

Liquid Biopsy in Glioma: Transforming Diagnosis and Monitoring Through Blood and Cerebrospinal Fluid

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Abstract

Gliomas are one of the most challenging types of cancer to date, due to their location in the brain and their highly spatial and temporal heterogeneity. Invasive biopsies show critical limitations in detecting and monitoring these cancers and their evolution. Liquid biopsy has emerged as a promising alternative to deal with gliomas detection and treatment. The goal of this research is to provide an assessment of the state of liquid biopsy development to date, its current prospects and limitations. A literature review was performed using PubMed and Science Direct, including the review of 29 articles and papers. This analysis demonstrates that liquid biopsy represents a potential step change in gliomas detection and treatment. A key issue revolves around the detection of biomarkers in the body fluids. New detection techniques and the development of advanced tumor-informed strategies also contribute to improving the effectiveness of liquid biopsy. Finally, the association of liquid biopsy with the use of artificial intelligence suggests radical improvements are at reach, and the possible advent of a truly personalized monitoring and treatment of gliomas, a revolution in clinical practice.

Keywords: Gliomas, tumor, brain, liquid biopsy, tumor-informed, tumor-naïve, artificial intelligence

● Introduction

There are over 300,000 brain and central nervous system cancers per year globally (Filho et al., 2025). Gliomas represent the most common form of these (Cancer Australia, 2025). They emerge from glial cells which typically protect neurons in the brain (Figure 1). Symptoms typically involve headaches, seizures, cognitive changes and potentially personality alterations (Gevorgyan, 2025).

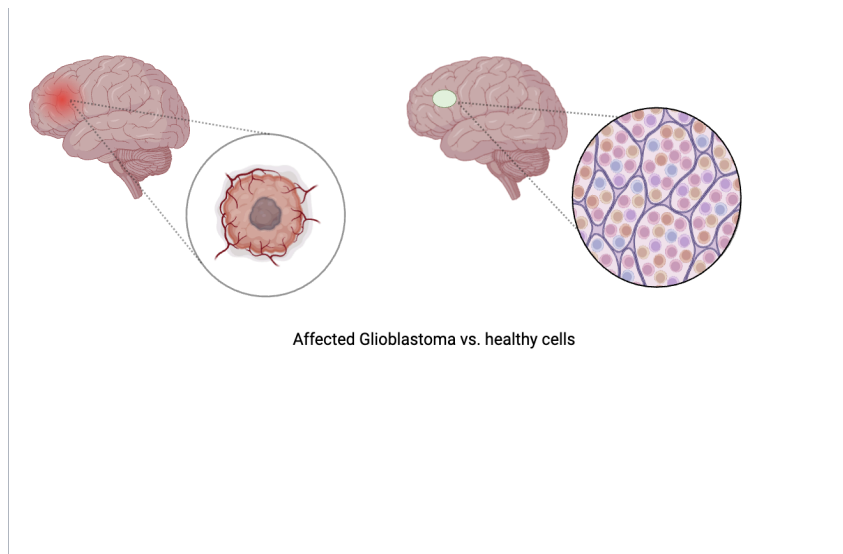


Figure 1. Comparison between a healthy brain vs. a brain affected by a glioma. The left image pictures a brain with a visible tumor (highlighted in red) demonstrating the presence of an abnormal tissue mass called glioma. Conversely, the picture on the right is a healthy brain. This comparison illustrates the structural difference between healthy brain tissue and an affected one. This disruption can lead to multiple complications such as loss of cognitive performance and overall brain activity.

Dealing with gliomas is complex and one of the most challenging types of cancer to date. They are characterized by a high spatial and temporal heterogeneity. Spatial heterogeneity accounts for the development of the tumor through the brain, while temporal heterogeneity relates to its development over time (Berzero et al., 2023; Birkó et al., 2020; Eibl & Schneemann, 2021; Soffietti et al., 2022).

