

Comparative Efficacy of Liquid Biopsies Versus Traditional Methods for Early Cancer Detection

Aaryan Kumar

American High School, Fremont, California, United States of America

Abstract

Colorectal cancer, breast cancer, and oral cancer are among the most common cancers worldwide and together represent a substantial share of global cancer mortality, though outcomes vary considerably by cancer type. For example, breast cancer has comparatively favorable survival in most settings, while colorectal and oral cancers carry a higher case-fatality burden (Bray et al., 2024). One of the ways to reduce the mortality rate associated with these cancers is through early detection. Unfortunately, the current methods used to detect cancer are plagued by issues including limited sensitivity, high expense, and patient discomfort. Together these issues contribute to delayed diagnosis and lost time. Therefore, in order to find a better method to detect cancer prior to metastasis, this study conducted a structured narrative review informed by PRISMA reporting principles (e.g., a systematic search strategy and flow diagram), without a registered protocol, formal risk-of-bias assessment, or meta-analysis, to assess a new emerging type of cancer detection. The findings demonstrated that while traditional methods are still considered the clinical standard for cancer screening, liquid biopsies show promising diagnostic performance in specific contexts, particularly in terms of specificity and sensitivity. For example, circulating tumor DNA (ctDNA)-based assays for breast cancer frequently reported sensitivities above 85% and specificities approaching or exceeding 95%, performance that in some contexts approaches mammography (sensitivity approximately 60%). ctDNA-based assays for colorectal cancer showed similarly high specificity (approximately 98 to 99%) but lower sensitivity for primary detection (approximately 65%), with sensitivity exceeding 85% reported specifically for detecting recurrence during post-treatment surveillance rather than initial diagnosis. Colonoscopy remains the more sensitive method for initial detection (sensitivity 98.5%; Yaghoobi et al., 2023), though considerably more invasive. Similarly, salivary biomarkers such as miR-210 and extracellular vesicle-derived microRNAs showed promising diagnostic accuracy for oral cancer, an area where traditional visual examination and autofluorescence techniques often show comparatively low specificity. However, the reliability of liquid biopsy findings varied considerably by cancer subtype and biomarker type, and few studies directly compared liquid biopsy against traditional methods within the same patient population.

Keywords: liquid biopsy, early cancer detection, ctDNA, diagnostic accuracy, non-invasive cancer screening, biomarkers, comparative effectiveness

1. Introduction

Recently there have been developments in the field of medicine related to liquid biopsies that may lead to improved early detection of cancer. Liquid biopsies are minimally invasive diagnostic tests that analyze a patient's blood, saliva, or other bodily fluids for tumor-derived material, in contrast to a traditional tissue biopsy, which requires a surgical sample (Pantel & Alix-Panabières, 2013). Conventional methods of detecting cancer include imaging techniques such as CT scans and MRI, laboratory-based testing, and physical examination. While these methods remain the primary means of diagnosing cancer, they carry several significant drawbacks, namely their invasive nature and high cost. Moreover, these methods may have limitations in detecting certain cancers at very early stages depending on modality and tumor characteristics (Pantel & Alix-Panabières, 2013).

Conversely, liquid biopsies offer potential advantages as they measure circulating tumor DNA (ctDNA), circulating tumor cells (CTCs) and other biomarkers present in blood samples. Liquid biopsies provide a potentially safer and more practical alternative than conventional methods for managing patients and facilitating early detection.

The clinical value of liquid biopsies is based on the numerous data points that can be collected from blood samples. Specifically, liquid biopsies measure the presence of circulating tumor DNA (ctDNA), which refers to short fragments of tumor-derived DNA that indicate mutations, copy number variations and methylation alterations. Tumor cells shed ctDNA into the bloodstream primarily through cell death (apoptosis and necrosis), which releases DNA fragments carrying the same mutations found in the original tumor; detecting these mutations in a blood sample can therefore indicate the presence of cancer without requiring a sample of the tumor tissue itself. Additionally, circulating tumor cells (CTCs) refer to intact malignant cells that break away from a tumor and enter the bloodstream, allowing for both molecular characterization and enumeration (Alix-Panabières et al., 2023); because these cells retain the physical and genetic characteristics of the original tumor, they can potentially be identified and counted directly, unlike ctDNA fragments. Finally, liquid biopsies can also quantify exosomes/extracellular vesicles (EVs), which are nanoscale vesicles released by tumor cells that carry nucleic acids, proteins, and metabolites reflecting the tumor's molecular profile; because EVs are released continuously and are relatively stable in bodily fluids, they offer another route for detecting tumor-derived signals outside of ctDNA or CTCs.

For decades, cancer screening has been widely practiced despite continued problems associated with traditional cancer screening methods. For example, mammography often produces overdiagnosis and false positive results. Studies have shown that up to 12% of women undergo abnormal mammography results but only approximately 5% of these cases result in cancer, and over a ten-year period of annual mammography screenings, 61% of women experience at least one false positive mammogram resulting in additional follow-up screening (Brill, 2020).

These three cancer types were selected because they are among the most prevalent cancers worldwide, each currently relies on an established but imperfect traditional screening method, and each has an expanding body of liquid biopsy research available for comparison. These newer forms of liquid biopsy technology (focused on ctDNA, CTC, miRNA, and salivary exosomes) show promise for increasing patient adherence, reducing diagnostic delay and identifying cancer in earlier stages when treatment is more effective. However, the relative efficacy of liquid biopsy technology compared to established "gold standard" screening and detection modalities continues to be investigated. This review addresses the question: How do adult populations at risk for developing colorectal, breast, oral cancer (population) utilize liquid biopsy



screening and detection methods (index test) when compared to traditional screening and detection modalities (comparators) regarding sensitivity, specificity, early detection, and patient compliance (outcomes)? Given the variability in study design and biomarker methodologies across the literature, this study adopts a structured narrative review approach to synthesize and interpret current evidence.

2. Methods

2.1. Search Strategy

This review sought to identify studies comparing the diagnostic performance of liquid biopsy techniques (ctDNA, CTCs, and salivary/extracellular vesicle biomarkers) against traditional detection methods (mammography, colonoscopy, tissue biopsy, and visual/clinical examination) for breast, colorectal, and oral cancer. As this is a narrative review rather than a full systematic review, no protocol was registered in advance. However, a structured literature search of several high-quality databases was conducted using structured search strategies to identify relevant and up-to-date literature, guided by the following search terms:

("Liquid Biopsy Cancer Detection" OR "Circulating Tumor DNA Early Detection" OR "Traditional Cancer Screening Comparison" OR "ctDNA Sensitivity Specificity" OR "Liquid vs Tissue Biopsy Accuracy" OR "Non-Invasive Cancer Diagnosis" OR "Liquid Biopsy" OR ctDNA OR "Circulating Tumor DNA" OR "Cell-Free DNA" OR cfDNA) AND (Breast OR Colorectal OR Colon OR Oral OR "Head And Neck") AND ("Early Detection" OR Screening OR Stage I OR "Stage II")

Using this strategy, the initial search yielded 2,847 records from database searching, plus 156 additional records identified through other sources. After removal of duplicates, 2,634 records remained for title/abstract screening. Following full-text review and application of inclusion criteria, 122 full-text articles were assessed for eligibility, and 25 studies were included in the final analysis (12 of which were liquid biopsy studies). All of the primary databases that were searched are listed below. Those include:

1. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>): July 9, 2025 – Aug 13, 2025.
2. ScienceDirect (<https://www.sciencedirect.com/>): July 10, 2025 – Aug 2, 2025.
3. Google Scholar (<https://scholar.google.com/>): July 15, 2025 – July 20, 2025.
4. The National Cancer Institute's Research Database (<https://www.cancer.gov/research>): July 13, 2025 – August 12, 2025.

Also, ongoing clinical trials related to the topic of interest were identified via ClinicalTrials.gov (<https://clinicaltrials.gov/>) [July 30, 2025–August 4, 2025] in order to identify potential future developments. Each database was searched once at the start of the review period; the date ranges above reflect the total window during which searches, screening, and reference checks were conducted across databases, rather than repeated re-runs of the same search.

