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REVIEW

Liquid Biopsy for Early Detection of Breast Cancer: Evidence and Public Health Implications from a Systematic Review

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Abstract

Objective: To assess how well liquid biopsy technologies work for early breast cancer detection and how they may be included in cancer control and public health screening initiatives. **Methods:** A thorough search of Web of Science, PubMed, Embase, and Scopus was done to locate research articles released between January 2015 and August 2025. Exosomes, circulating tumor cells (CTCs), or circulating tumor DNA (ctDNA) were tested in eligible studies as liquid biopsy biomarkers for the early detection of breast cancer in individuals who were asymptomatic or in the early stages of the disease. The study's quality was assessed by two reviewers who independently screened, extracted data, and followed PRISMA and QUADAS-2 recommendations. **Findings:** A total of forty-three (43) studies satisfied the requirements for inclusion. The majority concentrated on ctDNA tests, such as methylation signatures and mutation profiling. Specificities were usually above 90%, whereas reported sensitivities varied from 60% to 98%. Exosome-based methods and CTC assays offered supplementary diagnostic utility. New multi-omic systems decreased false positives and enhanced stage I detection. Ultra-sensitive ctDNA tests have been shown in recent research to be able to identify relapses up to 38 months prior to a clinical recurrence. However, few research were conducted in low- and middle-income countries (LMICs), and cost-effectiveness assessments were scarce. **Conclusion:** One promising minimally invasive method for the early diagnosis of breast cancer is liquid biopsy. Especially in LMICs with limited access to mammography, its incorporation into public health screening programmes could increase equity and decrease diagnostic delays. To promote fair worldwide acceptance, extensive prospective trials, health economic analyses, and implementation studies are desperately needed.

Keywords: Breast cancer- Liquid biopsy- Methylation- Fragmentomics- Early detection- Screening- Diagnostics

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Introduction

Breast cancer requires early detection because it remains one of the leading causes of cancer-related mortality among women globally [1, 2]. Despite the fact that early detection often improves survival, timely diagnosis is still not always available. In high-income countries, mammography-based screening programmes have reduced mortality; nonetheless, they have limitations, including false positives, low sensitivity in dense breasts, and expensive infrastructure needs of the screening system [3]. Mammography coverage is frequently less than 20%, and in low and middle-income countries (LMICs), more than 60% of breast cancers are discovered at an advanced stage [3]. The immunohistochemical reports by Fasogbon et al. [2] showed different vitamin D receptor (VDR) expression patterns in triple-negative invasive ductal carcinoma, highlighting biomarker variability that liquid biopsy approaches aim to non-invasively profile. Tissue-level heterogeneity is well documented.

Liquid biopsy, which involves analysing circulating tumour-derived material such as ctDNA, CTCs, or exosomes, is a minimally invasive procedure that may be used to identify early malignancies, track treatment, and direct individualised care [4, 5]. Developments in digital PCR, methylation profiling, and next-generation sequencing (NGS) have improved the sensitivity of identifying tiny tumour fractions [6-8]. In contrast to mammography, liquid biopsy can be included in a variety of health systems and requires less radiological infrastructure. The WHO Global Breast Cancer Initiative (GBCI) is the framework for this study, which summarises the most recent data on liquid biopsy for early breast cancer diagnosis and explores its public health implications, especially in LMIC settings.

Methods

Protocol and registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) declaration was adhered to in this systematic review [9]. A review protocol was developed a priori to guide the methods and reporting. Since no patient-level data were examined, the review was not prospectively registered in PROSPERO.

Eligibility criteria

We included original peer-reviewed and grey-literature studies that met all of the following:

• Population/setting: adult populations in any country setting (low-, middle-, and high-income). Evidence from high-income settings was added, with intensive interpretation on feasibility and implications for LMIC screening programmes.

• Condition: Breast cancer that has been clinically or histologically verified, including early-stage or asymptomatic cases.

• Index test: any liquid biopsy-based biomarker used for screening, early detection, or diagnostic discrimination, including circulating tumor DNA, circulating tumor cells, exosomes, cell-free DNA, RNA, or protein signatures [4, 5].