The spatial heterogeneity of tumor development in the brain from gliomas makes surgical procedures difficult to conduct effectively, as a multitude of tissue collections might be required for proper diagnosis and monitoring over time, a recognized issue as limited tissue availability from the brain makes an effective histopathological diagnosis difficult to conduct (Berzero et al., 2023; Eibl & Schneemann, 2021; Soffietti et al., 2022). This challenge is particularly evident in glioblastoma, where marked intra-tumoral heterogeneity further complicates representative sampling (Birkó et al., 2020; Shankar et al., 2017). The recourse to conventional tissue biopsy also makes it impossible to monitor over time the evolution of the tumor and thus address temporal heterogeneity (Berzero et al., 2023; Eibl & Schneemann, 2021; Soffietti et al., 2022). Finally, surgery in the brain is complex and prone to many risks such as infection, further neurological issues and anesthetic complications (Brennan, 2022; Shankar et al., 2017). The ability of traditional tissue biopsies to fully comprehend the state of development of gliomas is thus limited. Hence, lots of research has been engaged to find a less invasive approach and more comprehensive diagnostic and monitoring tools for gliomas (Figure 2) (Berzero et al., 2023; Soffietti et al., 2022).

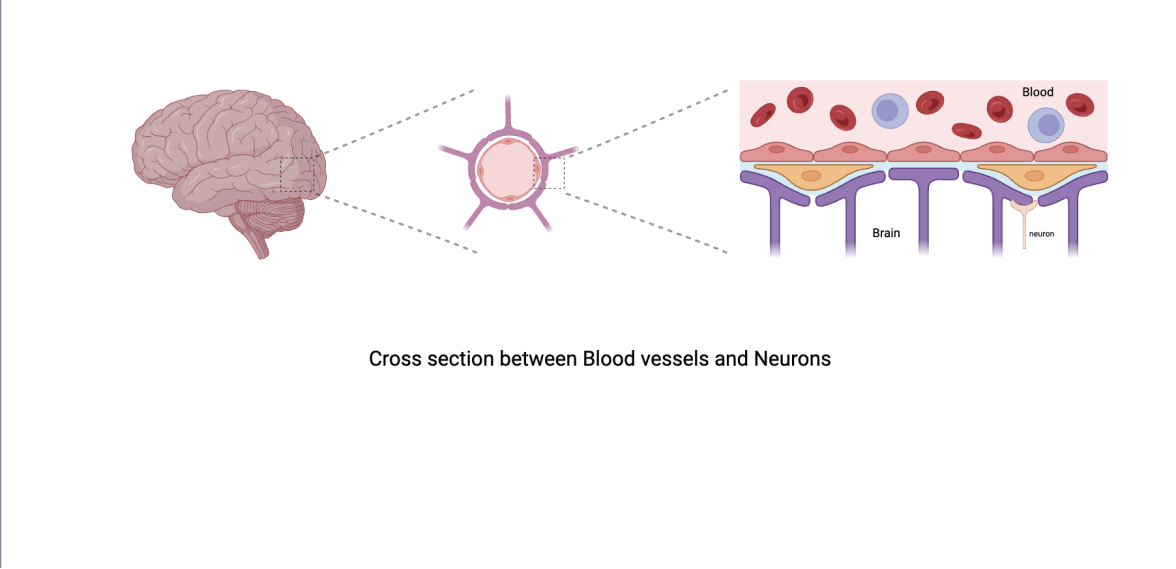


Figure 2. Timeline of major discoveries and developments regarding detection for brain cancer. The figure incorporates notable breakthroughs over time as well as the affiliation of AI integration in the field of brain cancer diagnostics.

A highly promising approach is liquid biopsy. It builds on biomarkers of residual tumor elements which penetrate body fluids such as the bloodstream or the cerebrospinal fluid (CSF) (Alix-Panabières & Pantel, 2021; An et al., 2021; Eibl & Schneemann, 2021).

Liquid biopsy faces however a key challenge with the brain blood barrier (BBB). The BBB is made of tightly joint endothelial cells which are supported by pericytes and astrocytes cells. Together, they form an impermeable barrier between the blood circulation and the nervous system (Figure 3). The BBB blocks harmful substances from entering brain tissue while enabling key nutrients, and contributes to maintaining a stable chemical environment for the brain. As a result, the BBB has long been a key impediment to such approach, also preventing the effectiveness of drug delivery and the recourse to many existing systematic therapies (Birkó et al., 2020; Mair & Mouliere, 2022; Shankar et al., 2017; Soffietti et al., 2022).

