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Liquid Biopsy: Flesh or blood?

8 MIN READ

RADAR

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A brief description

At its root, liquid biopsy is an in vitro diagnostic test, a test that takes place outside of a living organism, for example in a test tube or culture dish. In vitro tests are indispensable, informing approximately 70% of clinical decision-making.[1]

Liquid biopsies diagnose disease by identifying relevant biomarkers within a liquid substance. The World Health Organisation (WHO) defines biomarkers as “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease”. Well-known and widely-measured examples of biomarkers include glucose or cholesterol. Although liquid biopsy is commonly associated with blood samples, some biomarkers can also be detected in urine and saliva.

[1]CDC. https://www.cdc.gov/csels/dls/strengthening-clinical-labs.html

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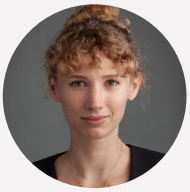

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A disruptive promise

Liquid biopsy aims to displace the current diagnostic paradigm in biopsy: tissue-based biopsy. Liquid biopsy has three critical advantages over its tissue-based counterpart.

1. Liquid biopsies are non-invasive, while tissue biopsies are an invasive, and at times risky procedures, especially when the tumour/disease site is difficult to access. In a tissue biopsy, a piece of tissue is identified through imaging, then surgically removed from the body and lastly, tested for biomarkers. In contrast, liquid biopsies only require a blood draw.
2. Liquid biopsies generate a complete genetic profile of the tumour/disease. This is in stark contrast to tissue biopsies, which are less effective for diseases characterised by regional heterogeneity, such as cancer.
3. Liquid biopsies enable repeat testing at fast turnaround times, which is critical for determining treatment efficacy and tumour/disease evolution. Due to their invasive nature, tissue biopsies are unable to offer either of these benefits.

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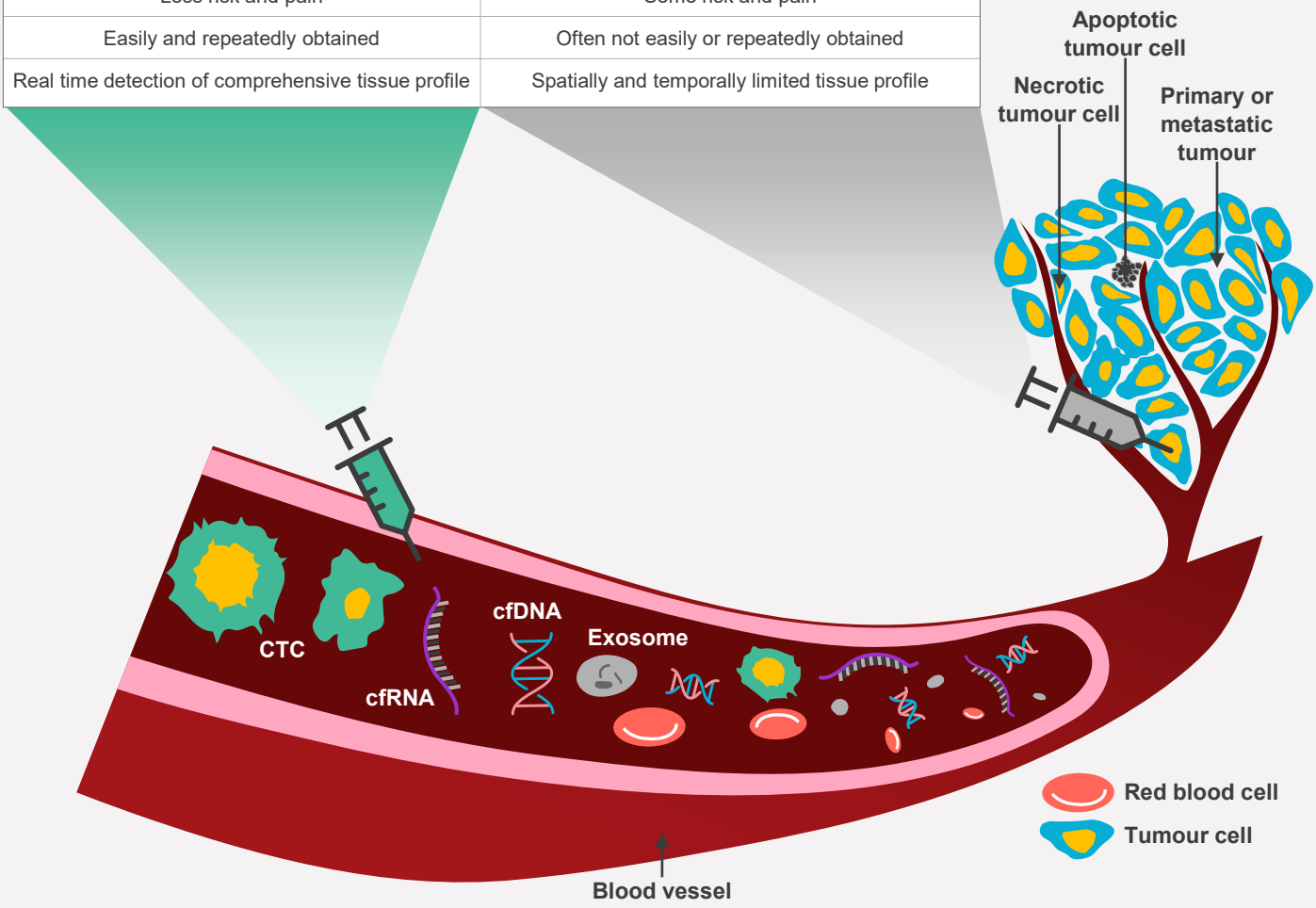
Liquid biopsy vs. traditional biopsy

