in biofluids may be used to profile the genomic landscape of a tumor. Firstly, circulating tumor cells (CTCs), released from the tumor into body fluids, provide a platform for functional testing and prognostic evaluation. Secondly, the tumor-derived fraction (ctDNA) in circulating cell-free DNA (cfDNA) shed by tumors may help circumvent the obstacle of intratumor heterogeneity by offering a more comprehensive view of genetic alterations in the lesion. Additionally, microRNAs isolated from body fluids serve as informative biomarkers for diagnosing and tracking cancer progression, as well as predicting treatment responses. Lastly, extracellular vesicles, that contain nucleic acids and proteins from their cells of origin, provide valuable information for understanding the tumor microenvironment and may provide RNA-based biomarker information[3,4].

The identification of cancer-specific alterations has advanced over the past few decades through the development and application of various "-omics" approaches including proteomics, lipidomics, and metabolomics. Cancer diagnostics leveraging FDG-PET imaging and similar approaches relying on metabolic biomarkers have explored the incorporation of omic analyses of low molecular weight metabolites. Despite the potential for non-invasive image-based cancer detection, these imaging approaches alone still suffer from limited specificity and sensitivity. The potential of liquid biopsy through direct metabolite analysis in clinical specimens is a promising advance. It offers non-invasive alternative for early cancer detection, tumor feature evaluation, and aggressiveness assessment[5]. This optimism is further supported by the success of proteomics in early cancer detection. For example, in endometrial cancer, elevated protein levels in uterine fluids have shown high sensitivity and specificity, potentially suitable for clinical use[6]. Similarly, lipidomic studies have demonstrated that changes in serum lipidome concentrations provide reliable indicators of the presence of a tumor mass, such as in the case of pancreatic cancer[7]. These emerging liquid "-omics" platforms are paving the way for more accurate and less invasive approaches to cancer detection and monitoring across various cancer types.

To date, LB has proven to be clinically useful for monitoring treatment response in metastatic settings for various tumor types. The presence of ctDNA in plasma serves as a potent prognostic biomarker in Stage IV tumors[8,9]. Current guidelines recommend ctDNA testing in routine clinical practice primarily for genotyping advanced disease, using validated and sufficiently sensitive assays[10]. Moreover, the clearance of ctDNA after treatment can indicate treatment success. This has been observed in colon cancer (CRC), both in early stages, where ctDNA-based detection of molecular residual disease (MRD) has been linked to recurrence risk and potential benefit from adjuvant chemotherapy[11], and in advanced stages, where an early reduction in ctDNA levels following chemotherapy has been predictive of improved progression-free survival[12]. Additionally, LB can guide therapy decisions in advanced setting. Several trials have explored the potential to redirect treatment strategies based on acquired somatic mutations of resistance detectable in plasma ctDNA. In advanced BC, the landmark PADA-1 trial investigated the potential of *ESR1* mutation levels detected in blood to guide therapy adjustments in patients with metastatic estrogen receptor-positive, HER2-negative BC without waiting for radiologic evidence of disease progression. The results of this trial demonstrated improved progression-free survival compared to the control group[13]. The plasmaMATCH study trial confirmed a high concordance rate between of LB assay and tissue sequencing (96-99%) when evaluating the accuracy of ctDNA in monitoring patients with advanced BC by detecting targetable mutations. The possibility of using mutation-matching therapies to treat disease, provided by this study supports the broader adoption of LB in clinical practice[14].

While the utility of LB in later disease stages has already been demonstrated, its application for the diagnosis and management of early disease presents significant challenges. This is mainly due to the low

abundance of tumor-derived analytes and genetic material in bodily fluids, insufficient assay sensitivity, and inadequate detection methods, all of which can lead to a risk of false-negative results. Additionally, maintaining the specificity of ctDNA detection presents a major challenge, as distinguishing cancer-related signals from normal biological variation within an individual is difficult. Most cfDNA (over 80% in healthy individuals[15]) originates from hematopoietic cells, which can accumulate somatic mutations due to aging processes without necessarily causing dysplasia. These mutations, known as clonal hematopoietic of indeterminate potential (CHIP) can serve as a confounding factor for early cancer detection assays[16]. These challenges underscore the need for further research and development in the field of LB to improve sensitivity and specificity for early-stage cancer detection.

A recent study evaluated the potential of plasma LB to stratify multi-cancer risk in symptomatic patients. The authors employed a methylation-based assay to prospectively test more than 5000 patients presenting with non-specific symptoms possibly indicative of gynecological, lung, or gastrointestinal malignancies. The test demonstrated a sensitivity of 66.3%, a specificity of 98.4%, and accurately identified the site of origin in 85.2% of cases[17]. The test's moderate sensitivity, which increased with age and cancer stage, suggests that a negative result should not be considered sufficient to rule out further investigations for patients with clinically significant symptom clusters.