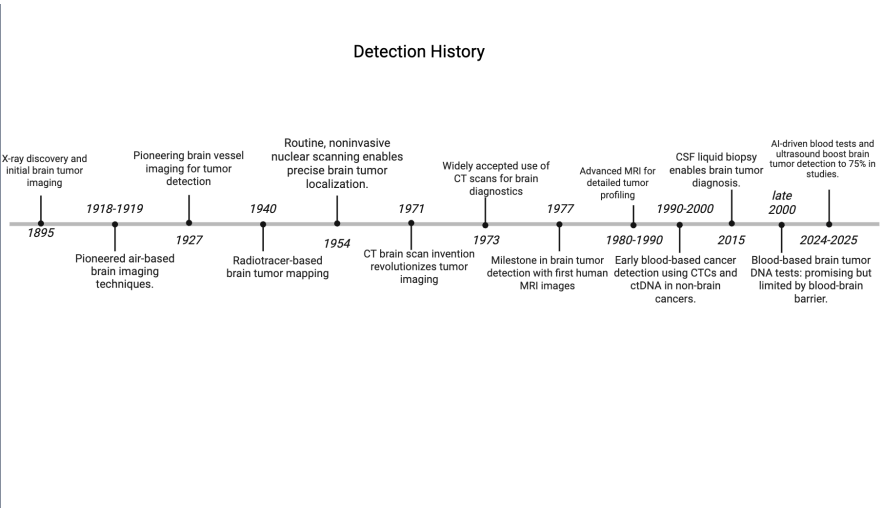


Figure 3. Cross section between blood vessels and neurons. This figure shows the cross section between blood vessels and neurons. On the left is a picture of the whole brain. On the right, a focused perspective of the blood brain barrier. This close-tied arrangement is crucial for maintaining a stable environment for neural activity as well as understanding the presence of ctDNA in blood or CSF during a liquid biopsy procedure.

- **Methods**

Significant progress has, however, been made recently on liquid biopsy techniques, building on biomarkers detection, detection strategies and the use of AI (Ma et al., 2024; Seyhan, 2024).

- **Biomarkers detection**

Liquid biopsy is based on the detection of selected biomarkers in the bloodstream or the CSF. These analytes involve circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), circulating tumor cells (CTCs), extracellular vesicles (EVs), and tumor-educated platelets (TEPs) (Alix-Panabières & Pantel, 2021; Birkó et al., 2020; Eibl & Schneemann, 2021).

ctDNA includes DNA fragments which cross the BBB into the body fluids (blood stream, CSF). These fragments carry tumor-specific mutations such as SNVs and CNAs which can be detected (Eibl & Schneemann, 2021; Heitzer et al., 2015; Sánchez-Herrero et al., 2022). cfDNA corresponds to DNA released when a cell dies; normal cells thus account for the majority of cfDNA. Therefore, ctDNA exists in low concentrations within a healthy individual, and its concentration increases as the tumor progresses (Birkó et al., 2020; Ma et al., 2024). Detection of analytes involves a variety of methodologies with a mix of separation techniques: PCR and/or RNA sequencing. For example: ctDNA and cfDNA analyses typically rely on PCR, a technique which amplifies specific DNA sequences (Friedman et al., 2022; Gatto et al., 2021; Mair & Mouliere, 2022). CTCs are cancer cells which enter the fluids intact. They are, however, rare in the case of gliomas. Their analysis generally uses the FDA-approved CellSearch System, based on immunomagnetic enrichment, a technique where antibodies bind on surface markers and are then expelled through the application of a magnetic field (Berzero et al., 2023; Brennan, 2022; Shankar et al., 2017).

EVs cross the BBB more easily than free DNA, and carry proteins, RNA and DNA from tumor cells. They are usually analyzed through ultracentrifugation - a separation technique using high centrifugal forces to separate particles based on size or density (An et al., 2021; Eibl & Schneemann, 2021; Seyhan, 2024).

