Liquid Biopsy: The Future of Cancer Screening

Pathologists are central to the diagnosis and treatment of disease, often working at the forefront of medical innovation. One exciting advancement that has been gaining widespread popularity is a technique known as 'liquid biopsy' – particularly the use of circulating tumour DNA (ctDNA) for early cancer detection. In contrast with current invasive methods, liquid biopsy requires only a simple blood test. This minimally invasive approach to cancer screening and diagnosis has the potential to significantly transform healthcare provision in the coming years.

Background

Liquid biopsy works by detecting ctDNA fragments. These are small pieces of DNA that cancer cells release into the bloodstream. These DNA fragments carry genetic mutations that are specific to tumour cells, allowing us to identify cancers before symptoms appear or tumours become visible on imaging scans (Figure 1). Thanks to advances in next-generation sequencing and bioinformatics, pathologists can now detect this genetic material with impressive accuracy and precision (Wan et al., 2017). This development opens up a new frontier for early detection and real-time cancer monitoring, reducing our reliance on more invasive, risk-prone procedures.

Figure 1:

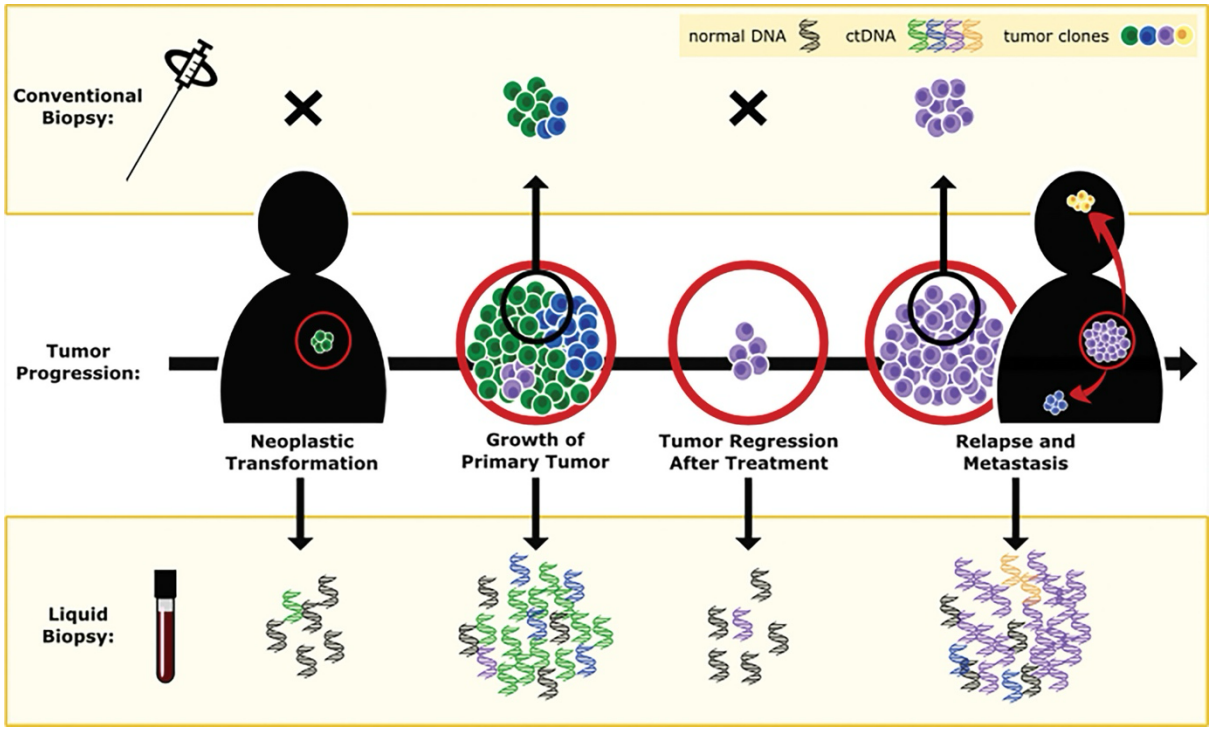

Figure 1 *– Use of circulating tumour DNA (ctDNA) as a liquid biopsy can help diagnose and monitor tumour progression. Conventional biopsy is invasive and can't be used when there is no visible tumour. ctDNA can detect low levels of disease and can more fully capture tumour heterogeneity (GEN, 2017).*

Benefits

Compared to traditional tissue biopsy, liquid biopsy offers many practical and clinical advantages. First, it is significantly less invasive – requiring only a routine blood draw – and can be repeated over time, enabling continuous monitoring of the progression and heterogeneity of the tumour (Figure 1). Second, ctDNA more comprehensively reflects tumour heterogeneity, as it can capture mutations from multiple tumour sites rather than just a single sampled region (Bettegowda et al., 2014). This provides a broader genetic snapshot of the cancer, which can be help personalise treatment. Lastly, ctDNA can be detected even in early-stage cancers, often before clinical or radiographic evidence emerges, offering a vital window of opportunity for early intervention (Cohen et al., 2018).