This study is a structured narrative review, not a systematic review: it adopts PRISMA-style reporting tools including a



systematic search strategy, explicit inclusion and exclusion criteria, and a study-selection flow diagram for transparency, but does not include a registered protocol, a formal risk-of-bias assessment (QUADAS-2 or GRADE framework), or a quantitative meta-analysis. A narrative synthesis was chosen instead of a meta-analysis because included studies varied substantially in cancer type, biomarker, outcome definitions, and reporting standards, making pooled quantitative comparison inappropriate.

A PRISMA-style flow diagram was used to illustrate the study selection process, while maintaining the flexibility of a narrative review framework. See Figure 1.

Cancer Screening Methods: Liquid Biopsy vs. Traditional Methods

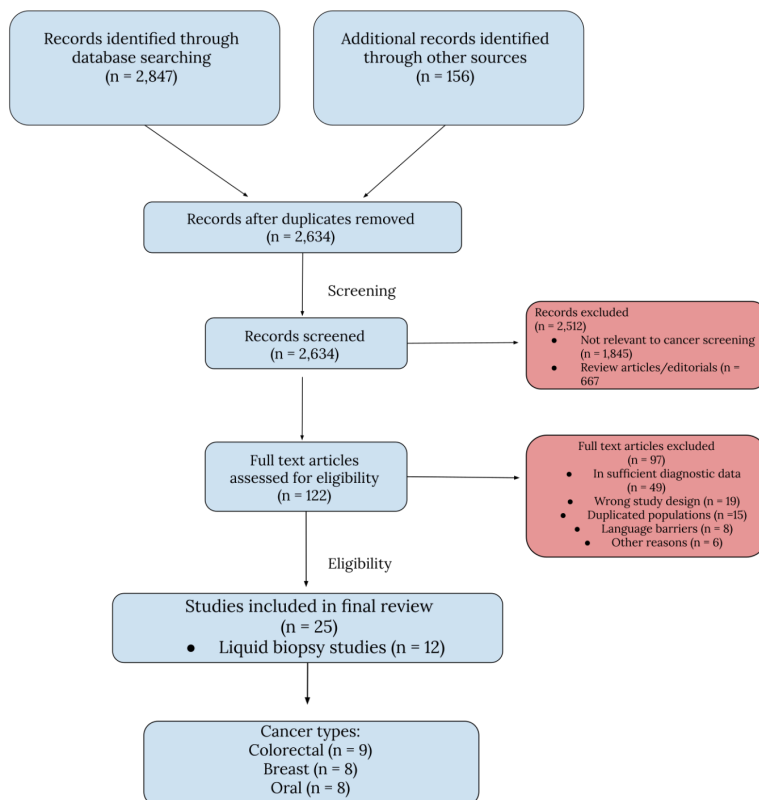


Figure 1: Study selection flow diagram for the narrative review comparing liquid biopsy and traditional cancer detection methods.

Records were identified through database searching ($n = 2,847$) and other sources ($n = 156$), then de-duplicated to 2,634 records. All 2,634 were screened by title/abstract, excluding 2,512 as not relevant to cancer screening or as review articles/editorials. The remaining 122 full-text articles were assessed for eligibility; 97 were excluded for insufficient diagnostic data, wrong study design, duplicated populations, language barriers, or other reasons. The final 25 studies were

included in the review (12 liquid biopsy studies), spanning colorectal (n = 9), breast (n = 8), and oral (n = 8) cancer.

2.2. Inclusion Criteria

The goal of ensuring high-quality, clinically relevant research was addressed by using defined inclusion criteria. The studies needed to be published between 2014–2025 in order to identify both early-stage liquid biopsy research as well as current developments. Since all articles in this review were written in English, were accessible online (full-text), and were found within a journal article or institutional publication from a reputable publisher, they met this criterion. Articles focusing on quantifiable diagnostic metrics (sensitivity, specificity, etc.) regarding clinical performance of liquid biopsy techniques (liquid biopsy techniques include but are not limited to, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs); liquid biopsy may also use nanoparticles to enhance assay sensitivity), as well as standard cancer screening modalities in colorectal, breast and oral cancers; articles evaluating non-clinical laboratory-based data with no corresponding clinical evidence were excluded.

2.3. Data Synthesis

These results came from a narrative review process to synthesize and interpret trends in diagnostic performance across different cancer detection methods, consistent with approaches used in prior comparative reviews of liquid biopsy technologies (Alix-Panabières et al., 2023). There were several types of statistical data collected in this study. Sensitivity refers to a test's ability to correctly identify patients who actually have cancer, meaning a highly sensitive test produces few false negatives. Specificity refers to a test's ability to correctly identify patients who do not have cancer, meaning a highly specific test produces few false positives. These two measures capture different types of error and are independent of one another: a highly sensitive test minimizes missed cancers at the potential cost of more false alarms, while a highly specific test minimizes false alarms at the potential cost of missing some true cases. A test can therefore be strong on one measure and weak on the other, which is why both are reported together throughout this review rather than either alone. Area Under the Curve (AUC) summarizes a test's overall diagnostic accuracy across all possible decision thresholds on a scale from 0.5 (no better than random chance) to 1.0 (perfect discrimination); as a general guide, an AUC below approximately 0.7 is considered weak, around 0.8 is considered good, and above 0.9 is considered excellent. Positive Predictive Value (PPV) indicates the probability that a patient who tests positive actually has cancer, while Negative Predictive Value (NPV) indicates the probability that a patient who tests negative is actually cancer-free; unlike sensitivity and specificity, both PPV and NPV are influenced by how common the cancer is in the population being tested. These five metrics collectively serve as the standard framework for evaluating and comparing diagnostic test performance, and were therefore used to assess both liquid biopsy and traditional detection methods in this review. Additionally, each type of these statistics were examined for the three separate cancers. They were then combined using an integrative approach that enabled a qualitative comparison and interpretation of trends between liquid biopsy and traditional cancer detection methods.

3. Results

The sensitivity and specificity figures reported below for each cancer type are drawn from separate single-arm studies conducted in different patient populations rather than from head-to-head trials, and therefore should not be interpreted as direct statistical comparisons between methods. Many of the liquid biopsy studies in particular relied on relatively small sample sizes or enriched patient cohorts, which may limit the generalizability of these findings to routine screening



settings. This caveat applies across all three cancer types discussed and is not repeated at each instance below.

Breast, colorectal, and oral cancers were selected for comparison not simply because of their high global incidence, but because each presents a distinct screening landscape that liquid biopsy could address differently. Breast cancer already has an established, population-level screening program in most developed countries, with routine mammography recommended for women over 50; the relevant question for liquid biopsy here is therefore whether it can improve upon or complement an already-functioning system, particularly for patients with dense breast tissue or higher-risk subtypes for whom mammography underperforms. Colorectal cancer similarly has a well-established gold-standard screening method, colonoscopy, but one limited by low patient compliance due to its invasiveness and the need for bowel preparation; liquid biopsy and stool-based tests are therefore positioned as ways to improve screening uptake rather than replace an already highly accurate test. Oral cancer, by contrast, has no organized population-level screening program in most countries despite carrying a substantial mortality burden, and is instead detected opportunistically through visual examination during routine dental or medical visits; liquid biopsy in this context represents a potential first step toward establishing systematic early detection where none currently exists. These differences in screening infrastructure, rather than incidence alone, motivate treating each cancer as a distinct case throughout this review.

3.1. Liquid Biopsy Detection Mechanisms

Before discussing performance by cancer type, it is worth briefly explaining how each liquid biopsy component is actually detected. ctDNA is typically identified using PCR-based methods, such as digital droplet PCR or next-generation sequencing, which can detect tumor-specific mutations even when they make up a very small fraction of the total DNA in a blood sample. CTCs are isolated using either their physical properties, such as their larger size compared to normal blood cells, or biological markers, such as EpCAM, a protein expressed on the surface of most epithelial tumor cells but absent from normal blood cells; this distinction allows CTCs to be separated and confirmed as tumor-derived even though they are vastly outnumbered by normal blood cells in circulation (Pantel & Alix-Panabières, 2013). EVs are typically isolated through ultracentrifugation or affinity-based capture methods and are then analyzed for the nucleic acids, proteins, or microRNAs they carry, which reflect the molecular profile of the tumor cells that released them.