Finally, TEPs undergo changes when in contact with a tumor cell, leading to a change in their RNA content or protein expression while relying on RNA sequencing (Ma et al., 2024; Sánchez-Herrero et al., 2022).

Other valuable techniques involve Next Generation Sequencing (NGS), Microfluidic Devices, or Immunocytochemistry. NGS differs from traditional sequencing as it sequences millions of DNA fragments simultaneously. Microfluidic devices are miniaturized systems which manipulate very small volumes of fluid with high precision. They can be used for cell sorting, single-cell analysis and the study of cell behaviors. Immunocytochemistry uses antibodies to detect and visualize proteins or other molecules within cells (Alix-Panabières & Pantel, 2021; Mair & Mouliere, 2022; Soffietti et al., 2022).

- **Tumor-informed and tumor-naïve strategies**

Liquid biopsy for brain cancer can broadly be categorized into two distinct strategy forms: tumor-informed and tumor-naïve strategies, depending on whether prior knowledge of the tumor exists or not (Ma et al., 2024; Sánchez-Herrero et al., 2022). Tumor-informed strategies use prior knowledge about the patient's tumor, knowledge usually acquired through tissue biopsy or previous resection. With such knowledge in hand, the liquid biopsy assay is customized to track patient-specific mutations. This technique requires initial tumor sequencing but offers a much higher sensitivity, both for detection and monitoring. It also offers high specificity for detecting minimal residual disease (MRD) and for tracking recurrence and mutations (Bartolomucci et al., 2025; Chahardehi et al., 2025).

In contrast, the tumor-naïve approach uses a standardized panel targeting recurrent mutations common to any cancer type. It will be used when no prior contextual information on the tumor is available. It is less sensitive, thus leading to potentially missing patient-specific mutations or resulting in false positives. This is particularly problematic for highly heterogeneous tumors such as gliomas (Table 1, Figure 4) (Dwarshuis et al., 2025; Soffietti et al., 2022). Tumor-naïve approaches will thus be favored when no information exists on the patient, typically at an initial stage of development.

Table 1. Comparative Table: Tumor-Informed vs. Tumor-Naïve Approaches. This table describes the differences between a tumor-informed and a tumor naïve approach. Both have their own advantages and disadvantages.

Feature	Tumor-Informed	Tumor-Naïve
Requires tumor tissue	Yes	No
Sensitivity	High (tracks patient-specific)	Lower (tracks common mutations in known cancer genes)
Specificity	High	Moderate
Clinical timing	Post-diagnosis, post-surgery	Any time (pre/post diagnosis)
Use in gliomas	Ideal for MRD, recurrence, and resistance	Useful when tissue is unavailable
Risk of false positives	Low	Higher (especially in heterogenous tumors)
Detection of new mutations	Limited (unless broad panel is used)	Possible but less sensitive