• Comparator/reference: conventional imaging, histopathology, or clinico-radiological diagnosis.

• Outcomes: diagnostic precision (sensitivity, specificity, AUC) or early detection implementation results.

Exclusions: animal/in vitro studies, metastatic-only cohorts, case reports, editorials, conference abstracts, and non-English papers without translation.

Information sources

The Web of Science Core Collection, PubMed/MEDLINE, Embase (Ovid), and Scopus were the four bibliographic databases that were searched. We looked for grey literature on the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, the European Clinical Trials Register, and the WHO Global Health Library. Relevant reviews and the reference lists of the included publications were manually searched. All searches covered 1 January 2015 to 31 August 2025.

Search strategy

Controlled vocabulary and free-text phrases were integrated in search strings for (1) breast cancer, (2) liquid biopsy biomarkers, (3) early detection, and (4) diagnostic accuracy. The full electronic search strategies for the entire databases are available in the Supplementary Materials. Below is an example of a PubMed strategy:

("breast neoplasms"[MeSH] OR "breast cancer"[tiab]) AND

("liquid biopsy"[tiab] OR "circulating tumor DNA"[tiab] OR ctDNA[tiab]

OR "circulating tumor cells"[tiab] OR exosome*[tiab] OR "cell-free DNA"[tiab]) AND

("early detection"[tiab] OR "screening"[tiab] OR "diagnosis"[tiab]) AND

("sensitivity and specificity"[MeSH] OR accuracy[tiab] OR ROC[tiab])

Selection process

Every record was deduplicated and exported to EndNote v20 (Clarivate Analytics). After screening titles and abstracts in Rayyan (Qatar Computing Research Institute), two impartial reviewers conducted a full-text review in accordance with the inclusion criteria. Third-reviewer arbitration or consensus were used to settle disagreements. The study selection process is summarised in Figure 1 (PRISMA 2020 flow diagram) [9].

Data collection process

A standardized data extraction form (Microsoft Excel) was piloted on five studies. Metadata, nation income group, design, biomarker type, platform, sample size, stage distribution, reference standard, sensitivity/specificity/AUC, and any public-health or implementation metrics were all separately extracted by two reviewers. Discussions were used to settle disagreements.

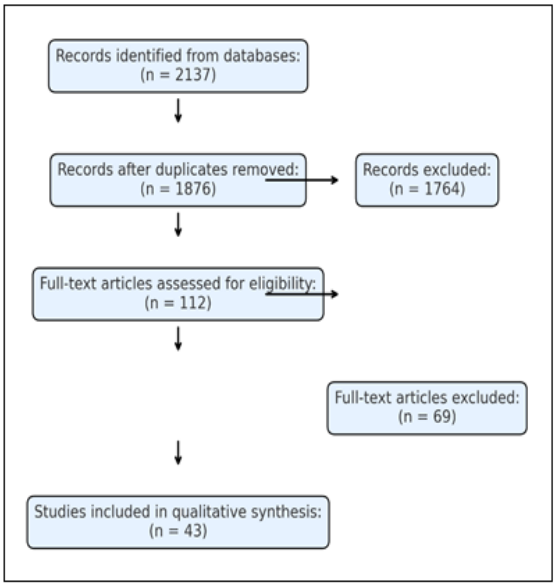

Figure 1. PRISMA 2020 Research Selection Flow Diagram. After searching the database, 2,137 records were discovered. 261 duplicates were eliminated. 1,876 records (duplicates removed) were analyzed. 1,764 title/abstract records were excluded. A total of 112 full-text papers were evaluated for eligibility. 69 full-text articles were excluded. The qualitative synthesis included 43 studies.

Data items

Variables captured included:

• Biomarker type and detection platform;

• Diagnostic performance indices (sensitivity, specificity, AUC with 95 % CI);

• Pre-analytical factors (specimen type, processing time, storage);

• Study context (LMIC region, clinical pathway integration, screening population);

• Health-system variables (cost, infrastructure, workforce requirements).

