MICRORNAS AS LIQUID BIOMARKERS OF CANCER: A REVIEW OF CURRENT APPROACHES TO CIRCULATING MICRORNAS IN ONCOLOGICAL DIAGNOSTICS

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Abstract. *Cancer remains one of the leading causes of death worldwide, and the stage at which a tumour is detected continues to be among the strongest determinants of patient survival. Although early diagnosis markedly improves outcomes, the screening tools currently in routine use are frequently limited by insufficient sensitivity and specificity. This shortfall has fuelled an active search for minimally invasive biomarkers capable of flagging malignancy at an early, ideally pre-symptomatic, stage. Circulating microRNAs - short non-coding RNAs that are readily detectable in blood and other body fluids - have drawn particular attention in this regard. Owing to their remarkable stability and their tumour-type-specific expression patterns, these molecules are widely viewed as promising candidates for a blood-based "liquid biopsy". The present review brings together current evidence on the diagnostic value of circulating microRNAs across the major categories of malignancy and weighs the prospects for translating them into clinical practice. As the surveyed data show, circulating microRNAs - especially when assembled into multi-marker panels or combined with conventional tumour markers - can deliver sensitivity and specificity high enough to make them a credible tool for minimally invasive cancer diagnostics.*

Keywords: *microRNA, circulating microRNAs, cancer biomarkers, liquid biopsy, oncological diagnostics, early cancer detection, non-invasive biomarkers, tumour markers, miRNA panels, serum biomarkers, plasma biomarkers, personalized oncology.*

INTRODUCTION

MicroRNAs (miRNAs) are a class of short non-coding RNAs, typically 19-24 nucleotides in length, that govern gene expression at the post-transcriptional level. Once processed within the cell, a mature miRNA is loaded into the RNA-induced silencing complex (RISC) and guided to complementary sequences in target messenger RNAs (mRNAs), where it triggers either transcript degradation or translational repression. Through this mechanism miRNAs help orchestrate a broad range of physiological processes, and their dysregulation has been linked to numerous diseases, malignant tumours among them. Cancer cells harbour both oncogenic miRNAs (so-called oncomiRs), whose overexpression silences tumour-suppressor genes, and tumour-suppressive miRNAs, whose loss drives unchecked proliferation, impaired apoptosis and enhanced angiogenesis - changes that together favour tumour progression [35].

Of particular interest is the detection of miRNAs outside the cell, in the circulating blood. The first evidence that tumour-derived miRNAs are present in-patient serum - and that they persist there in a form resistant to RNase activity - was obtained in 2008 [22]. miRNAs released by tumours can be recovered from plasma or serum, where they are shielded from degradation either by binding to proteins such as Argonaute2 or by packaging into extracellular vesicles (exosomes and microvesicles). This stability underlies their considerable promise as non-invasive cancer biomarkers. Over the past ten to fifteen years, research on circulating miRNAs in oncology has expanded rapidly, uncovering numerous associations between blood miRNA profiles and the presence of a tumour, its histological type, stage and prognosis. It has been proposed that characteristic shifts in the levels of particular miRNAs may signal an early, still asymptomatic tumour or a recurrence following treatment [33].

MICRORNAS AND CANCER

miRNAs perform key regulatory roles across cellular processes [4, 11, 18]. The biogenesis of miRNAs and the ways in which they take part in the control of gene expression have been described in detail elsewhere [3, 13]. Since the first miRNAs were identified in *C. elegans*, roughly 1,500 such molecules have been catalogued in humans [26].

The earliest studies - centred on lin-4 and let-7 - revealed the part these miRNAs play in embryogenesis and developmental timing in C. elegans, where they operate within intricate circuits of gene regulation [23]. Biochemical work subsequently showed that such small RNAs can both inhibit protein translation and influence mRNA stability [19]. Current estimates suggest that miRNAs regulate the expression of about half of all protein-coding genes in humans [23].

The pioneering work of Calin and et al. in 2002 was the first to demonstrate a central role for miRNAs in oncogenesis. They found that miR-15 and miR-16 are markedly reduced in chronic lymphocytic leukaemia (CLL) as a consequence of deletions at the 13q14 locus [5]. These early observations also showed that more than half (52%) of miRNA genes lie within genomic regions that are frequently disrupted in cancer; later mapping reinforced the point, pinpointing 186 miRNAs located at fragile sites and other vulnerable parts of the genome [5].