3.2. Breast Cancer

Traditional Detection Methods

Traditional methods of breast cancer diagnosis have shown varying degrees of reliability when compared. The most commonly used form of screening is mammography; however, mammography has demonstrated sensitivity at 60% and specificity at 80%, and an area under the curve (AUC) of 0.73; these values indicate that mammography's diagnostic performance, while clinically established, is comparatively limited (Fitzjohn et al., 2023). Due to anatomical limitations, ultrasound offers an additional modality for obtaining images. Specifically, ultrasound can provide additional image information in individuals whose mammograms were difficult to interpret due to body type or other limiting factors, with ultrasound demonstrating significantly higher sensitivity than mammography alone, and the combination of mammography and ultrasound increasing detection sensitivity to 93.3% (Chen et al., 2021). Traditional methods also include magnetic resonance imaging (MRI); MRI is the most sensitive method, with sensitivity ranging from 71 to 100% and specificity ranging from 81 to 98% in high-risk screening cohorts (Sardanelli et al., 2024). Combining mammography with clinical



breast examinations results in improved detection rates; specifically, using both mammography and clinical breast examination in parallel achieved the highest sensitivity of the modalities studied (95.6%, compared with 78.3% for mammography alone), though typically at some cost to specificity. As such, the combination of multiple traditional approaches appears to be effective in increasing detection sensitivity (Alba et al., 2018). A comparison of these traditional methods alongside liquid biopsy performance is provided in Table 1.

Table 1: Comparative diagnostic performance of traditional and liquid biopsy detection methods for breast cancer.

Method	Sensitivity	Specificity	Advantages	Limitations	Reference
Mammography	60%	80% (AUC 0.73)	Widely available; established standard-of-care	Comparatively limited diagnostic performance; misses a substantial portion of tumors	Fitzjohn et al., 2023
Mammography + Ultrasound	93.3% (combined)	Not reported	Additional imaging value for dense breast tissue	Specificity not separately reported for ultrasound alone	Chen et al., 2021
MRI	71–100% (range as reported in source)	81–98% (range as reported in source)	Highest sensitivity of traditional methods	Costly; not designed for longitudinal monitoring; reserved for high-risk patients	Sardanelli et al., 2024
Mammography + Clinical Breast Exam	95.6% (vs. 78.3% mammography alone)	–	Highest sensitivity among traditional combinations	Typically at some cost to specificity	Alba et al., 2018
PIK3CA mutation detection (cfDNA)	86–91%	98%	Minimally invasive; enables ongoing monitoring	Performance varies by subtype (lower in luminal breast cancer)	Zhou et al., 2016



Method	Sensitivity	Specificity	Advantages	Limitations	Reference
AnchorIRIS cfDNA assay	89.37%	100%	Minimally invasive; highest specificity of liquid biopsy studies reviewed	Single-study result; not yet independently replicated	Zhang et al., 2021

Note. All values are reported exactly as stated in the cited sources; ranges reflect genuine variability reported in the original studies rather than approximation.

Liquid Biopsy Detection

The literature suggests that liquid biopsies represent a viable method for detecting and monitoring breast cancer through their relatively high sensitivity, specificity, and diagnostic accuracy. For example, PIK3CA is one of the most frequently mutated genes in breast cancer, and detecting its mutations in circulating cell-free DNA (cfDNA) offers a way to identify tumors carrying this alteration without a tissue sample; cfDNA refers to all DNA fragments freely circulating in the blood, most of which come from normal cell turnover, whereas ctDNA specifically denotes the tumor-derived subset of cfDNA carrying cancer-associated mutations. Assays such as this one detect ctDNA by testing a cfDNA sample and identifying which fragments carry the cancer-specific mutation. However, PIK3CA mutations are present in only about 30–40% of breast cancers overall (Keraite et al., 2020), meaning this marker alone would miss the majority of tumors that do not carry the mutation; a reliable liquid biopsy strategy for universal breast cancer detection would therefore need to test for a panel of biomarkers covering multiple mutation types, rather than relying on any single marker such as PIK3CA. A systematic review specifically focused on detecting PIK3CA mutations this way noted that sensitivity ranged from 86% to 91%, while specificity was 98%. This suggests the capability of liquid biopsies to indicate the presence of a tumor's mutation status in a significant proportion of breast cancer patients (Zhou et al., 2016). An additional diagnostic study evaluating the "AnchorIRIS" cfDNA assay found that this assay exhibited a sensitivity of 89.37% and a specificity of 100% in differentiating malignant disease from normal tissue, further validating its use as a diagnostic device and the ability to limit false positives (Zhang et al., 2021). This specificity is the highest reported among the breast cancer liquid biopsy studies included in this review, though as a single-study result it should be interpreted cautiously pending validation in larger, independent cohorts. Beyond sensitivity and specificity, liquid biopsies are also significantly less invasive than traditional tissue biopsies; as opposed to requiring a tissue sample extraction, only a blood or urine sample is required. On the other hand, the invasive nature of tissue biopsies may deter some patients from participating in screening for certain types of cancer. However, various patient-specific risk factors exist that affect the reliability of liquid biopsies. For instance, there exists variation in the detection sensitivity among different subtypes of breast cancer. Specifically, tumors classified as HER2-positive (tumors that overexpress the HER2 growth-promoting protein) and triple-negative (tumors lacking estrogen, progesterone, and HER2 receptors) breast cancers produce more circulating tumor DNA (ctDNA) in the bloodstream resulting in greater detection rates of these tumors. Prior studies have reported ctDNA detection rates at diagnosis ranging from 45 to 50% in hormone receptor-positive and HER2-negative breast cancer to 91% in triple-negative breast cancer, illustrating this



subtype-dependent variability; a more recent whole-genome-sequencing-based assay has since improved detection to 98% across all subtypes, suggesting this variability is a solvable technical limitation rather than a fixed biological ceiling (Garcia-Murillas et al., 2025). These findings are summarized in Table 2.

Table 2: Diagnostic performance of liquid biopsy biomarkers for breast cancer detection.

Biomarker/Method	Study Context	Metric	Value	Reference
PIK3CA mutation detection (cfDNA)	Meta-analysis of cfDNA mutation detection in breast cancer	Sensitivity	86-91%	Zhou et al., 2016
PIK3CA mutation detection (cfDNA)	Meta-analysis of cfDNA mutation detection in breast cancer	Specificity	98%	Zhou et al., 2016
AnchorIRIS cfDNA assay	Clinical evaluation of methylation-based cfDNA assay	Sensitivity	89.37%	Zhang et al., 2021
AnchorIRIS cfDNA assay	Clinical evaluation of methylation-based cfDNA assay	Specificity	100%	Zhang et al., 2021
ctDNA detection – HR+/HER2-negative subtype (prior assays)	Rates reported in earlier literature, cited by Garcia-Murillas et al.	Detection rate	45-50%	Garcia-Murillas et al., 2025
ctDNA detection – Triple-negative subtype (prior assays)	Rates reported in earlier literature, cited by Garcia-Murillas et al.	Detection Rate	91%	Garcia-Murillas et al., 2025



Biomarker/Method	Study Context	Metric	Value	Reference
ctDNA detection – all subtypes (WGS-powered assay)	Whole-genome-sequencing-powered ctDNA assay	Detection rate	98%	Garcia-Murillas et al., 2025

Note. Sensitivity and specificity are reported for assay-level studies (PIK3CA, AnchorIRIS); detection rate is reported for subtype-specific ctDNA shedding, since specificity is not a meaningful metric when comparing tumor subtypes rather than cancer-versus-no-cancer status. The 45–50% and 91% rates reflect earlier-generation assays as summarized in Garcia-Murillas et al. (2025); the same study's own whole-genome-sequencing-powered assay achieved 98% detection across all subtypes. Note that PIK3CA's reported sensitivity and specificity apply only to the ~30–40% of breast cancers that carry a PIK3CA mutation (Keraite et al., 2020); it is not a universal breast cancer marker.