Liquid biopsy				Traditional biopsy
CTCs	cfNA		Exosomes	Sample cells or tissues
	cfDNA	cfRNA		
Sample derived from body fluid (usually blood)				Sample derived from surgical biopsy or needle biopsy
Non-invasive				Invasive
Less risk and pain				Some risk and pain
Easily and repeatedly obtained				Often not easily or repeatedly obtained
Real time detection of comprehensive tissue profile				Spatially and temporally limited tissue profile



Source: researchgate.net

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A promising solution for cancer diagnosis

Although it can be used for other applications, the excitement around liquid biopsy springs from its potential to diagnose cancer. Cancer remains one of the world's deadliest and fastest growing diseases . According to the WHO, cancer is responsible for 1 in 6 deaths worldwide, 70% of which occur in low- to middle-income countries.

Cancer diagnosis and treatment remains a gargantuan challenge due to the disease's insidious, shapeshifting quality:

> "Cancer is an expansionist disease; it invades through tissues, sets up colonies in hostile landscapes, seeking "sanctuary" in one organ and then immigrating to another. It lives desperately, inventively, fiercely, territorially, cannily, and defensively—at times, as if teaching us how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are."
>
> Source: Siddhartha Mukherjee, The Emperor of All Maladies

Cancer diagnosis and treatment remains an immense challenge due to the disease's insidious, shapeshifting quality. Liquid biopsy could prove a revolutionary diagnostic weapon against cancer due to its potential to monitor disease progression in real-time, allowing clinicians to rapidly adapt the treatment response to the quickly-evolving cancer. Cancer 'invades' the body through the bloodstream, via a process called metastasis. As they metastasize, most solid cancers shed either entire cells, or fragments of cells into said bloodstream. Both cells and cellular fragments are biomarkers which liquid biopsies aim to detect.

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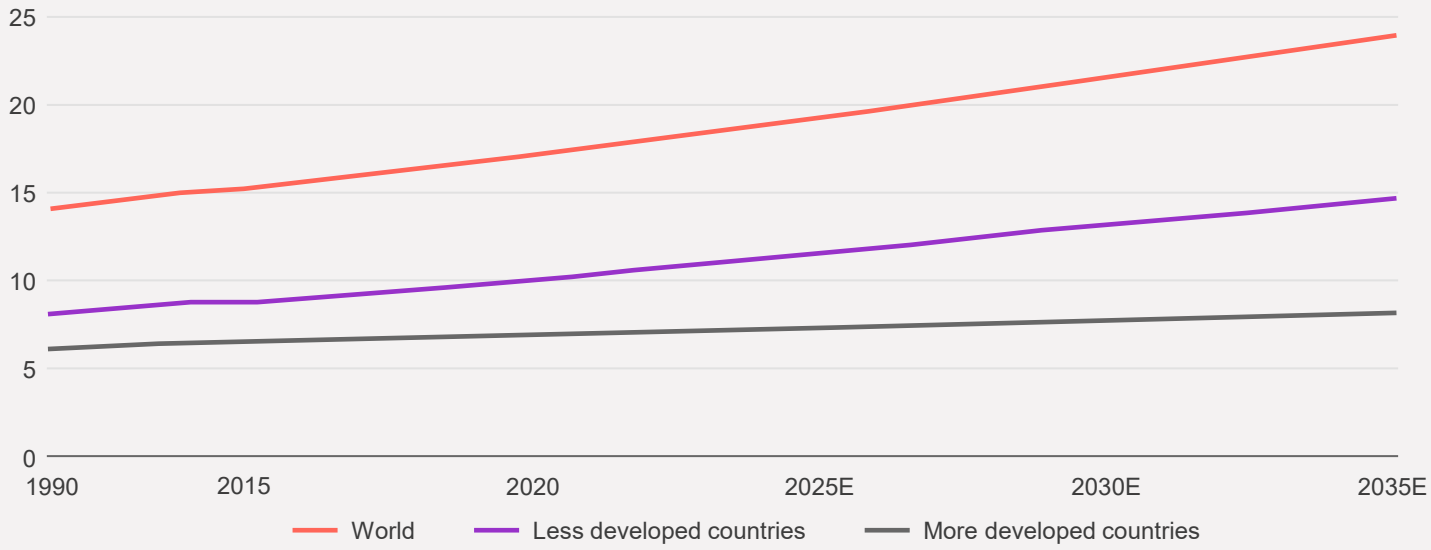
Predicted global cancer cases, 2012–2035
Cases (millions)