In the years since, miRNAs have been tied to a wide variety of cancers, contributing to neoplastic transformation, tumour progression and clinical outcome [7, 16, 20, 32]. Depending on the set of target genes it regulates, a given miRNA may act either as an oncogene that promotes malignant growth or as a tumour suppressor that restrains carcinogenesis, placing miRNAs at the very heart of the signalling networks that drive cancer.

The involvement of miRNAs in gene regulation underscores their importance both in maintaining normal physiology and in the emergence of disease [19, 24]. Single-nucleotide polymorphisms within the 3′ untranslated regions of mRNAs can, moreover, alter the way miRNAs exert their regulatory effects - a phenomenon that has been associated with an elevated risk of cancer [10].

CIRCULATING MICRORNAS

Drawing a blood sample remains the most accessible and least invasive way to obtain biomarkers. A large body of work has confirmed that distinctive circulating miRNA profiles accompany various pathological states, with expression levels that track disease stage [12, 28, 31]. In oncology, the appearance of specific circulating miRNA signatures reflects the passive escape of these molecules from tumour cells as a result of their heightened proliferation and apoptosis. Contemporary views on the biogenesis, classification and analysis of circulating microRNAs, together with their diagnostic potential, have been reviewed extensively [1, 21, 38].

A comparative analysis by Yu and et al. highlighted appreciable differences between the metabolite profiles of plasma and serum, with serum showing higher metabolite concentrations and, correspondingly, greater diagnostic sensitivity [42]. The study by Lawrie and co-workers was the first to report a diagnostically meaningful rise in serum miR-155, miR-210 and miR-21 in patients with diffuse large B-cell lymphoma relative to healthy donors [22].

Subsequently, miRNA expression profiles were obtained from the serum or plasma of patients with a range of malignancies, including acute leukaemia [36], breast cancer [43], colorectal cancer [29], gastric cancer [37], glioblastoma [34], hepatocellular carcinoma [40], lung cancer [8], ovarian cancer [30] and prostate cancer [27].

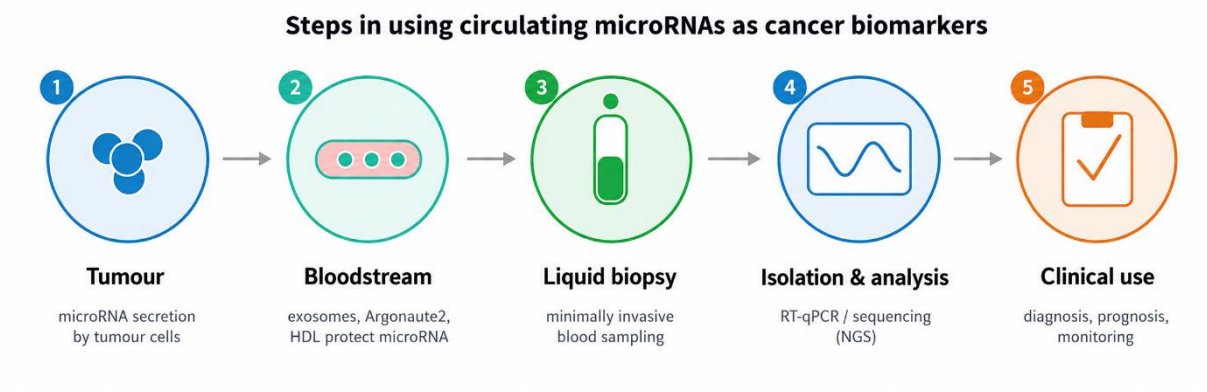


Figure 1. Schematic overview of the steps involved in using microRNAs as cancer biomarkers [9]

CLINICAL EVIDENCE ON THE USE OF MICRORNAS IN ONCOLOGICAL DIAGNOSTICS

Breast cancer (BC), the most common malignancy in women, was among the first tumours for which circulating miRNAs were proposed as diagnostic biomarkers. Breast tumour tissue frequently shows dysregulation of miR-21, miR-155, miR-10b and others, all of which promote invasion and metastasis. These same miRNAs are likewise found at elevated concentrations in the blood of BC patients compared with healthy controls.