3.3. Oral Cancer

Traditional Detection Methods

The majority of traditional oral cancer detection methods are either visually dependent or require the application of chemical dyes to be able to identify potential cancers. Specifically, visual inspection conducted by trained medical professionals has shown high degrees of sensitivity and specificity. In fact, studies have demonstrated that, depending on the experience level of the clinician conducting the visual examination, a pooled meta-analysis estimate found a sensitivity of 71% and specificity of 85% for conventional oral examination, though individual study estimates vary depending on clinician experience (Essat et al., 2022). However, these values show significant variability depending on both the experience level of the examining professional and how the cancer presents itself within the mouth. The addition of Toluidine Blue dye enhances the detection capabilities for dysplastic tissue; when compared with clinical examination alone across four studies, toluidine blue achieved a sensitivity of 89.1% and specificity of 73.9% (Kim et al., 2021). Although, it is worth noting that this dye may result in false positive results when used alone due to inflammatory responses. Additionally, autofluorescence and chemiluminescence devices are capable of detecting oral premalignant and malignant lesions without an invasive biopsy. These types of technology demonstrate highly variable diagnostic performance: autofluorescence sensitivity has been reported from 22 to 100% with specificity from 16 to 100%, while chemiluminescence sensitivity has ranged from 77.1 to 100% with specificity as low as 0 to 27.8% (Nagi et al., 2016). As a result, they can be utilized as supplementary tools; however, they would be incapable of identifying oral cancers on their own. Historically, biopsy has been considered the gold standard for oral cancer diagnosis, since histopathological examination serves as the reference standard against which other diagnostic methods are measured, making it definitionally reliable (Cristaldi et al., 2019). However, its invasiveness and cost make it less than ideal for large-scale screening purposes (Cristaldi et al., 2019). Lastly, there are several patient-specific risk factors that affect the diagnostic yield. For example, smoking and drinking,



HPV infection status, and the anatomical site of the lesion all affect the likelihood of accurately diagnosing an oral cancer. These traditional detection methods are compared against liquid biopsy approaches in Table 3.

Table 3: Comparative diagnostic performance of traditional and liquid biopsy detection methods for oral cancer.

Method	Sensitivity	Specificity	Advantages	Limitations	References
Conventional Visual Examination	71%	85%	Simple; low-cost; widely accessible	Performance varies significantly by clinician experience	Essat et al., 2022
Toluidine Blue Dye	89.1%	73.9%	Enhances visual detection of dysplastic tissue	May cause false positives due to inflammatory response	Kim et al., 2021
Autofluorescence (VELscope)	22–100%	16–100%	Non-invasive; highlights lesions beyond visible margins	Highly variable performance; operator-dependent	Nagi et al., 2016
Chemiluminescence (ViziLite)	77.1–100%	0–27.8%	Non-invasive; may highlight lesions beyond visible margins	Very low specificity; high false-positive rate	Nagi et al., 2016
Tissue Biopsy	Reference standard	Reference standard	Highly reliable; definitive diagnosis	Invasive; costly; not repeatable for surveillance	Cristaldi et al., 2019
Liquid Biopsy (miR-210, Alu amplicon,	83–92%	73–87% (AUC 0.98 for combined	Minimally invasive; repeatable for	Below near-perfect tissue biopsy	Bigagli et al., 2021; Rapado-González et al., 2022; Romani



Method	Sensitivity	Specificity	Advantages	Limitations	References
EV-miRNA)		salivary miRNA panel)	high-risk surveillance	accuracy	et al., 2021

Note. All sensitivity and specificity values are reported exactly as stated in the cited sources.

Liquid Biopsy Detection

The data collected from previous studies related to oral cancer diagnosis demonstrate that liquid biopsies appear to hold great promise as an effective diagnostic tool due to their relatively high diagnostic performance. MicroRNAs, in particular, are well-suited as cancer biomarkers for several reasons: they are small, highly stable molecules that resist degradation in bodily fluids, particularly when packaged within extracellular vesicles, they play direct regulatory roles in gene expression that are frequently disrupted during tumor development, and their expression patterns often differ measurably between cancerous and healthy tissue, making them detectable through relatively simple laboratory techniques. For example, one extracellular-vesicle-associated microRNA referred to as miR-210 shows great potential as an oral cancer biomarker.

Studies have revealed that miR-210 offers sensitivity and specificity values of 92.31% and 86.67%, respectively, for discriminating oral squamous cell carcinoma patients from healthy controls (Bigagli et al., 2021). Additionally, studies utilizing saliva-derived cfDNA have examined Alu amplicons, short, highly repetitive DNA sequences that make up a large portion of the human genome; because they are so abundant and easy to amplify via PCR, they serve as a convenient proxy for measuring total cell-free DNA concentration in a sample, which tends to be elevated in cancer patients due to increased tumor cell turnover. Using this approach, one study was able to predict oral cancer with a sensitivity of 83.33% and a specificity of 73.33% (Rapado-González et al., 2022). Moreover, a specificity rate of 100% for salivary ctDNA in oral cancer detection has been reported, the highest specificity among the oral cancer liquid biopsy findings summarized in this review, which indicates strong diagnostic potential, though the original finding requires independent validation before broader conclusions can be drawn (Cristaldi et al., 2019). Furthermore, a panel of three salivary miRNAs, namely miR-106b-5p, miR-423-5p, and miR-193b-3p, was able to achieve an area under curve (AUC) value of 0.98 when combined (Romani et al., 2021). AUC reflects a test's overall ability to distinguish between patients with and without disease, ranging from 0.5 (no better than chance) to 1.0 (perfect discrimination); a value of 0.98 is therefore considered excellent. Finally, because liquid biopsy approaches for oral cancer are minimally invasive (blood or saliva samples instead of tissue biopsies) patients experience less discomfort during testing and repeat tests are possible (Kinane et al., 2024). A summary of these biomarker performance metrics is provided in Table 4.



Table 4: Diagnostic performance of liquid biopsy biomarkers for oral cancer detection.

Biomarker/Method	Study Context	Metric	Value	Reference
miR-210 (extracellular-vesicle-associated microRNA)	Discrimination of OSCC patients from healthy controls	Sensitivity	92.31%	Bigagli et al., 2021
miR-210 (extracellular-vesicle-associated microRNA)	Discrimination of OSCC patients from healthy controls	Specificity	86.67%	Bigagli et al., 2021
Alu amplicon (salivary cfDNA)	Prediction of oral cancer via cell-free DNA integrity	Sensitivity	83.33%	Rapado-González et al., 2022
Alu amplicon (salivary cfDNA)	Prediction of oral cancer via cell-free DNA integrity	Specificity	73.33%	Rapado-González et al., 2022
Salivary ctDNA	Oral cancer detection via salivary ctDNA analysis	Specificity	100%	Cristaldi et al., 2019
Combined salivary miRNA panel (miR-106b-5p, miR-423-5p, miR-193b-3p)	Whole-saliva miRNA panel (microarray/RT-qPCR)	AUC	0.98	Romani et al., 2021

Note. Sensitivity and specificity are reported where both were available (miR-210, Alu amplicon); only specificity is reported for salivary ctDNA, as sensitivity was not given in the source study; AUC is reported for the combined salivary miRNA panel as its own composite performance metric rather than separate sensitivity or specificity values.



3.4. Colorectal Cancer

Traditional Detection Methods

The primary methods in traditional colorectal cancer (CRC) detection are stool tests such as fecal immunochemical tests (FIT) and stool DNA (sDNA) assays, as well as colonoscopy. FIT detects invasive CRC with a pooled sensitivity of 79% (ranging up to 89% at lower positivity thresholds) and specificity of 94%. However, sensitivity is lower than expected for detecting advanced adenomas, and therefore FIT may have limitations for early detection (Lee et al., 2014). When combining sDNA tests with FIT, it results in higher sensitivity rates for CRC (92.3%) and advanced adenoma (42.4%) compared to FIT alone (73.8% and 23.8%, respectively). Specificity is approximately 86.6%, though this could result in false positive rates due to non-neoplastic DNA alterations (Anand & Liang, 2022). Colonoscopy is the gold standard for CRC detection, with a pooled sensitivity of 98.5% and specificity of 100% for detecting advanced neoplasia (Yaghoobi et al., 2023). However, colonoscopy is an invasive procedure requiring bowel preparation, and there may be some level of patient resistance to comply with screening recommendations based on cost and invasiveness of the test (Quintero et al., 2012). Furthermore, patient-specific variables including age, family history, and the presence of inflammatory bowel disease will likely determine screening options as well as diagnostic yields, supporting the use of risk-adapted approaches. A side-by-side comparison of these methods is presented in Table 5.

Table 5: Comparative diagnostic performance of traditional and liquid biopsy detection methods for colorectal cancer.