Study risk-of-bias assessment

QUADAS-2 was used to evaluate diagnostic-accuracy studies, analyzing flow/timing, reference standard, index test, and patient selection [10]. The Joanna Briggs Institute critical-appraisal methods were used to evaluate observational or non-comparative studies [11]. Each domain was given an independent risk rating of low, high, or unclear by two reviewers.

Effect-measure synthesis

When possible, summary medians and ranges were computed in addition to tabulating the sensitivity, specificity, and AUC values. The platforms' heterogeneity precluded the attempt at formal meta-analysis. Findings were categorized using narrative synthesis according to stage, health-system setting, and biomarker type (ctDNA, CTC, exosome). New policy implications were charted against the pillars of the WHO Global Breast Cancer Initiative (GBCI) [27].

Certainty of evidence

The GRADE-CERQual method was used to grade confidence for both qualitative and implementation themes [9, 10]. Risk of bias, consistency, and relevance to LMIC situations were taken into account when interpreting the overall strength of the evidence.

Patient and public involvement

Since this systematic review was based solely on available literature, neither patients nor the general public were engaged in its planning or execution.

Results

Using database searching, 2,137 records were identified. A total of 1,876 records were filtered by title and abstract after duplicates were eliminated. Forty-three (43) papers satisfied the inclusion criteria and were added to the final synthesis after 112 full-text publications were evaluated for eligibility (Figure 1).

Study Characteristics

Forty-three studies that enrolled 42–2,500 people in cohorts that were primarily hospital-based satisfied the inclusion criteria. The majority were case-control studies that examined diagnostic accuracy; a smaller percentage were prospective cohorts that were integrated into actual diagnostic processes. Usually, reference standards included interdisciplinary clinico-radiological consensus or histology (for biopsy/surgical specimens), with index-test interpreters being blinded to varying degrees. The varied reporting of pre-analytical circumstances (such as plasma vs serum, collection tubes, and processing time) and analytic details (such as input cfDNA mass, library preparation, and thresholds) limited the comparability of the studies.

Risk of bias (QUADAS-2)

Reference standards were generally appropriate (histopathology or clinico-radiological consensus), but flow/timing varied (particularly in prospective pathways); index test blinding was reported inconsistently; and patient selection was frequently done using case-control designs with potential spectrum bias. In general, the risk of bias was rated as unclear to high for patient selection in case-control designs, unclear to low for the reference standard domain, and unclear for index test blinding in many reports. With the possible exception of hospital-based cohorts that might not accurately represent population screening settings, applicability problems were largely minimal.

Assays for ctDNA (n=28). Two main ctDNA techniques were assessed in these studies:

• Mutation-based (tumour-informed or tumour-agnostic) profiling, usually employing NGS, ddPCR, or ultra-deep sequencing to identify recurring changes like PIK3CA and TP53 [6, 7, 12].

• Epigenetic tests, particularly of methylation signatures (targeted panels or genome-wide models), and fragmentomics based on whole-genome sequencing in certain reports [8, 13].

Table 1. Representative Studies of Liquid Biopsy for early Breast Cancer Detection (evidence-anchored exemplars)

Biomarker/ approach	Platform	Sample size (cases/controls)	Stage focus	Sensitivity	Specificity	Primary exemplar (footnote)
ctDNA methylation panel	NGS (targeted)	196 / 186	I–III (early-stage enriched)	80%	97%	a
CTCs (functional enrichment + ICC)	BrAD-CTC	548 / 9632 (case-control); 141 suspected (prospective)	Early & mixed	92.1% (case-control); 94.6% (prospective)	100%; 93.1%	b
Exosomal miRNA (miR-1246)	Electrochemical / qPCR	46 / 28	Early & mixed	100%	92.90%	c
Circulating miRNA panel (8-miRNA)	RT-qPCR	~600 (multi-cohort)	Early & mixed	72.20%	91.50%	d
cfDNA fragmentomics	WGS	Multi-cancer cohort with breast subgroup	Mixed (incl. early)	—	—	e
ctDNA tumour-informed (MRD/recurrence)*	Personalized NGS/ ddPCR	Early breast cohorts	Post-op / surveillance	—	—	f