In 2021, Canatan and et al. examined the expression of nine candidate miRNAs in the serum of BC patients and identified three - miR-21, miR-125a and miR-155 - that were significantly elevated and offered the greatest diagnostic accuracy [6]. In their data, miR-155 separated patients from healthy individuals with a sensitivity of 83% and a specificity of 82%, while the corresponding figures for miR-125a were 78% and 84%.

Circulating microRNAs are also being explored within diagnostic panels: Hagrass and et al. showed that a serum miRNA panel comprising miR-155, miR-10b and miR-34a reliably distinguishes BC patients from healthy women. Taken together, circulating miR-21, miR-125a and miR-155 are regarded as promising non-invasive markers for the early detection of breast cancer [17].

Lung cancer is the leading cause of cancer death worldwide, in large part because it is so difficult to detect early. Circulating miRNAs are under intensive study as potential early markers of non-small-cell lung cancer (NSCLC) and its other forms [25]. In 2018, Yu and et al. conducted a systematic review of 17 studies on the early diagnosis of lung cancer with miRNAs in Western populations, drawing together data on 35 individual miRNA markers and 19 marker combinations. Single miRNAs achieved a median sensitivity of 78% and specificity of 79%, whereas multi-miRNA panels performed better, with a median sensitivity of 83% and specificity of 85% [42].

Combinations of two to five circulating miRNAs thus detected early lung cancer considerably more accurately than individual markers; the miR-223/miR-20a/miR-21 panel, for instance, reached an AUC of 0.90 in NSCLC patients relative to healthy smokers [42]. The use of miRNA expression ratios proved a further useful strategy: as Yu and et al. noted, computing the ratio between paired miRNAs helps offset inter-individual variability and improves the reproducibility of the test.

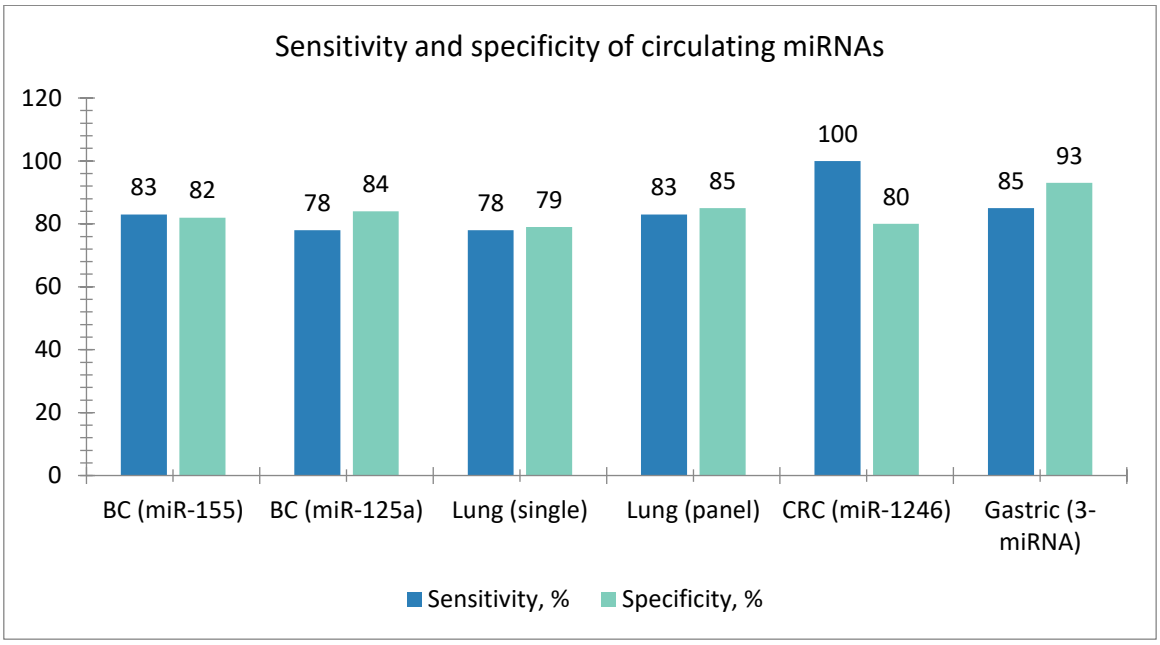


Figure 2. Sensitivity and specificity of circulating miRNAs across different cancer types.