Method	Sensitivity	Specificity	Advantages	Limitations	Reference
FIT	79% (up to 89% at lower positivity thresholds)	94%	Non-invasive	Lower sensitivity for advanced adenomas	Lee et al., 2014
sDNA + FIT	92.3% (CRC); 42.4% (advanced adenoma)	86.6%	Higher sensitivity than FIT alone	False positives from non-neoplastic DNA alterations	Anand & Liang, 2022
Colonoscopy	98.5%	100%	Gold standard; allows polyp removal during procedure; high patient compliance value despite invasiveness	Invasive; requires bowel prep; poor repeat compliance	Yaghoobi et al., 2023; Quintero et al., 2012



Method	Sensitivity	Specificity	Advantages	Limitations	Reference
Liquid Biopsy (ctDNA)	65% (Cohen, detection); ~88% (Reinert, recurrence surveillance)	99% (Cohen); 98% (Reinert)	Non-invasive; detects recurrence months before imaging	Biomarker release variability; standardization challenges	Cohen et al., 2018; Reinert et al., 2019

Note. All sensitivity and specificity values are reported exactly as stated in the cited sources.

Liquid Biopsy Detection

Advancements made in applying liquid biopsy methods for the detection of colorectal cancer have shown strong potential across multiple parameters. Studies have demonstrated that blood based tests combining circulating tumor DNA (ctDNA) mutations with protein biomarkers provided a sensitivity of approximately 65% and a specificity of 99% in detecting early stage colorectal cancer (Cohen et al., 2018). Similar results were seen with circulating tumor DNA analysis for predicting relapse, with 98% specificity and recurrence detected at a mean of 8.7 months (range, 0.8 - 16.5 months) prior to standard-of-care imaging (Reinert et al., 2019). Of all the findings reviewed here, this lead time represents the most clinically distinctive advantage liquid biopsy offers over traditional methods, since no imaging or endoscopic technique can provide comparable advance warning of recurrence, demonstrating the clinical benefit of liquid biopsies for ongoing monitoring of patients. Additionally, serial ctDNA analysis detected postsurgical recurrence with a sensitivity of approximately 88% in patients with stage I to III colorectal cancer while maintaining strong specificity, reinforcing its utility for post-treatment surveillance rather than initial detection (Reinert et al., 2019). Moreover, ctDNA detection after surgery was associated with increased risk of recurrence in stage II CRC patients with a hazard ratio of 18 ($p < .01$) (Tie et al., 2016); a hazard ratio expresses how much more likely an event (here, cancer recurrence) is to occur in one group relative to another at any given time, so a hazard ratio of 18 indicates an 18-fold higher rate of recurrence in patients with detectable post-surgical ctDNA compared to those without. Additionally, a large cohort study demonstrated that ctDNA was detectable in 73% of localized (stage I-III) colorectal cancers and in more than 75% of advanced/metastatic colorectal cancers, with detection strongly correlated with tumor burden, while minimizing invasiveness compared to colonoscopies (Bettegowda et al., 2014). These findings are summarized in Table 6.

Table 6: Diagnostic performance of liquid biopsy biomarkers for colorectal cancer detection.



Biomarker/Method	Study Context	Metric	Value	Reference
ctDNA + protein (blood based)	Early-stage colorectal cancer detection	Sensitivity	65%	Cohen et al., 2018
ctDNA + protein biomarkers (blood-based)	Early-stage colorectal cancer detection	Specificity	99%	Cohen et al., 2018
ctDNA analysis (relapse monitoring)	Predicting relapse prior to imaging	Specificity	98%	Reinert et al., 2019
ctDNA analysis (relapse monitoring)	Lead time before standard-of-care imaging	Mean lead time	8.7 months (range 0.8–16.5)	Reinert et al., 2019
ctDNA detection (recurrence surveillance)	Serial analysis, stage I–III colorectal cancer	Sensitivity	88%	Reinert et al., 2019
Post-surgical ctDNA detection	Recurrence risk in stage II CRC patients	Hazard Ratio	18 ($p < .01$)	Tie et al., 2016
ctDNA detectability (large cohort)	Correlation with tumor burden across CRC cases	Detection Rate	73% (localized); >75% (advanced)	Bettegowda et al., 2014

Note. Metrics vary by study: sensitivity/specificity are reported where both were available; mean lead time reflects how far in advance ctDNA detected recurrence relative to imaging; hazard ratio reflects relative recurrence risk rather than a diagnostic accuracy measure; detection rate reflects the proportion of cases in which ctDNA was detectable.



4. Discussion

While comparisons are discussed, differences in study design, patient populations, and biomarker detection methodologies limit direct equivalence between studies. Liquid biopsy techniques demonstrate strong potential to complement conventional detection techniques.

4.1. Breast Cancer

The limited diagnostic efficiency of mammography has nonetheless been widely accepted for decades, given the lack of a superior population-level screening alternative. Mammography detects approximately 60% of all breast tumors and has an average area under the curve (AUC) of about 0.73 (Fitzjohn et al., 2023). Thus, there exists a substantial portion of breast tumors which will be missed using this technique. However, mammography remains the accepted standard-of-care primarily due to the fact that the alternatives have other serious deficiencies. For example, while MRI provides higher sensitivity than does mammography, its high cost and limited availability restrict its routine use to high risk screening populations rather than the general population (Sardanelli et al., 2024). In addition, MRI is typically scheduled at fixed intervals for high risk surveillance and is not practical for frequent monitoring of a specific tumor's response to treatment. The literature suggests that liquid biopsy may help address both of these limitations, although its effectiveness depends on tumor subtype and biomarker availability. cfDNA-based technologies, such as PIK3CA mutation testing and AnchorIRIS methylation analysis, demonstrate sensitivity greater than 85% and specificity approaching 100% (Zhou et al., 2016; Zhang et al., 2021). These levels of performance suggest potential competitiveness with mammography, though differences in study design and patient populations limit direct comparison. Furthermore, liquid biopsy allows for ongoing monitoring of patients undergoing therapy and experiencing relapse. Neither MRI nor mammography is routinely used to monitor a specific patient's disease status over time. Their primary clinical role is periodic screening for new or recurrent disease rather than serial tracking of an existing tumor's response to treatment (Sardanelli et al., 2024). There is a caveat to the use of liquid biopsy for breast cancer screening. While performance of liquid biopsy is acceptable for patients with HER2-positive and triple negative cancers who tend to release more cell free DNA into the bloodstream than patients with luminal breast cancers (hormone-receptor-positive, HER2-negative tumors), the reliability of this technique varies depending upon the type of breast cancer. For example, reported sensitivities ranging from 86 to 91%, with specificities as high as 98-100% for ctDNA-based assays (Zhou et al., 2016; Zhang et al., 2021), indicate that liquid biopsy could be capable of achieving similar diagnostic accuracy to traditional imaging modalities in some clinical applications. Nevertheless, this data is usually generated under controlled conditions and does not necessarily represent how it would perform in a larger population screening context. Thus, this variability represents a critical limitation of liquid biopsy for breast cancer screening; however, it is based upon biological differences among breast cancer types and does not reflect a technical deficiency inherent to liquid biopsy.

4.2. Oral Cancer

The comparison between liquid biopsy and conventional oral cancer screening and detection methods (visual examination/autofluorescence) may be the greatest difference observed in the three examples listed. Reported diagnostic performance for these light-based adjuncts varies widely across studies: autofluorescence (VELscope) sensitivity ranged from 22 to 100% with specificity from 16 to 100%, while chemiluminescence (ViziLite) showed sensitivity of 77.1 to 100% but



notably low specificity, ranging from 0 to 27.8% (Nagi et al., 2016). Therefore, there exists a large amount of false positives resulting from these methods. Tissue biopsy will resolve this issue by providing nearly perfect accuracy; however, it is invasive and will never be possible to repeat frequently enough for surveillance purposes. Liquid biopsy using salivary fluid to provide biomarkers such as miR-210, Alu amplicons, and EV-associated miRNAs provide sensitivities ranging from approximately 83 to 92% and specificities ranging from approximately 73 to 87% (Bigagli et al., 2021; Rapado-González et al., 2022), with the combined salivary miRNA panel achieving an AUC of 0.98 (Romani et al., 2021). An AUC value of 0.98 for salivary miRNAs indicates excellent discriminative ability, approaching the near-perfect diagnostic accuracy achieved by tissue biopsy, though independent validation in larger cohorts is still needed before it could be considered a substitute for histopathological confirmation. The significance of this is based upon the biological rationale behind this approach. Since the oral cavity is directly exposed to saliva, it serves as a natural reservoir for tumor derived products. As such, salivary liquid biopsy represents not only a less invasive alternative to tissue biopsy; but also serves as a more practical tool for repeatedly screening patients at high risk for developing oral cancer over long periods of time.