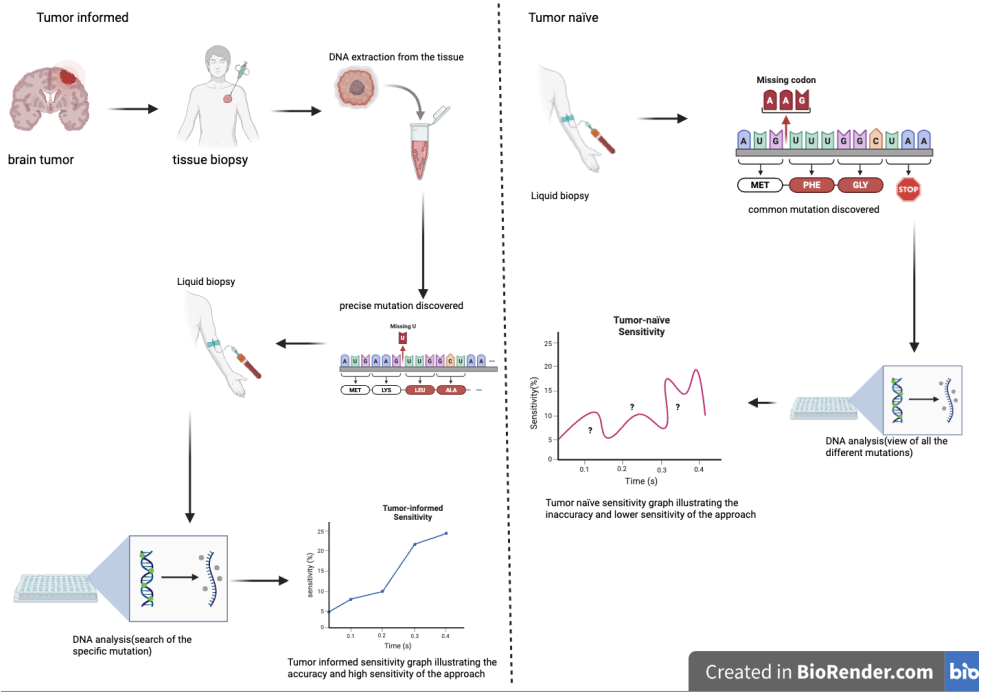


Figure 4. Comparison of Tumor-informed and Tumor naïve Liquid Biopsy workflows and diagnostic effectiveness in brain cancer. This figure illustrates the tumor-informed and tumor-naïve approaches in the liquid biopsy workflow. Tumor-informed is represented on the left. Key steps are described, with notable focus on identifying a specific mutation, after DNA extraction from tissue biopsy. In contrast, on the right, the tumor-naïve approach is represented. It focuses on detecting existing known mutations.

- **Liquid biopsy and AI**

Detection of biomarkers through a variety of techniques and strategies faces a data collection and interpretation challenge, including the sensitivity and accuracy of each measure (Ma et al., 2024), the conclusions which can be derived from different measures of different biomarkers with different accuracy (Birkó et al., 2020; Sánchez-Herrero et al., 2022), and more importantly the multidimensional aspect of analysis - a known issue in molecular research - where the number of variables to explore is large relative to the sample available, leading to statistical interpretation challenges (Berzero et al., 2023; Chahardehi et al., 2025; Mair & Mouliere, 2022).

Artificial Intelligence (AI) is efficiently put to use to deal with such datasets through the use of reduction techniques or feature selection (Ma et al., 2024; Mair & Mouliere, 2022). Machine learning algorithms can also be considered to detect thin relationships or patterns within the data (Berzero et al., 2023; Seyhan, 2024). Deep learning can analyze gene expression patterns across millions of samples and identify disease types or predict treatment responses (Bartolomucci et al., 2025).

• Results

Liquid biopsy effectiveness has considerably increased over the years as a result of these improvements, making it a viable alternative option to tissue biopsy (Figure 5).

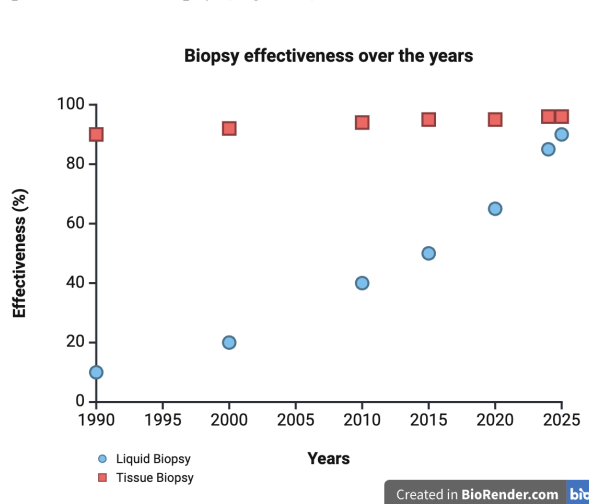


Figure 5. Biopsy effectiveness over the years. This figure illustrates the comparison of two biopsy techniques, tissue biopsy (in red) and liquid biopsy (in blue), and their effectiveness over the years, starting from 1990 to 2025. The y-axis represents the effectiveness in % and the x-axis represents the years. Liquid biopsy showed a significant improvement in effectiveness, achieving a similar effectiveness to tissue biopsy over time.