Colorectal cancer (CRC) is one of the most common malignancies of the gastrointestinal tract, and blood miRNAs are being actively studied to enable its early detection. In their 2024 meta-analysis, AlZaabi and Shalaby reported that the circulating miRNA profiles of CRC patients differ substantially from those of healthy individuals, with frequent increases in miR-21, miR-20a and miR-223 and decreases in a number of other miRNAs. miR-21 has attracted special attention, as it is detected consistently in CRC and is linked to tumour progression. The same meta-analysis noted that the diagnostic performance of miR-21 varies widely across studies, from a modest AUC of 0.55 to a very high 0.97. More reproducible markers were nonetheless identified: circulating miR-1246, for example, showed strong diagnostic accuracy in several reports, and in one study it detected CRC with an AUC of 0.924 at 100% sensitivity and 80% specificity - figures comparable to, or better than, those of established non-invasive tests such as the faecal occult blood test [2].

Gastric cancer (GC) carries high mortality, again largely because of late detection. Circulating miRNAs are being assessed as a possible tool for the non-invasive screening of early gastric cancer. In the blood of GC patients, increases in miR-21, miR-20a, miR-221/222, miR-423-5p and several others are reported most often, alongside reductions in the tumour-suppressive miR-375, miR-148a and others. In 2021, Yao and et al. analysed miRNA expression profiles in two independent cohorts of GC patients and healthy individuals and, using machine learning, singled out three key miRNAs (miR-320a, miR-1260b and miR-6515-5p) that together delivered excellent diagnostic performance. In both cohorts this trio separated gastric cancer patients with an AUC above 0.95 at a sensitivity exceeding 85% and a specificity above 93%. Validation on additional datasets further showed that each of the three markers individually provided a sensitivity of 92-100% with a specificity of 89-100%, while their combined use approached 100% accuracy

(AUC 0.99) [41]. Pancreatic cancer (PaC), and pancreatic ductal adenocarcinoma (PDAC) in particular, is notable for its extremely aggressive course and the lack of effective methods for early diagnosis. Circulating miRNAs are of special interest here, since the conventional marker CA 19-9 is insufficiently sensitive at early stages.

In 2021, Vieira and et al. demonstrated the diagnostic value of several miRNAs in PDAC: plasma levels of miR-181c and miR-210 were markedly elevated in patients relative to healthy controls and could be used to flag the presence of a tumour. Strikingly, in pancreatic tissue samples the combined expression of miR-21 and miR-210, considered together with serum CA 19-9, achieved 100% accuracy in diagnosing pancreatic cancer. This suggests that pairing classical tumour markers with a miRNA profile can substantially improve diagnostic reliability. Overall, miR-21, miR-155, miR-181c and miR-210 are viewed as leading candidates for multi-marker panels in pancreatic cancer; their use, especially alongside CA 19-9, could improve early detection of this tumour - a matter of considerable importance given its rapid progression [39].

Prostate cancer (PC) is among the most common malignancies in men. The standard screening marker, prostate-specific antigen (PSA), has limited specificity, so the search for additional non-invasive biomarkers is relevant for improving early diagnosis and curbing overdiagnosis.

In a large 2025 study, Gomez-Acebo and et al. analysed 46 candidate miRNAs in 203 prostate cancer patients and 54 controls, then built predictive models from the best-performing markers. They identified 14 miRNAs robustly associated with the presence of prostate cancer. Among them were miR-199a-5p, which was elevated in patients, and miR-150-5p, which was conversely reduced across all risk categories. Several miRNAs - miR-145-5p, miR-93-5p and miR-182-5p, for example - already differed significantly at early disease stages, pointing to their potential for detecting localised cancer. Logistic models built on panels of several miRNAs performed well: for the low-risk (early-stage) group the classifier reached an AUC of 0.93, whereas the overall model distinguished patients from healthy individuals with an AUC of 0.82 [15].