4.3. Colorectal Cancer

Colorectal cancer presents a unique situation since the established gold standard (colonoscopy), although imperfect, is indeed good. Colonoscopy has a pooled sensitivity of 98.5% (Yaghoobi et al., 2023), thereby presenting a challenge while attempting to compare it to liquid biopsy based solely on diagnostic efficacy. Colonoscopy also carries a therapeutic advantage that no liquid biopsy method can currently replicate. Precancerous polyps identified during the procedure can be removed immediately in the same session, meaning the test itself can prevent a cancer from ever developing rather than simply detecting one that already exists. Instead, a more realistic comparison would be one of utility. Colonoscopy is an invasive procedure requiring considerable resources and patient compliance. Due to the factors mentioned above, colonoscopy is unlikely to be used repetitively. On the other hand, stool-based tests (FIT/sDNA) provide a less burdensome option compared to colonoscopy; however, they exhibit poor performance when attempting to identify adenomatous polyps (the pre-cancerous lesions representing the optimal opportunity for early intervention). Similarly, ctDNA-based liquid biopsies have demonstrated high specificity (exceeding 95%) and low invasiveness compared with colonoscopy, though their reported sensitivity varies considerably by clinical context and is generally lower than colonoscopy for primary detection. Their strongest performance has been in the post-treatment surveillance setting, where serial ctDNA analysis detected recurrence with roughly 88% sensitivity and high specificity (Reinert et al., 2019), rather than as a first-line detection tool. Moreover, studies employing ctDNA assays have demonstrated the potential to identify recurrent cancer prior to visualization through imaging techniques: capabilities not available using traditional methods. The ability of ctDNA to detect recurrence months prior to imaging highlights a distinct clinical advantage, suggesting that liquid biopsy may offer greater utility in longitudinal monitoring rather than initial diagnosis alone. Such findings support the position that liquid biopsy should not be viewed as a substitute for colonoscopy; instead, it should be considered a useful adjunct to colonoscopy, specifically during post-treatment surveillance evaluations.

The quality of included studies varied across the literature reviewed. Many studies were observational or single-cohort designs, which may introduce moderate risk of selection and verification bias. It is useful to distinguish two different sources of variability affecting liquid biopsy performance across this review. The first is biological: differences in how much ctDNA, how many CTCs, or how many tumor-derived EVs a given cancer sheds into blood or saliva are determined by the tumor's own biology, such as subtype, size, and vascularization, and are not something a better assay can fully overcome;



this type of variability tends to primarily affect sensitivity, since a test can only detect what the tumor actually releases. The second is technical: differences in assay platform, sample handling, detection threshold, and laboratory protocol, all of which can, in principle, be standardized and improved over time; this type of variability tends to primarily affect specificity, since it governs how many false positives a given method generates rather than how much signal is available to detect. Distinguishing these two sources matters for interpreting the findings in this review: performance gaps driven by biological variability (such as lower ctDNA shedding in luminal breast cancers) point to a genuine ceiling on what liquid biopsy can currently achieve for certain tumor types, whereas performance gaps driven by technical variability (such as inconsistent thresholds across cfDNA assays) represent a solvable engineering problem rather than a fundamental limitation. Additionally, variability in study populations and biomarker detection methodologies further limits the generalizability of findings across the studies reviewed. Future research should incorporate standardized assessment tools such as QUADAS-2 to more rigorously evaluate study quality and strengthen the evidence base.

5. Summary

Together, these three scenarios illustrate a common theme: each traditional method excels in one parameter while performing inadequately in another. Colonoscopy is very accurate; however, it is not accessible. Mammography is widely accessible and remains the standard-of-care for breast cancer screening; however, its sensitivity is comparatively limited, and supplementary tools such as MRI, while more sensitive, are reserved for high-risk patients due to their cost rather than used as a first-line screening replacement. Tissue biopsy is virtually definitive; however, it is non-repeatable. Liquid biopsy may help reduce this compromise by offering the potential for high accuracy along with low invasiveness and longitudinal monitoring. Although several issues exist that limit the broad applicability of liquid biopsy (ctDNA shedding variability among cancer subtypes; lack of platform standardization; etc.), they represent engineering and implementation issues rather than conceptual flaws. The clinical rationale supporting the development and deployment of liquid biopsy for cancer diagnosis is well-established; however, establishing the clinical infrastructure necessary to support liquid biopsy remains an outstanding task. Beyond diagnostic performance, cost and patient trust represent two additional barriers to adoption that are distinct from technical accuracy. Many liquid biopsy assays, particularly cfDNA sequencing panels, currently carry substantially higher per-test costs than established tools like mammography or FIT, and are not yet uniformly covered by insurance (Douglas et al., 2023), which limits real-world accessibility even where diagnostic performance is comparable. Physician and patient trust also plays a meaningful role in adoption: clinicians have decades of accumulated experience interpreting colonoscopy or mammography results and integrating them into established treatment pathways, whereas liquid biopsy results, especially borderline or discordant ones, currently lack the same degree of clinical familiarity and standardized guidance, which may lead to hesitancy in acting on them without confirmatory traditional testing (Li et al., 2025). These adoption barriers are separate from, and in some cases more difficult to resolve than, the assay-level technical limitations discussed above. Regulatory approval status further illustrates the gap between liquid biopsy's promise and its current clinical role. Several ctDNA-based liquid biopsy tests, including Guardant360 CDx and FoundationOne Liquid CDx, received FDA approval in 2020, but specifically as companion diagnostics that guide treatment selection in patients already diagnosed with advanced or metastatic cancer, rather than as tools approved for population-level early detection or screening in asymptomatic individuals (OncoLive, 2020; Foundation Medicine, 2020). By contrast, stool-based DNA tests such as Cologuard and its successor, Cologuard Plus, are FDA-approved specifically for colorectal cancer screening in asymptomatic, average-risk adults, reflecting a more mature regulatory pathway for that particular liquid biopsy modality (Imperiale et al., 2024). This distinction is important: the ctDNA- and CTC-based liquid biopsies discussed throughout this



review, particularly for breast and oral cancer, have not yet achieved regulatory approval for the screening use case this paper primarily examines, and therefore remain investigational tools whose path to clinical adoption for early detection specifically will depend on additional prospective validation and regulatory clearance beyond their current, treatment-selection-focused approvals.

6. Limitations

These findings should be interpreted within the context of rapidly evolving liquid biopsy technologies, where ongoing advancements may significantly influence future diagnostic performance. Consequently, the majority of the references used in this narrative review came from PubMed due to its reliability and comprehensiveness. In order to avoid a potential source of bias within the results portion of this document, several efforts were made to ensure that this would not occur. Additionally, although efforts were made to gather information from all over the world, a significant number of sources obtained for this paper were primarily based out of the Americas. Fewer than 5% of the sources gathered for this paper were from Asia, less than 2% were from Europe, and no sources were located from anywhere else. As such, geographic bias may be included in this paper. A final consideration must be publication bias. Many researchers know that studies which report medical advances (or "breakthroughs") are significantly more likely to be published and easily accessible than studies reporting medical failures. Therefore, the data will be slightly skewed because virtually all of the data collected is positive, or supportive of liquid biopsies. It is also worth noting that several of the strongest performance figures reported in this review come from single studies rather than replicated findings. The 100% specificity reported for the AnchorIRIS cfDNA assay (Zhang et al., 2021) is drawn from an individual study with a comparatively small sample size and has not yet been independently replicated in a larger cohort. The 100% specificity reported for salivary ctDNA in oral cancer detection, summarized in Cristaldi et al. (2019), likewise originates from a single primary study whose sample size and replication status could not be independently confirmed for this review. Both figures should therefore be treated as promising preliminary results rather than established performance benchmarks. This is a meaningful limitation of the underlying evidence base itself, distinct from the review's own methodological limitations discussed elsewhere in this section: a narrative review can only synthesize the quality of evidence that exists, and in several cases here, that evidence consists of a single small study rather than a body of converging research. Lastly, the variability in both the samples tested and testing procedures must also be taken into account when assessing the differences between various liquid biopsy techniques and established methods for detecting cancer. These represent the primary limitations encountered in preparing this document.