• Applications of liquid biopsy in the management of brain tumors

Liquid biopsy can serve as an initial diagnosis tool when tissue biopsy is not feasible (Berzero et al., 2023; Eibl & Schneemann, 2021; Shankar et al., 2017; Soffietti et al., 2022). It is a particularly relevant method at initial stages of cancer detection (An et al., 2021; Gatto et al., 2021).

Liquid biopsy strategies also significantly improve molecular profiling (Ma et al., 2024). Tumor-naïve panels provide a broad screening, but they may lack depth for rare variants or mutations, and consequently miss on patient-specific tumor developments (Sánchez-Herrero et al., 2022). In contrast, tumor-informed liquid biopsies are more precise and able to track tumor evolutions, mutations and resistance mechanisms in more detail (Bartolomucci et al., 2025; Chahardehi et al., 2025; Guo et al., 2025).

Liquid biopsy also materially improves the monitoring of disease progression and the effectiveness of treatment (Bartolomucci et al., 2025; Guo et al., 2025). Tumor-naïve liquid biopsy can be used as a first-order or complementary option for general surveillance. Tumor-informed liquid biopsy will, however, be highly efficient to track progress in treatment and eventual relapse, as it is highly sensitive to MRD detection (Bartolomucci et al., 2025; Soffietti et al., 2022).

Liquid biopsy is finally well-suited to track and reveal actionable mutations (Berzero et al., 2023; Ma et al., 2024). It comes as a particularly efficient approach in the tumor-informed strategy, thereby ensuring that the therapy is tailored to the evolving landscape of the tumor molecular patterns (Chahardehi et al., 2025; Ma et al., 2024).

• Tumor-informed vs tumor-naïve strategies

As discussed, a key issue with liquid biopsy is the sensitivity of the detection, given the very limited amount of infected material circulating in the body fluids (Ma et al., 2024; Sánchez-Herrero et al., 2022). This is why different strategies have emerged. Tumor-naïve strategies are not context specific and do not involve prior tissue collection. They are typically more useful for

initial diagnosis but lack sensitivity. In contrast, tumor-informed approaches are based on the existing data and known condition of a patient, through, for instance, prior tissue biopsy. The recourse to more context-specific, tumor-informed strategies considerably enhances the precision of the analysis - a procedure which can then be used for monitoring the evolution of the tumor over time (Bartolomucci et al., 2025; Ma et al., 2024).

The analysis of biomarkers in the CSF rather than in the bloodstream has also emerged as a promising alternative given the higher concentration of infected material in the CSF (Friedman et al., 2022; Hickman et al., 2023; Mattox et al., 2019; Otsuji et al., 2024).

- **Technological innovations**

Liquid biopsy is a dynamic field of medical research (Alix-Panabières & Pantel, 2021; Ma et al., 2024). Key innovations are emerging to further improve its effectiveness. These revolve around two main dimensions: enhancing the volume of biomarkers in the bloodstream (or CSF), and improving molecular detection methodologies (Ma et al., 2024).

Focused ultrasounds (FUS) are a promising technique to increase the volume of biomarkers released in the body fluids. When FUS are applied, the BBB can be transiently disrupted, increasing the release of biomarkers in the body fluids (Ahluwalia et al., 2024; Pacia et al., 2020; Zhu et al., 2018).

As discussed, molecular detection rests on a number of techniques involving separation and sequencing (Heitzer et al., 2015; Mair & Mouliere, 2022). New techniques are currently emerging, including high-sensitivity sequencing as an alternative to traditional sequencing (Ma et al., 2024; Sánchez-Herrero et al., 2022), digital PCR as an alternative to traditional quantitative PCR (Heitzer et al., 2015), and combining cfDNA and cfRNA panels (Ma et al., 2024; Seyhan, 2024).

The recourse to AI tools is also promising. AI-driven classification models can first be used to improve the liquid biopsy profiles and detect the different glioma subtypes (Berzero et al., 2023; Brennan, 2022; Ma et al., 2024; Seyhan, 2024). AI can also be used for predictive analysis and the analysis of time-series of liquid biopsy data over time (Dwarshuis et al., 2025; Guo et al., 2025).