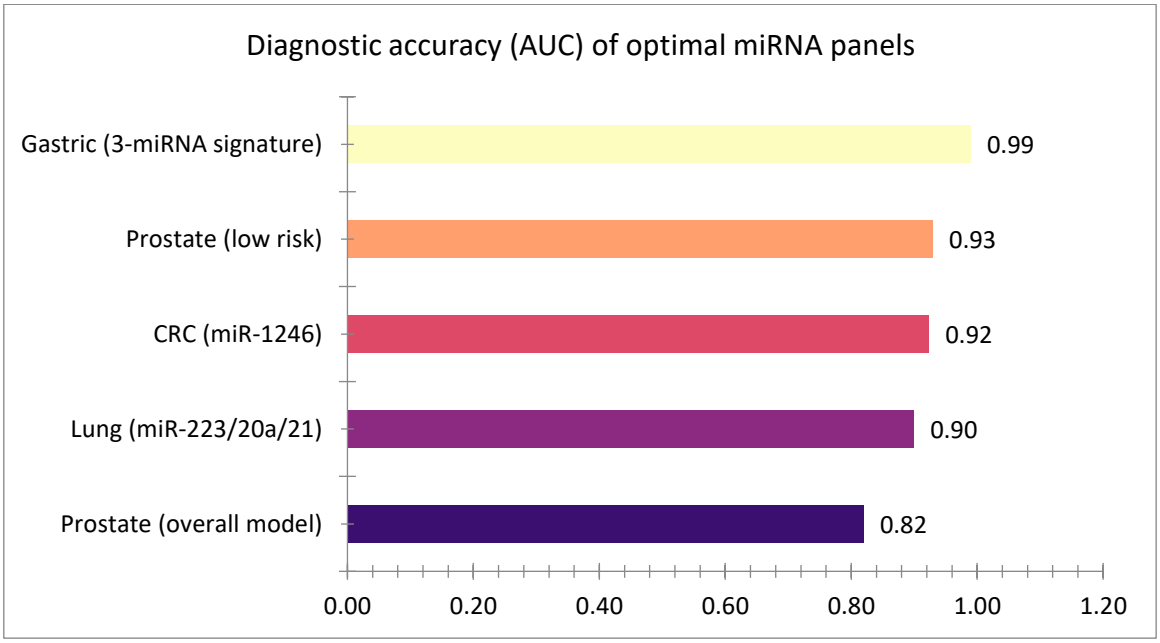


Figure 3. Diagnostic accuracy (AUC) of optimal miRNA panels by cancer type.

Ovarian cancer (OC) is frequently diagnosed at an advanced stage because it lacks specific symptoms and reliable screening tests. The main marker in current use, CA 125, is not sensitive enough for early detection.

In their 2023 meta-analysis, Frisk and et al. pooled data from 44 studies of circulating miRNAs in OC, 22 of which entered the quantitative analysis. The authors highlighted nine miRNAs that were most reproducibly altered in ovarian cancer - miR-21, miR-125b, miR-141, miR-145, miR-200a, miR-200b, miR-200c, miR-205 and miR-328 - all of which were significantly higher in-patient blood than in healthy controls; miR-21 and miR-205 ranked among the most consistently confirmed markers. The same meta-analysis showed that integrating a miRNA (such as miR-205 or miR-132) with CA 125 raised the AUC to 0.95-0.98, compared with 0.85 for CA 125 alone [14].