7. Future Directions

The potential of liquid biopsies for the detection of cancer has been demonstrated. However, because of variability among the many liquid biopsy technologies that have been developed in terms of how well they work (sensitivity), how often they produce false positives (specificity), and how consistently they provide consistent results from one test to another (standardization) for various forms of cancer, liquid biopsies are not ready to become the leading technology in cancer detection.

For this reason, in the immediate future, hospitals should consider incorporating liquid biopsies as a supplementary tool alongside existing, validated methods of cancer detection, rather than as a substitute for them. Traditional methods should remain the primary basis for diagnosis and screening decisions in the near term, with liquid biopsy findings used to flag



patients for closer monitoring or earlier follow-up with established diagnostic tools, rather than acted upon independently. As additional large-scale validation studies and expanded regulatory approvals accumulate, the balance of confidence between the two approaches may shift; until then, incorporating liquid biopsy in this supportive, rather than parallel or interchangeable, role will increase the likelihood of identifying specific cancers (such as colorectal, breast, and oral cancer) before they reach a potentially lethal stage, while avoiding premature reliance on a still-maturing technology.

Development of standardized testing procedures and clinical guidelines could also help reduce variability in what physicians interpret from tests based upon liquid biopsy and increase the degree to which physicians are willing to routinely utilize liquid biopsy.

There is a clear opportunity for future research to include large-scale, multiple round studies designed to confirm biomarker panels used to detect cancer through liquid biopsy and compare them to each other using the same number of samples. Additionally, studies focused on using liquid biopsy over time to monitor treatment responses and recurrences of cancer could lead to expanded uses of liquid biopsy beyond early detection into long term management of patients.

8. Conclusions

The role that liquid biopsy is likely to play in the health care system, particularly through ctDNA assays, was highlighted in this research. Liquid biopsy represents a promising and evolving diagnostic approach in detecting cancers that traditional methods may miss including colorectal, breast and oral cancers. When compared to traditional screening methods, liquid biopsy may offer advantages in sensitivity, specificity, and invasiveness depending on clinical context. Therefore, liquid biopsy is an attractive alternative or complement to currently available diagnostic strategies. As shown by the evidence reviewed here, it appears that the liquid biopsy holds significant potential for identifying cancers at a much earlier stage than traditional methods. At an early stage of cancer development, the effectiveness of treatments increases. However, liquid biopsy still has several limitations that are preventing widespread acceptance. Among these limitations is the lack of standardization in terms of how liquid biopsies are performed and variability among liquid biopsy data. These findings support the potential integration of liquid biopsy into clinical practice to facilitate improved early cancer detection. By doing so, we anticipate enhanced survivorship rates, decreased burdens associated with late stage diagnoses and increased opportunities for personalized and effective cancer care. However, the traditional cancer detection methods covered in this paper remain the gold standard and should continue to be the main factor in detection. Further large-scale, standardized studies will be essential to validate these findings across diverse patient populations.

9. References

- Alba, L. H., Díaz, S., Gamboa, O., Poveda, C., Henao, A., Perry, F., Duggan, C., Gil, F., & Murillo, R. (2018). Accuracy of mammography and clinical breast examination in the implementation of breast cancer screening programs in Colombia. *Preventive Medicine*, 115, 19–25. <https://doi.org/10.1016/j.ypmed.2018.08.005>
- Alix-Panabières, C., Marchetti, D., & Lang, J. E. (2023). Liquid biopsy: From concept to clinical application. *Scientific Reports*, 13, 21685. <https://doi.org/10.1038/s41598-023-48501-x>
- Anand, S., & Liang, P. S. (2022). A practical overview of the stool DNA test for colorectal cancer screening. *Clinical and*



Translational Gastroenterology, 13(4), e00464. <https://doi.org/10.14309/ctg.0000000000000464>

- Bettegowda, C., Sausen, M., Leary, R. J., Kinde, I., Wang, Y., Agrawal, N., ... Diaz, L. A. (2014). Detection of circulating tumor DNA in early- and late-stage human malignancies. *Science Translational Medicine*, 6(224), 224ra24. <https://doi.org/10.1126/scitranslmed.3007094>
- Bigagli, E., Locatello, L. G., Di Stadio, A., Maggiore, G., Valdarnini, F., Bambi, F., Gallo, O., & Luceri, C. (2021). Extracellular vesicles miR-210 as a potential biomarker for diagnosis and survival prediction of oral squamous cell carcinoma patients. *Journal of Oral Pathology & Medicine*, 51(4), 350–357. <https://doi.org/10.1111/jop.13263>
- Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 74(3), 229–263. <https://doi.org/10.3322/caac.21834>
- Brill, J. V. (2020). Screening for cancer: The economic, medical, and psychosocial issues. *The American Journal of Managed Care*, 26(Suppl. 14), S300–S306. <https://doi.org/10.37765/ajmc.2020.88534>
- Chen, H.-L., Zhou, J.-Q., Chen, Q., & Deng, Y.-C. (2021). Comparison of the sensitivity of mammography, ultrasound, magnetic resonance imaging and combinations of these imaging modalities for the detection of small (≤ 2 cm) breast cancer. *Medicine (Baltimore)*, 100(26), e26531. <https://doi.org/10.1097/MD.00000000000026531>
- Cohen, J. D., Li, L., Wang, Y., Thoburn, C., Afsari, B., Danilova, L., ... Papadopoulos, N. (2018). Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*, 359(6378), 926–930. <https://doi.org/10.1126/science.aar3247>
- Cristaldi, M., Mauceri, R., Di Fede, O., Giuliana, G., Campisi, G., & Panzarella, V. (2019). Salivary biomarkers for oral squamous cell carcinoma diagnosis and follow-up: Current status and perspectives. *Frontiers in Physiology*, 10, 1476. <https://doi.org/10.3389/fphys.2019.01476>
- Douglas, M. P., Ragavan, M. V., Chen, C., Kumar, A., Gray, S. W., Blakely, C. M., & Phillips, K. A. (2023). Private payer and Medicare coverage policies for use of circulating tumor DNA tests in cancer diagnostics and treatment. *Journal of the National Comprehensive Cancer Network*, 21(6), 609–616. <https://doi.org/10.6004/jnccn.2023.7011>
- Essat, M., Cooper, K., Bessey, A., Clowes, M., Chilcott, J. B., & Hunter, K. D. (2022). Diagnostic accuracy of conventional oral examination for detecting oral cavity cancer and potentially malignant disorders in patients with clinically evident oral lesions: Systematic review and meta-analysis. *Head & Neck*, 44(4), 998–1013. <https://doi.org/10.1002/hed.26992>
- Fitzjohn, J., Zhou, C., & Chase, J. G. (2023). Critical assessment of mammography accuracy. *IFAC-PapersOnLine*, 56(2), 5620–5625. <https://doi.org/10.1016/j.ifacol.2023.10.472>
- Foundation Medicine. (2020). FDA approves Foundation Medicine's FoundationOne Liquid CDx, a comprehensive pan-tumor liquid biopsy test with multiple companion diagnostic indications for patients with advanced cancer. <https://www.foundationmedicine.com/press-releases/fda-approves-foundation-medicine's-foundationone%C2%AELiquid-cdx,-a-comprehensive-pan-tumor-liquid-biopsy-test-with-multiple-companion-diagnostic-indications-for>



[-patients-with-advanced-cancer](#)