Another study was conducted to evaluate a multi-modal ctDNA blood-based test for detecting CRC in a population eligible for screening (asymptomatic 45–84 years old patients considered at average risk of CRC, without personal or familial history of CRC)[18]. The test showed a specificity of nearly 90% for identifying any advanced neoplasia, a sensitivity of 87.5% for detecting CRC stage I to III, and a sensitivity of 13.2% for advanced precancerous lesions. Although the test displayed promising results, its relatively low sensitivity for identifying advanced precancerous lesions remains a limitation, especially when compared to colonoscopy, which not only detects but also removes these lesions. Nevertheless, the study confirmed the feasibility of using cfDNA for non-invasive CRC screening, which could potentially improve screening adherence. This paves the way for further investigation to determine whether its cost-benefit ratio justifies its implementation in clinical practice[19].

One strategy employed to overcome the limitations of low sensitivity is evaluating organ-specific biofluids, such as urine for bladder and renal malignancies, and saliva for head and neck cancer (Fig. 1). Biofluids in direct contact with tumor or its microenvironment can provide more insights into cancer development, offering a favorable avenue for early diagnosis and monitoring. Several studies have shown potential for early detection using these alternative biofluids[20,21].

Recent work from our group illustrates the potential to impact screening and early detection protocols for PrBC through the detection of cfDNA in serum breast milk (sBM), which reflects the environment of the mature gland[22]. At early disease stages, this approach can help identify carcinogenesis by analyzing tumor-derived shedding in sBM. The study found ctDNA variants in sBM mirrored those in the tumor, resulting in higher sensitivity than concurrent plasma testing. Despite the relatively small cohort size, ctDNA was detectable in sBM samples collected up to 18 months before a diagnosis in two participants. These results highlight the potential superiority of sBM as a source for LB, suggesting its possible role in the context of PrBC screening. The prospective clinical study, MMA-TERNA, aims to clinically validate our LB panel in sBM for early PrBC detection, based on the innovative concept that sBM from lactating women

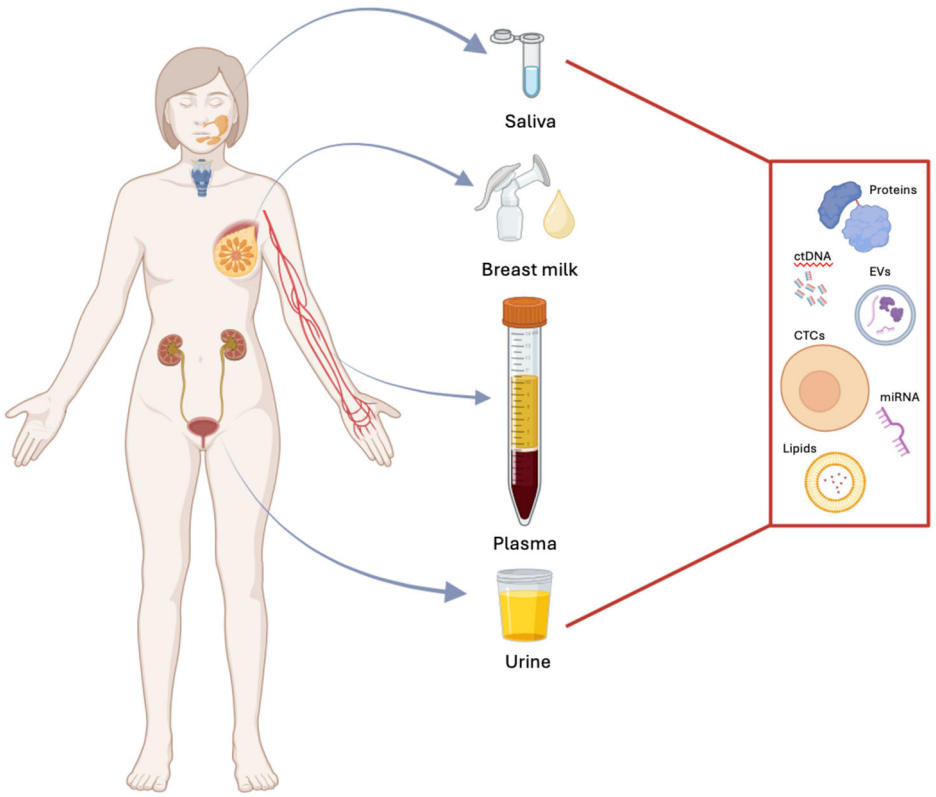

Fig. 1 | Local body fluids offer a promising LB source for multi-analyte biomarker detection and early cancer diagnosis. ctDNA circulating tumor DNA, EVs extracellular vesicles, CTCs circulating tumor cells, miRNA micro RNA. Created with Biorender.com.

can serve as a reliable source of ctDNA from early-onset BC. The results of this trial could improve early diagnosis of PrBC, confirming the clinical utility of sBM as a reliable source for screening in a high-risk population and addressing an unmet need.

Conclusively, ensuring exceptionally high sensitivity and specificity is crucial when implementing a screening program in the general population. The clinical development of a ctDNA-based approach for early detection requires large-scale clinical evidence to demonstrate an assays performance and to prove its clinical utility. While an earlier diagnosis might introduce "lead-time bias", which might not necessarily affect cancer-specific mortality, following patients for an adequate period and conducting serial ctDNA testing to assess signal kinetics dynamically is essential to refining patient stratification.

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Competing interests

The authors declare no competing interests.

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