*Note: tumour-informed ctDNA studies do not assess population screening; rather, they assess molecular relapse detection (prognostic/monitoring). a = Moss 2020 (bd-cfDNA methylation panel; 80% sensitivity at 97% specificity) [19]. b = Crook 2022 (BrAD-CTC; 92.1%/100% in case-control; 94.6%/93.1% in a prospective cohort) [15]. c = Zhai 2018 (exosomal miR-1246; 100% sensitivity, 92.9% specificity) [17]. d = Zou 2022 (serum 8-miRNA panel; AUC 0.915; 72.2% sensitivity; 91.5% specificity) [18]. e = Cristiano 2019 (DELFI fragmentomics; multi-cancer method with breast subgroup; report breast metrics as applicable; see Supplementary Table S1 for details) [20]. f = Examples include Garcia-Murillas [15]; Coombes et al. [17]; McDonald et al. [16] demonstrating lead-time molecular relapse detection in early breast cancer cohorts (monitoring context, not screening) [15–17]. Table note. The exemplar studies mentioned are the source of values; case-control and diagnostic-pathway cohorts are included in the designs. See Supplementary Table S1 for additional exemplars (e.g., methylation + fragmentomics, PBMC methylome) and confidence intervals unique to assays and cohorts.

• Nearly all of the sample matrices were plasma. Several studies combined mutation calls with methylation/ fragmentomic features to enhance identification at low tumour fractions [6-8, 12, 13].

Tumour cells in circulation (CTCs; n = 9). For enumeration and immunocytochemistry, CTC investigations employed the CellSearch platform or more recent microfluidic/functional enrichment techniques [14, 15].

Proteomics/exosomes (n = 6). These studies evaluated serum/plasma proteomic signatures and exosomal RNA (including miRNA cargo) utilising mass spectrometry-based systems, targeted assays, or qPCR [16-18].

Diagnostic Performance

While sensitivity varied roughly from 60% to 95% for early-stage illness, specificity was typically >90% across all ctDNA mutation assays [6, 7, 12]. In certain stage I-enriched cohorts, methylation-based panels demonstrated the highest reported sensitivities, up to about 98% [8, 19]. While sensitivity ranged more significantly, ranging from roughly 45% to 80%, CTC-based tests typically showed specificity above 90% [14, 15]. Exosome-based biomarkers looked promising, but the evidence is still sparse and inconsistent, with small sample sizes and non-standardized techniques [17, 18] (Table 1).

Emerging Findings (2019–2025)

According to recent research, molecular relapse can be detected months before clinical or radiological recurrence in early breast cancer cohorts using tumor-informed ctDNA assays [15-17]. Further validation research indicates that multi-omic integration, including fragmentomics and methylation, enhances diagnostic discrimination and tissue-of-origin prediction [8, 20]. Health-system trials, as those carried out within NHS England, show the practical viability of liquid biopsy-supported diagnostic pathways and decreased time to treatment decisions, despite not being intended as population screening programs [21].

Discussion

Liquid biopsy has great potential as a minimally invasive method for the early identification of breast cancer, as this systematic review shows. The majority of research examined ctDNA, and assays based on mutation and methylation routinely showed good specificity (>90%) and sensitivity between 60% and 98% [6-8, 12]. These results are in line with other assessments that showed ctDNA can be a valid biomarker for recurrence risk and minimal residual disease [22, 23]. Crucially, methylation-based panels addressed one of mammography's major drawbacks: decreased sensitivity in early-stage disease and in women with dense breast tissue [3, 24, 25].

Strengths and Limitations of the Evidence

The most researched analyte is ctDNA; however, complementary methods like exosomal profiling and CTC enumeration also show potential. However, many of these studies were varied in design, small-scale, and single-centre, making meta-analysis impossible. Cross-study comparisons become more difficult when assays are not standardised across laboratories [12]. Additionally, the majority of research was carried out in high-income environments, and there is little data from LMICs, where late-stage breast cancer has the highest public health burden [1, 26].