- Garcia-Murillas, I., Abbott, C. W., Cutts, R. J., ... Turner, N. C. (2025). Whole genome sequencing-powered ctDNA sequencing for breast cancer detection. *Annals of Oncology*, 36(6), 673–681. <https://doi.org/10.1016/j.annonc.2025.01.021>
- Imperiale, T. F., Porter, K., Zella, J., Zhao, X., Berger, B. M., & Lidgard, G. P. (2024). Next-generation multitarget stool DNA test for colorectal cancer screening. *New England Journal of Medicine*, 390(11), 984–993. <https://doi.org/10.1056/NEJMoa2310336>
- Keraite, I., Alvarez-Garcia, V., Garcia-Murillas, I., Beaney, M., Turner, N. C., Bartos, C., Oikonomidou, O., Kersaudy-Kerhoas, M., & Leslie, N. R. (2020). PIK3CA mutation enrichment and quantitation from blood and tissue. *Scientific Reports*, 10, Article 17082. <https://doi.org/10.1038/s41598-020-74086-w>
- Kim, D. H., Song, E. A., Kim, S. W., & Hwang, S. H. (2021). Efficacy of toluidine blue in the diagnosis and screening of oral cancer and pre-cancer: A systematic review and meta-analysis. *Clinical Otolaryngology*, 46(1), 23–30. <https://doi.org/10.1111/coa.13613>
- Kinane, D. F., Gabert, J., Xynopoulos, G., & Guzeldemir-Akcakanat, E. (2024). Strategic approaches in oral squamous cell carcinoma diagnostics using liquid biopsy. *Periodontology 2000*, 96(1), 316–328. <https://doi.org/10.1111/prd.12567>
- Lee, J. K., Liles, E. G., Bent, S., Levin, T. R., & Corley, D. A. (2014). Accuracy of fecal immunochemical tests for colorectal cancer: Systematic review and meta-analysis. *Annals of Internal Medicine*, 160(3), 171–181. <https://doi.org/10.7326/M13-1484>
- Li, H.-Y., Chang, C.-C., Yang, Y.-H., Yao, C.-Y., Hsieh, J. C.-H., & Chang, S.-H. (2025). The prospects and limitations of liquid biopsy utilization for clinical practice in Taiwan. *The Journal of Liquid Biopsy*, 7, Article 100290. <https://doi.org/10.1016/j.jlb.2025.100290>
- Nagi, R., Reddy-Kantharaj, Y. B., Rakesh, N., Janardhan-Reddy, S., & Sahu, S. (2016). Efficacy of light based detection systems for early detection of oral cancer and oral potentially malignant disorders: Systematic review. *Medicina Oral, Patología Oral y Cirugía Bucal*, 21(4), e447–e455. <https://doi.org/10.4317/medoral.21104>
- OncLive. (2020). FDA approves Guardant360 CDx liquid biopsy for comprehensive genomic profiling across all solid cancers. <https://www.onclive.com/view/fda-approves-guardant360-cdx-liquid-biopsy-for-comprehensive-genomic-profiling-across-all-solid>
- Pantel, K., & Alix-Panabières, C. (2013). Real-time liquid biopsy in cancer patients: Fact or fiction? *Cancer Research*, 73(21), 6384–6388. <https://doi.org/10.1158/0008-5472.CAN-13-2030>
- Quintero, E., Castells, A., Bujanda, L., Cubiella, J., Salas, D., Lanás, Á., & COLONPREV Study Investigators. (2012). Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *New England Journal of Medicine*, 366(8), 697–706. <https://doi.org/10.1056/NEJMoa1108895>
- Rapado-González, Ó., López-Cedrún, J. L., Lago-Lestón, R. M., Abalo, A., Rubin-Roger, G., Salgado-Barreira, Á., López-López, R., Muínelo-Romay, L., & Suárez-Cunqueiro, M. M. (2022). Integrity and quantity of salivary cell-free DNA as a



- potential molecular biomarker in oral cancer: A preliminary study. *Journal of Oral Pathology & Medicine*, 51(5), 429–435. <https://doi.org/10.1111/jop.13299>
- Reinert, T., Henriksen, T. V., Christensen, E., Sharma, S., Salari, R., Sethi, H., ... Andersen, C. L. (2019). Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncology*, 5(8), 1124–1131. <https://doi.org/10.1001/jamaoncol.2019.0528>
- Romani, C., Salviato, E., Paderno, A., Zanotti, L., Ravaggi, A., Deganello, A., ... Bignotti, E. (2021). Genome-wide study of salivary miRNAs identifies miR-423-5p as a promising diagnostic and prognostic biomarker in oral squamous cell carcinoma. *Theranostics*, 11(6), 2987–2999. <https://doi.org/10.7150/thno.45157>
- Sardanelli, F., Magni, V., Rossini, G., Kilburn-Toppin, F., Healy, N. A., & Gilbert, F. J. (2024). The paradox of MRI for breast cancer screening: High-risk and dense breasts—available evidence and current practice. *Insights into Imaging*, 15, 96. <https://doi.org/10.1186/s13244-024-01653-4>
- Tie, J., Wang, Y., Tomasetti, C., Li, L., Springer, S., Kinde, I., ... Gibbs, P. (2016). Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Science Translational Medicine*, 8(346), 346ra92. <https://doi.org/10.1126/scitranslmed.aaf6219>
- Yaghoobi, M., Mehraban Far, P., Mbuagbaw, L., Yuan, Y., Armstrong, D., Thabane, L., & Moayyedi, P. (2023). Head-to-head diagnostic test accuracy meta-analysis of colonoscopy and fecal immunochemical test in detecting advanced colon neoplasia. *Middle East Journal of Digestive Diseases*, 15(1), 5–11. <https://doi.org/10.34172/mejdd.2023.313>
- Zhang, X., Zhao, D., Yin, Y., Yang, T., You, Z., Li, D., ... Pang, D. (2021). Circulating cell-free DNA-based methylation patterns for breast cancer diagnosis. *npj Breast Cancer*, 7, 106. <https://doi.org/10.1038/s41523-021-00316-7>
- Zhou, Y., Wang, C., Zhu, H., Lin, Y., Pan, B., Zhang, X., Huang, X., Xu, Q., Xu, Y., & Sun, Q. (2016). Diagnostic accuracy of PIK3CA mutation detection by circulating free DNA in breast cancer: A meta-analysis of diagnostic test accuracy. *PLOS ONE*, 11(6), e0158143. <https://doi.org/10.1371/journal.pone.0158143>

Data & Code Availability Statement

This is a structured narrative review; no new primary data or code were generated. The search strategy used to identify included studies is fully reported in the Methods section (Search Strategy), including the exact Boolean search string, the five databases searched (PubMed, ScienceDirect, Google Scholar, the National Cancer Institute's Research Database, and ClinicalTrials.gov), and the date range searched in each. Direct links to all sources analyzed in this review are provided as DOIs in the References section, and all cited studies are publicly available through their publishing journals or institutional repositories.

AI Tools Statement

No AI or LLMs were used in the creation of this paper besides the use of Grammarly (Grammarly, Inc) and the online service Citation Machine (Chegg).



Acknowledgements

The author thanks his parents for their support and encouragement throughout the research and writing of this paper.

Author Biography

Aaryan Kumar is a student at American High School in Fremont, California, with a long standing interest in medicine, oncology, and the intersection of technology and healthcare. His research background includes the IYRC Columbia Medicine and Research program, the UCLA Emerging Scientists Program, a Harvard research conference, and the New York Academy of Sciences Junior Academy, where he has worked with students internationally on projects addressing energy and food waste through nanotechnology. He has also pursued hands-on research through a Stanford University anesthesia summer internship and an NC State Global Training Initiative project developing hemp based textile bandages.

Kumar has shadowed physicians in anesthesiology, breast surgical oncology, and cardiology, observing pre operative consultations, surgical procedures, and cardiac evaluations. He is active in cancer advocacy as a Grassroots and Recruitment Lead and Fundraising Lead for the American Cancer Society Cancer Action Network in Alameda County, and serves as a Legislative Delegate for ACSEF. Outside of academics, he competes on his high school's water polo and swim teams and with club teams in the Bay Area. He has also pursued an interest in the social sciences through college level courses in Anthropology and Sociology. This paper, comparing the efficacy of liquid biopsies to traditional methods for early cancer detection, reflects his ongoing interest in how emerging diagnostic technologies can improve outcomes in oncology.

Mentor Contribution Statement

Emma Van Praagh is an undergraduate researcher in biomedical engineering at Columbia University's Fu Foundation School of Engineering and Applied Science, where she is a member of the MR Science Laboratory studying magnetic resonance imaging and spectroscopy. Her own research has focused on spinal cord imaging and its applications to neurodegenerative conditions such as multiple sclerosis, building on earlier work she conducted at Vanderbilt University examining spinal cord imaging techniques and their relationship to motor impairment in multiple sclerosis patients.

Van Praagh served as a mentor to the author during the early stages of this project. She looked over the author's initial research plans and helped set the groundwork for the review, including guidance on defining its scope and framing the comparison between liquid biopsy and traditional cancer detection methods. Van Praagh also taught the author how to structure a narrative review, including how to organize a search strategy, apply inclusion and exclusion criteria, and present findings across multiple cancer types in a coherent format.