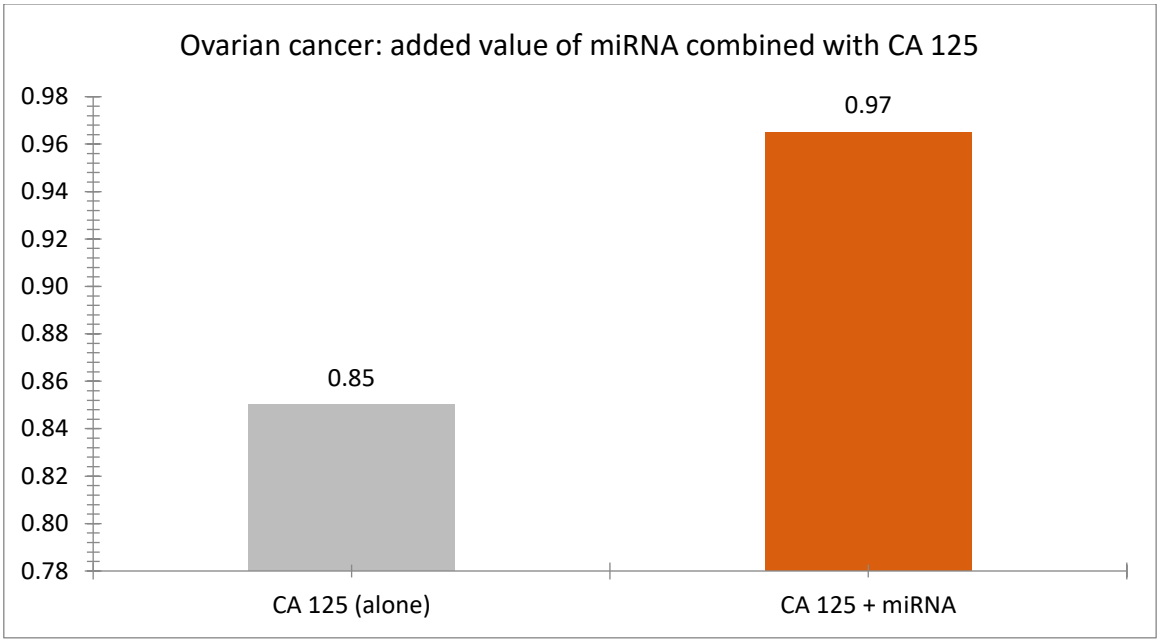


Figure 4. Improvement in diagnostic accuracy when miRNA is added to the CA 125 tumour marker (ovarian cancer) [14].

Table 1. Examples of circulating miRNAs in the diagnosis of various cancers.

Disease	**microRNA**	**Diagnostic role of microRNA**	**Study**
Breast cancer	miR-21 ↑ miR-125a ↑ miR-155 ↑	Early BC diagnosis; distinguish patients from healthy controls with high sensitivity and specificity	Canatan et al. 2021 [6]
Lung cancer (NSCLC)	miR-21 ↑	Non-invasive screening of early lung cancer; 2-4-miRNA panels give AUC 0.80-0.85	Yu et al. 2018 [42]

Colorectal cancer	miR-1246 ↑	Detection of colorectal cancer; one of the most accurate markers (AUC 0.92, 100% sens., 80% spec.)	AlZaabi & Shalaby, 2024 [2]
Gastric cancer	miR-320a ↑ miR-1260b ↑ miR-6515-5p ↑	Three-miRNA signature for early diagnosis; validation showed >95% detection accuracy	Yao et al. 2021 [41]
Pancreatic cancer	miR-21 ↑ miR-155 ↑	PDAC markers; associated with tumour presence and aggressiveness, proposed for early diagnosis (combined with CA 19-9)	Vieira et al. 2021 [39]
Prostate cancer	miR-199a-5p ↑ miR-150-5p ↓	Early diagnosis and risk stratification of PC; part of a 14-miRNA set for discriminating prostate cancer	Gómez-Acebo et al. 2025 [15]
Ovarian cancer	miR-21 ↑ miR-125b ↑ miR-200c ↑	Screening of epithelial OC; combining several miRNAs with CA 125 improves early-diagnosis accuracy	Frisk et al. 2023 [14]

CONCLUSION

Recent research has made a compelling case that circulating miRNAs hold considerable promise as early cancer biomarkers. For virtually all of the major tumour types - lung, breast, colorectal, pancreatic, ovarian and prostate cancer among them - specific blood miRNA patterns have been identified that set patients apart from healthy individuals. These short RNAs are highly stable in plasma and serum, and their profiles mirror the molecular and genetic alterations characteristic of the corresponding tumours. In this review we have surveyed current approaches to miRNA detection and presented examples of diagnostic panels that achieve sensitivity and specificity matching or surpassing those of conventional markers. It is worth emphasising that the most promising direction lies in combining several miRNAs and in integrating miRNAs with classical tumour markers and clinical variables, an approach that appreciably increases diagnostic accuracy.

That said, a number of hurdles must be cleared before miRNA tests can enter routine clinical practice. These include standardising the methods used to isolate and analyse circulating

RNA, developing reliable normalisation controls, validating the identified biomarkers at scale in prospective patient cohorts, and accounting for the influence of comorbidities and other conditions on miRNA levels. Meeting these challenges will demand concerted effort from research groups and clinicians alike, as well as well-designed multicentre studies.

In closing, circulating miRNAs open up new possibilities for non-invasive cancer diagnosis. They offer several clear advantages - minimally invasive sampling, high stability, tissue specificity and the ability to capture the dynamics of disease. Within the next few years one can anticipate the emergence of miRNA-panel-based test systems for the early detection of cancer, the monitoring of treatment response and the identification of recurrence. Further research and clinical trials will reveal whether these molecules can live up to the hopes placed in them and secure a lasting place in the diagnostic arsenal of personalised oncology.

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