AI can also assist in matching molecular profiles to targeted therapies, leading to patient-specific therapies (Bartolomucci et al., 2025; Ma et al., 2024). AI will also play a significant role in error correction, large-scale data interpretation, and automated variant calling (Bartolomucci et al., 2025; Ma et al., 2024; Sánchez-Herrero et al., 2022). Finally, in the context of the development of FUS, AI tools can be used for precision targeting of the zones where to affect the BBB while maximizing safety (Ahluwalia et al., 2024; Pacia et al., 2020; Zhu et al., 2018).

- **Discussion**

- **Limitations and Challenges of Liquid Biopsy**

As promising as liquid biopsy is for cancer diagnosis, it nevertheless shows several limitations. First, it rests on biomarkers identification in body fluids, which remain scarce due to the BBB (Berzero et al., 2023; Birkó et al., 2020; Mair & Mouliere, 2022). The use of CSF rather than the bloodstream helps to rely on increased concentrations, but the problem of accurate detection due to low concentrations remains a challenge (Hickman et al., 2023; Otsuji et al., 2024; Soffietti et al., 2022).

Second, tumor-naïve assays, while useful for initial monitoring, lack precision and sensitivity, and may lead to a lack of detection or false positives (Ma et al., 2024; Sánchez-Herrero et al., 2022). In contrast, tumor-informed assays will be more precise and represent a useful strategy for monitoring over time, *once* the tumor has been detected (Bartolomucci et al., 2025; Berzero et al., 2023; Soffietti et al., 2022). It, however, requires initial samples retrieved from conventional biopsy, a highly sensitive surgical operation in the brain (Ma et al., 2024).

Liquid biopsy still requires the development of consistent and standardized protocols to ensure reliable use in clinical practice (Alix-Panabières & Pantel, 2021; Brennan, 2022; Ma et al., 2024; Sánchez-Herrero et al., 2022; Soffietti et al., 2022). These will involve standardized sampling and processing methods, assay protocols and quality control, and reporting standards.

Finally, while the use of AI combined with liquid biopsy is highly promising, it also requires to be grounded on specific ethical rules, including respect for patient privacy, ensuring non-biased analysis and maintaining a high level of explainability (Berzero et al., 2023; Future Market Insights, 2025; Ma et al., 2024).

- **Future directions**

Currently, clinical trials have begun, leveraging both tumor-informed and tumor-naïve liquid biopsy strategies (Ahluwalia et al., 2024; Berzero et al., 2023; Brennan, 2022). They need to be continued and standardized protocols established (Soffietti et al.,

2022). Methodologies of analysis must also be reinforced, including multi-modal monitoring, combining traditional imaging, liquid biopsy and the use of AI (Bartolomucci et al., 2025; Dwarshuis et al., 2025; Ma et al., 2024). In the future, the development of AI suggests the possible advent of AI-driven personalized medicine, where diagnostic and treatment may be personalized to the specific development of a patient's disease, controlled and adapted over time (Ma et al., 2024). There are, however, ethical, legal and social implications of the use of AI which will need to be overcome (Seyhan, 2024).

● Conclusion

Liquid biopsy has emerged as a promising alternative to gliomas detection and treatment monitoring. Tumor-informed strategies, when available, are particularly suited for monitoring the evolution of tumors over time, and for the development of better classification towards personalized approach to treatment.

The key issue of detection of biomarkers within the bloodstream or the CSF remains, however, a key difficulty because their low concentration makes the analysis more complex and potentially prone to missed detection of false positives. Technological innovations such as FSU or new molecular detection techniques focus on addressing such limitations.

The use of AI combined with sample acquisition also offers a promising route to refine the efficiency of liquid biopsy for both tumor-naïve and tumor-informed strategies. It is a fundamental improvement to traditional clinical practice and will help to further personalize detection and treatment for patients, a new frontier of modern medicine.

The further development of liquid biopsy will rest on successful clinical trials and the elaboration of standardized protocols for implementation and methodologies for analysis. The broader use of AI in clinical practice will also require to be done under strict ethical guidelines.

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