Public Health Implications

The WHO Guide to early cancer diagnosis [24] and the Global Breast Cancer Initiative [27] emphasise the importance of timely detection and diagnosis, especially in resource-constrained settings. Mammography remains the cornerstone of screening in high-income countries, but it is resource-intensive, requires radiological infrastructure, and is less effective in younger women. In contrast, liquid biopsy offers a blood-based test that could be deployed in primary health care, potentially expanding coverage where mammography programmes are infeasible [3, 26, 28].

Health Systems and Equity Considerations

Implementation of liquid biopsy within public health programmes requires more than technical validation. Laboratory infrastructure, trained personnel, supply chains, and quality assurance must be in place [27, 29]. Without deliberate efforts to ensure affordability, there is a risk that liquid biopsy will widen existing inequities in cancer outcomes, disproportionately benefiting high-resource settings while leaving LMIC populations behind [24, 26]. Experiences from the NHS England pilot, where liquid biopsy reduced diagnostic turnaround times by 16 days, highlight the feasibility but also the need for equitable global access strategies [21].

Ethical and Social Considerations

The use of early detection technologies presents ethical dilemmas. Health systems may experience stress due to overdiagnosis and overtreatment. Lessons from mammography overuse and prostate-specific antigen (PSA) testing highlight the dangers of introducing new screening technologies in the absence of strong proof of their overall benefits [30, 31].

Research Priorities

Conducting extensive, prospective validation studies across a variety of populations is one of the top research priorities, especially in low- and middle-income nation settings [22, 23, 26]. In health systems with limited resources, comparative studies and reliable cost-effectiveness modeling are required to evaluate liquid biopsy as an alternative or supplement to mammography [24, 28, 29]. To guarantee equitable access and prevent growing worldwide disparities, implementation studies should concentrate on integration into national cancer control programs, workforce training, and equity-sensitive deployment strategies [26, 27, 29].

Policy Relevance

As the three pillars of breast cancer control, the WHO GBCI advocates for increasing early detection, prompt diagnosis, and all-encompassing therapy [27]. All three could be influenced by liquid biopsies. In addition to lowering care expenses related to late-stage disease, moving the diagnosis to earlier stages may lower mortality by permitting curative therapy. However, to guarantee fair implementation globally, attaining these advantages will necessitate international cooperation, funding for LMIC research capacity, and unambiguous policy advice from WHO and IARC [26, 29].

In conclusion, Implications for practice

• Liquid biopsy provides a less intrusive method with promising sensitivity and high specificity for the identification of early-stage breast cancer.

• It may decrease false positives and increase diagnostic accuracy when used in conjunction with mammography, particularly in women with dense breasts.

• Expanding early detection services in LMICs, where mammography coverage is limited, may be possible with liquid biopsy.

Implications for policy

• WHO's Global Breast Cancer Initiative framework should serve as a roadmap for integrating liquid biopsy into country cancer control programmes [27].

• By negotiating reasonable prices, making investments in laboratory equipment, and integrating quality assurance mechanisms, policymakers can guarantee equal access.

• To prevent growing global disparities, early adoption should give priority to high-risk groups and health systems with diagnostic gaps.

Implications for research

• To confirm liquid biopsy's diagnostic efficacy in a variety of contexts, including LMICs, extensive prospective population-based research is required [22, 23, 26].

• Cost-effectiveness in comparison to mammography and combination screening methods should be ascertained through health economic studies.

• Research on implementation should look at workforce training, integration into primary care pathways, and practical viability.

• Research with an equity focus should evaluate whether liquid biopsy lessens or increases inequalities in cancer outcomes.

Competing interests

The authors declare no competing interests.

Ethics statement

Not applicable (systematic review of published data).

Protocol registration

Not registered.

Data availability

All data relevant to this study are included in the article and in Supplementary Table S1.