Source: WHO GloboCan, BBC.

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A multi-market opportunity

Although the origins of liquid biopsy date back to the 19th century, it was the rapid evolution and plummeting costs of its two base technologies, next-generation sequencing (NGS) and polymerase chain reaction (PCR), that propelled it into commerciality in the 21st century. However, the liquid biopsy market remains nascent and future market size estimates diverge significantly, spanning from approximately $20 to $100 billion Notably, the size of the entire *in vitro* diagnostics market is estimated to be approximately $60 billion.

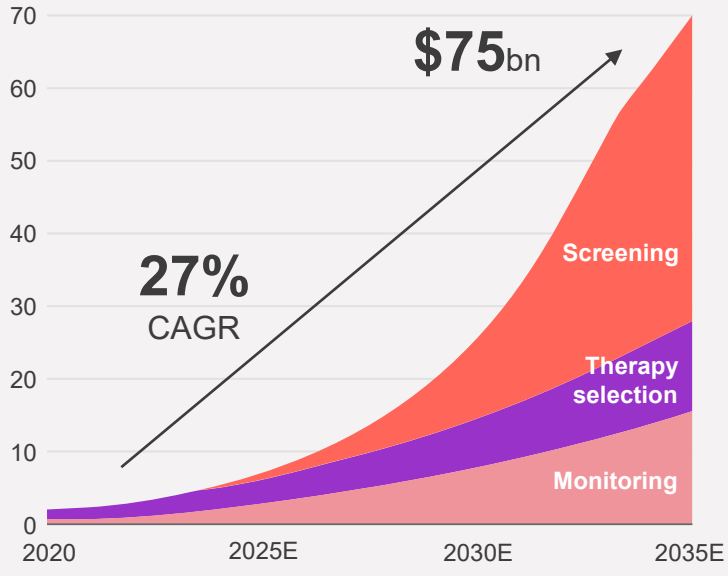
To put it simply, the size of the total addressable market depends on how early liquid biopsy can diagnose cancer. Earlier-stage cancers are easier to treat as they are more localised and are unlikely to have metastasized significantly beyond their place of origin. The importance of earlier detection applies to almost all cancers: the average the 5-year survival rate of early-stage cancer is 91%, which drops to 26% for later stage cancers. However, the significance of early detection can vary significantly between cancers: The five-year survival rate for prostate cancer for instance is 99%, in stark contrast to the five-year survival rate for pancreas cancer, which is 8% .

The problem is that early cancer detection is technically more difficult. Earlier-stage, localised cancers shed less genetic material into the bloodstream. This low volume of cancerous cells or cellular fragments results in a high signal-to-noise ratio, making detection more difficult.

The most established but smallest market for liquid biopsy is therapy selection for late-stage cancers. Here, the clinical evidence base is most robust, and liquid biopsy is used for both companion diagnostics, a test associated with a targeted therapy, and clinical diagnostics. Today, liquid biopsy is thus mainly used to predict treatment response. A less established but bigger market is the monitoring market. Here, liquid biopsy can be used on a long-term basis to monitor treatment response and disease recurrence.

However, the real excitement is sparked by liquid biopsy's potential for early detection and screening of cancers

The majority of cancers today have no associated screening tests, and a number of companies are developing 'pan-cancer' screening tests which aim to detect over 50 types of cancer in a single blood sample.



Source: Illumina.

Target population

Screening — 75% CAGR
~150m tests
Asymptomatic population at heightened risk

Therapy selection — 16% CAGR
~7m tests
Population diagnosed with cancer

Monitoring — 27% CAGR
~20m tests
Population monitored for therapeutic response or disease recurrence

[2]Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. CA: a cancer journal for clinicians, 68(1), 7–30. https://doi.org/10.3322/caac.21442
[3]Siegel, R. L., Miller, K. D., & Jemal, A. (2018). Cancer statistics, 2018. CA: a cancer journal for clinicians, 68(1), 7–30. https://doi.org/10.3322/caac.21442

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Remaining challenges

Clinically useful outcomes

Earlier diagnosis is only useful if the diagnosed cancers can also be treated earlier. In other words, liquid biopsy only lives up to its promises if it improves survival rates of cancer patients. However, increased screening in and of itself creates the illusion of improving 5-year survival rates, even if it doesn't enable more effective treatment. This is due to the lead time bias, in which a disease is detected earlier, but earlier detection does not change the standard treatment paradigm or course of the disease. Statistics will therefore need to be interpreted with great care.