These benefits are not just theoretical, they're already starting to reshape clinical practice. The ECLIPSE trial – a landmark study involving over 8,000 average-risk adults – evaluated Guardant Health's Shield test, a ctDNA-based liquid biopsy for colorectal cancer screening. The test demonstrated a sensitivity of 83% and a specificity of 90%, which is comparable to long-established stool-based tests (Chung et al., 2024). Shield offers a less burdensome option for patients who may be reluctant to undergo colonoscopy or who are non-compliant with stool tests. Increased uptake of this test could substantially improve early cancer detection and outcomes on a population level.

Even more groundbreaking is the emergence of multi-cancer early detection (MCED) blood tests. GRAIL's Galleri test uses methylation patterns in ctDNA to screen for more than 50 types of cancer with a single blood sample. In a recent study with over 6,000 participants, Galleri achieved an impressive specificity of over 99% and successfully predicted the tissue of origin in most of the positive cases (Liu et al., 2020). This test represents a paradigm shift in oncology – moving from single-cancer screening to a universal test capable of detecting multiple cancers at an early stage, many of which currently lack routine screening methods.

To assess the real-world impact of Galleri, the NHS launched the world's largest MCED trial, enrolling over 140,000 participants aged between 50-77. The NHS-Galleri trial aims to evaluate whether this test can reduce the number of late-stage cancer diagnoses, with outcomes expected in 2026 (NHS England, 2024). Early data suggests that the test's specificity does indeed hold in a larger population, meaning it could soon become a staple in routine health checks. If successful, Galleri could significantly shift the cancer diagnostic landscape, enabling earlier intervention and improving survival rates across many types of cancer.

ctDNA liquid biopsies are already having a tangible impact beyond screening. Minimal residue disease (MRD) refers to the traces of cancer that remain in the body after surgery or treatment. This can, and often does, lead to recurrence. In colorectal cancer, ctDNA-MRD testing has helped clinicians decide whether

adjuvant chemotherapy is needed. A landmark study showed that ctDNA-positive patients had a significantly higher risk of recurrence, while ctDNA-negative patients could often avoid additional treatment (Tie et al., 2016). This approach reduces unnecessary exposure to chemotherapy and its associated side effects.

Limitations

Despite these promising developments, challenges do remain. The biggest of these is sensitivity – especially when detecting small, early-stage tumours that shed very little DNA (Figure 2). In other words, some early-stage cancers might go undetected simply because they don't release enough ctDNA to trigger a positive result. The PATHFINDER study showed that while specificity was high, detection of early-stage cancers remained relatively low (Liu et al., 2020).

Figure 2:

Method	Advantages	Disadvantages
ctDNA	Minimally invasive, no radioactive contamination, new DNA no preservative contamination Early diagnosis or prediction of recurrence Real-time monitoring of treatment response Determining survival expectations and risk of recurrence in tumor patients	Cannot be detected in some patients with early or advanced cancers Limited sensitivity and specificity Undiagnosed
Imaging	Tumor location and size can be localized Minimally invasive	Difficulty in detecting microscopic lesions Possible false positives and negatives
Tissue biopsy	Tumor typing can be determined	Invasive testing
Tumor marker	Low cost of testing, minimally invasive	Poor sensitivity and specificity

Figure 2 – *Advantages and disadvantages of ctDNA, imaging, tissue biopsy, and tumour markers (Xu, 2024).*

False positives are another big issue. Non-cancerous conditions (e.g. clonal haematopoiesis) can introduce DNA mutations into the bloodstream that mimic tumour signals, leading to unnecessary follow-up and patient anxiety (Razavi et al., 2019). While specificity in tests like Galleri is high, even a small false-positive rate can have significant consequences when scaled to cover a broad population.

Cost is a further barrier. ctDNA sequencing and analysis remain expensive, and widespread adoption will require not only cost reductions, but also careful health economic evaluation. Policymakers and healthcare providers will need to weigh the up-front costs of testing against the potential savings from earlier cancer detection. Initial studies suggest that the cost-effectiveness of these tests improves significantly when targeted at older or high-risk populations, but more data from long-term trials will be important.

To realise the full potential of ctDNA-based screening, several key steps must be taken. Continued support for large-scale, long-term clinical trials like the NHS-Galleri study is essential to validate effectiveness and guide future screening protocols. Clear clinical guidelines must be developed for managing positive results including pathways for follow-up imaging and specialist referral. Investment in laboratory infrastructure and workforce training will also be needed to ensure the health system is prepared for broader implementation. Equitable access is also an important ethical concern. Strategies such as public funding, insurance reimbursement, and tiered pricing models could help make these tests available to all – not just those who can afford it.

Conclusions

ctDNA-based liquid biopsy is a transformative innovation in pathology, offering a minimally invasive, broadly applicable, and increasingly accurate method for early cancer detection. With applications in colorectal cancer screening and MRD monitoring – and with massive promise in multi-cancer detection – this technology is already redefining what's possible. As clinical trials progress and real-world data accumulates, the role of the pathologist in interpreting and applying the results of these tests will only become more important. With widespread implementation, ctDNA liquid biopsy could help shift cancer care from reactive to proactive, catching cancers before they spread and saving countless lives in the process.

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