Supplementary Materials

Supplementary Table S1 (uploaded with the manuscript submission: Characteristics and diagnostic performance of included liquid biopsy studies for early breast cancer detection (n = 43).

• Part A: Study metadata and assay details (author, year, country/setting, biomarker class, assay/platform, targets/panels, sample size, and stage focus).

• Part B: Performance metrics and bibliographic

identifiers (sensitivity, specificity, AUC, PMID, DOI, and verification status).

Author contributions

Samuel Ayobami FASOGBON: Conceptualization, Methodology, Literature search, Data extraction, Formal analysis, Writing – original draft, Supervision, Project administration, Correspondence. Olumide Faith AJANI: Data curation, risk-of-bias, Literature review, Writing – review & editing. Akinpelu MORONKEJI: Screening, Validation, References, Writing – review & editing. Oluwadamilola Janet OLATUNDE: Resources, Data verification, Writing – review & editing. Comfort E. WILLIAMS: Literature search, Writing – review & editing. Ima Obot JIMMY: Resources, Writing – review & editing. Kevin ODEGA: Data interpretation, Writing – review & editing. Bob-Manuel Chinonso OSUJI: Validation, Writing – review & editing. Precious Oluwamosope OKUNOLA: References, Writing – review & editing. Peter O. OBAMI: Formal analysis, Writing – review & editing. Rofiah Busayo OLAYINKA: Data curation, Writing – review & editing. Afamefuna Cyril EGBO: Visualization, Figures, Writing – review & editing. Sagir SANI: Formatting, Writing – review & editing. Chimnaza C. NKWAM-UWAOMA: Formatting, Writing – review & editing. Iniobong Anselem UDO: Formatting, Writing – review & editing.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 05;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Fasogbon SA, Okechi OO, Adisa JO, Madukwe JU. Immunohistochemical Correlation between the Expression of Vitamin D receptor (VDR) and Triple Negative Invasive Ductal Carcinoma Tissues. American Journal of Biomedical Sciences. 2017 Oct;:237-243. https://doi.org/10.5099/aj170400237
3. Ginsburg O, Yip C, Brooks A, Cabanes A, Caleffi M, Dunstan Yataco JA, Gyawali B, et al. Breast cancer early detection: A phased approach to implementation. Cancer. 2020 05 15;126(S10):2379-2393. https://doi.org/10.1002/cncr.32887
4. Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, Pacey S, Baird R, Rosenfeld N. Liquid biopsies come of age: towards implementation of circulating tumour DNA. Nature Reviews. Cancer. 2017 04;17(4):223-238. https://doi.org/10.1038/nrc.2017.7
5. Chen M, Zhao H. Next-generation sequencing in liquid biopsy: cancer screening and early detection. Human Genomics. 2019 08 01;13(1):34. https://doi.org/10.1186/s40246-019-0220-8
6. Dawson S, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin S, Dunning MJ, et al. Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer. New England Journal of Medicine. 2013 03 28;368(13):1199-1209. https://doi.org/10.1056/NEJMoa1213261
7. Reinert T, Henriksen TV, Christensen E, Sharma S, Salari R, Sethi H, Knudsen M, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. JAMA Oncology. 2019 08 01;5(8):1124. https://doi.org/10.1001/jamaoncol.2019.0528
8. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2020 06;31(6):745-759. https://doi.org/10.1016/j.annonc.2020.02.011
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed.). 2021 03 29;372:n71. https://doi.org/10.1136/bmj.n71
10. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine. 2011 Oct 18;155(8):529-536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
11. Hall PS, Mitchell ED, Smith AF, Cairns DA, Messenger M, Hutchinson M, Wright J, et al. The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation. Health Technology Assessment (Winchester, England). 2018 05;22(32):1-274. https://doi.org/10.3310/hta22320
12. Easaw S, Hsu J, Steuerwald N, Heeke AL. Liquid clues: tracking early-stage breast cancer with ctDNA - a mini review. Frontiers in Oncology. 2025;15:1634859. https://doi.org/10.3389/fonc.2025.1634859
13. Mathios D, Johansen J, Cristiano S. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun. 2021;12(5060). https://doi.org/10.1038/s41467-021-24994-w.
14. Cristofanilli M, Budd G, Ellis M. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med. 2004;351(8):781–791. https://doi.org/10.1056/NEJMoa040766.
15. Garcia-Murillas I, Schiavon G, Weigelt B. Mutation tracking in circulating tumour DNA predicts relapse in early breast cancer. Sci Transl Med. 2015;7(302). https://doi.org/10.1126/scitranslmed.aab0021.
16. McDonald B, Contente-Cuomo T, Sammut S. Personalized circulating tumour DNA analysis to detect residual disease after neoadjuvant therapy in breast cancer. Sci Transl Med. 2020;11(504). https://doi.org/10.1126/scitranslmed.aax7392.
17. Coombes R, Page K, Salari R. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence. Clin Cancer Res. 2019;25(14):4255–4263. https://doi.org/10.1158/1078-0432.CCR-18-3663.
18. Garcia-Murillas I, Chopra N, Comino-Méndez I. Assessment of molecular relapse detection in early-stage breast cancer using circulating tumor DNA analysis. JAMA Oncol. 2019;5(10):1473–1478. https://doi.org/10.1001/jamaoncol.2019.1838.