Even more importantly, current treatment paradigms will need to evolve in order to make early detection of cancer clinically useful. A key hurdle to treatment of early-stage tumours is the identification of their location of origin, which remains a challenge within liquid biopsy. A thyroid cancer screening programme, rolled out in South Korea in 1999 for an asymptomatic population, provides a good example. While it resulted in a higher incidence rate, it did not have an impact on mortality rates[4].

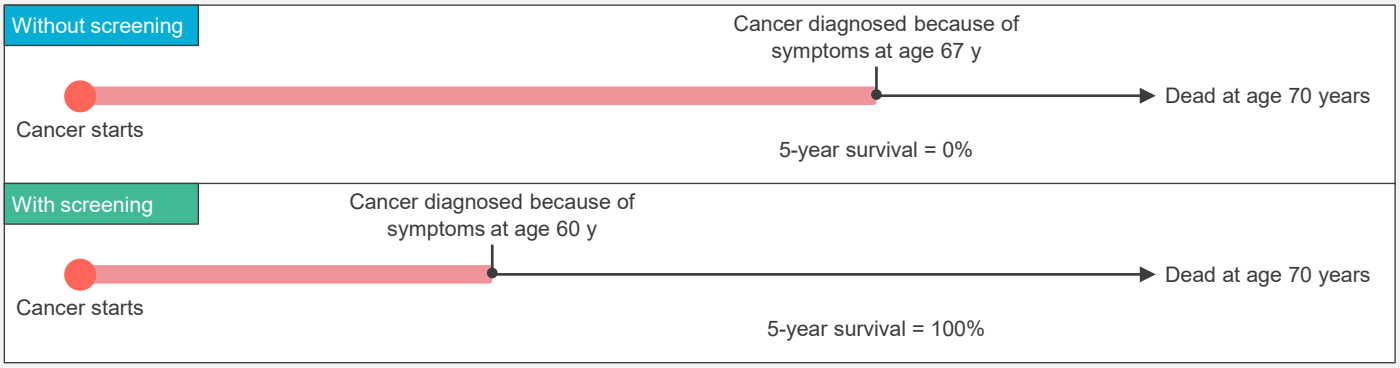
Sensitivity and specificity

Sensitivity and specificity remain a challenge for this fledgling diagnostic tool. As illustrated previously, early-stage tumours only shed low concentrations of cancerous cells or fragments. Low sensitivity in detection results in false negatives, by not being able to detect these low concentrations and means incidents of a disease may go undetected. Low specificity in detection, on the other hand, leads to false positives, whereby the detected biomarkers do not lead to the patient developing the disease at a later stage. Liquid biopsy companies aim to overcome these challenges by combining several tumour-specific biomarkers into a single test. Although the critical threshold levels for each are hotly debated, and vary between different tumours, both remain a challenge for the field.

Reimbursement

The pathway to financial reimbursement for diagnostic tests is complex and lengthy, particularly in the US. While liquid biopsies for later-stage cancers benefit from a better-established path, the reimbursement landscape for pan-cancer screening test is much more uncertain. The viability of pan-cancer screening, in terms of coverage from large payors, is likely to hinge on both legislative change and the industry's ability to drive cost reductions, as molecular diagnostic tests account for a fast-growing share of their expenditure . The onus to demonstrate clinically useful outcomes will therefore be critical to justify the potentially significant expense borne by insurers.

Lead-time bias



Source: Wegwarth, O., Schwartz, L. M., Woloshin, S., Gaissmaier, W., & Gigerenzer, G. (2012). Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. Annals of internal medicine, 156(5), 340-349.

[4]Ahn, H. S., Kim, H. J., Kim, K. H., Lee, Y. S., Han, S. J., Kim, Y., ... & Brito, J. P. (2016). Thyroid cancer screening in South Korea increases detection of papillary cancers with no impact on other subtypes or thyroid cancer mortality. Thyroid, 26(11), 1535-1540.

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Summary

Liquid biopsy's promise is clear: a noninvasive means to identify and track the evolution of a disease, which in turn allows for continuous tweaking of the treatment regimen. This promise is particularly salient for cancer, a disease characterised by its shapeshifting quality, late-stage detection and more generally, limited diagnostic tests. Nevertheless, liquid biopsy has significant technical and reimbursement hurdles to overcome before it can realise its promise.

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