19. Moss J, Zick A, Grinshpun A. Circulating breast-derived DNA allows universal detection and monitoring of localized breast cancer. Ann Oncol. 2020;31:395–403. https://doi.org/10.1016/j.annonc.2019.11.014.
20. Cristiano S, Leal A, Phallen J. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature. 2019;570:385–389. https://doi.org/10.1038/s41586-019-1272-6.
21. Wise J. Liquid biopsy for lung and breast cancers becomes available across the NHS in England. BMJ. 2025;389:r1130. https://doi.org/10.1136/bmj.r1130.
22. Parsons H, Rhoades J, Reed S. Sensitive detection of minimal residual disease in patients treated for early-stage breast cancer. Clin Cancer Res. 2020;26(11):2556–2564. https://doi.org/10.1158/1078-0432.CCR-19-2500.
23. Tie J, Cohen J, Wang Y. Circulating tumor DNA analyses as markers of recurrence risk and benefit of adjuvant therapy for stage III colon cancer. JAMA Oncol. 2019;5(12):1710–1717. https://doi.org/10.1001/jamaoncol.2019.3616
24. World Health Organization. Guide to cancer early diagnosis. Geneva: WHO; 2017. URL: https://iris.who.int/handle/10665/254500 Accessed 30 September 2025...
25. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, Straif K. Breast-cancer screening--viewpoint of the IARC Working Group. The New England Journal of Medicine. 2015 06 11;372(24):2353-2358. https://doi.org/10.1056/NEJMsr1504363
26. World Health Organization. Breast cancer: key facts. 2025. URL: https://www.who.int/news-room/fact-sheets/detail/breast-cancer Accessed 30 September 2025.
27. World Health Organization. Global breast cancer initiative implementation framework: assessing, strengthening and scaling up of services for the early detection and management of breast cancer. Geneva: WHO; 2023. URL: https://www.who.int/publications/i/item/9789240065987 Accessed 30 September 2025..
28. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. International Journal of Cancer. 2021 04 05;. https://doi.org/10.1002/ijc.33588
29. International Agency for Research on Cancer (IARC). World Cancer Report 2020. Lyon: IARC; 2020. URL: https://publications.iarc.fr/586 Accessed 30 September 2025..
30. Mukherjee BS. The catch in catching cancer early. The New Yorker. 2025 Jun 23. URL: https://www.newyorker.com/magazine/2025/06/23/the-catch-in-catching-cancer-early Accessed 30 September 2025..
31. International Agency for Research on Cancer (IARC). IARC Handbooks of Cancer Prevention, Volume 15: Breast Cancer Screening. Lyon: IARC; 2016. URL: https://publications.iarc.who.int/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Breast-Cancer-Screening-2016 Accessed 30 September 2025.