







# Circulating microRNAs: A remarkable opportunity as non-invasive biomarkers from adult to pediatric brain tumor patients

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## Highlights

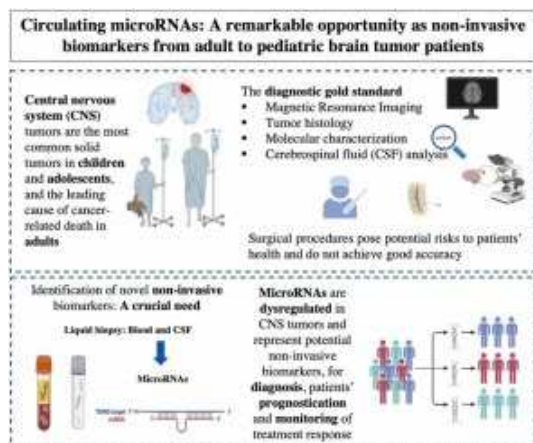
- **Prevalence and Impact:** CNS tumors are the most common solid tumors in pediatric age and the top cause of cancer-related death in adults.

- **Diagnostic Challenges:** Current protocols (MRI, histology, molecular characterization, and CSF cytology) require invasive procedures with limited accuracy.
- **Need for Non-Invasive Biomarkers:** Identifying reliable non-invasive biomarkers can improve diagnosis, stratification and follow-up.
- **Role of MicroRNAs (miRNAs):** miRNAs, dysregulated in brain tumor patients, are measurable in liquid biopsies.
- **Review Aim:** This review examines circulating miRNAs in liquid biopsy as potential cancer biomarkers for adults and children and explores their potential impact on clinical trials.

## Abstract

Central nervous system (CNS) tumors represent the most frequent solid tumors among adolescents and children, and the leading cause of cancer-related death in men < 40 and women < 20 years of age. Brain tumors are challenging to diagnose, monitor, and treat. The current diagnostic approach involves magnetic resonance imaging (MRI), tumor histology, molecular characterization and cytologic analysis of cerebrospinal fluid (CSF). However, surgical procedures pose potential risks to the patient's health, not achieving good accuracy. For these reasons, it is crucial to identify new non-invasive disease biomarkers to improve patients' stratification at diagnosis and during follow-up and prognosis. MicroRNAs (miRNAs) are a class of short RNA molecules that have been demonstrated in numerous studies to be dysregulated in brain tumor patients. As a result, they may be used as biomarkers of brain tumors. Additionally, miRNAs can be analyzed in liquid biopsy samples, such as blood and CSF, providing a non-invasive source of biomolecular data on patients' disease status. This review aims to highlight the role of miRNAs in liquid biopsy, also known as circulating miRNAs, as potential non-invasive cancer biomarkers in both adult and pediatric populations and to suggest their potential impact on clinical trials.

## Graphical Abstract



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### Methods

**Search strategy.** PubMed electronic database was queried for circulating miRNAs differentially expressed in plasma, serum, CSF or microvesicles/exosomes derived from plasma or serum of pediatric and adult brain tumors' patients between January 2000 and January 2024, using the following terms: ('circulating,' 'microRNA,' 'brain tumor' in the title/abstract) or ('circulating,' 'microRNA,' 'pediatric brain tumor' in the title/abstract) or ('plasma,' 'microRNA,' 'brain tumor' in the title/abstract) ...

### Towards clinical application in pediatric and adult brain tumors

As previously outlined, the clinical management of brain tumors both in pediatric and adults ages represents an ongoing challenge. Therefore, it is of utmost importance the identification of new biomarkers that might improve or replace current gold standard approaches at all levels, including diagnosis, prognosis and follow up after therapy. Over the past decade, improvements in detection technologies have made possible to measure miRNAs in LB, such as plasma, serum and CSF, and miRNAs ...

### Conclusions and future perspectives

Adult and pediatric brain tumors are leading causes of poor quality of life and mortality, and the development of miRNAs as biomarkers may offer a valuable tool to integrate clinical information at the onset of cancer or during follow-up and treatment.

However, although the role of circulating miRNAs as biomarkers in these tumors is increasingly recognized, several challenges remain. Single or signature of miRNAs from LB have a promising

diagnostic and prognostic power in adult brain cancer, as ...

## Ethics approval and consent to participate

Not applicable. ...

## Author's contribution

F.D., Z.S., and G.C. conceptualized the manuscript; F.D., Z.S., L.B., and G.C. wrote the manuscript; F.D. and Z.S. generated figures and tables. G.C., L.M., A.M., E.F. and F.L. supervised in writing, reviewing, and editing, L.B., and E.S., S.R. assisted in reviewing the literature; G.C., L.M., E.F., A.M., and F.L. reviewed and edited the manuscript. ...

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## Declaration of Competing Interest

The authors declare no conflicts of interest. ...

## Acknowledgments

Not applicable ...

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**Lavinia Bargiacchi**, MD, is a dedicated pathologist and PhD student at Sapienza University of Rome, with a focused expertise in the study and diagnosis of central nervous system (CNS) tumors. She completed her residency in pathology at Sapienza University, where she cultivated a strong foundation in diagnostic pathology. Under the esteemed mentorship of Prof. Felice Giangaspero, Dr. Bargiacchi honed her skills in advanced diagnostic techniques and gained extensive experience in the characterization of CNS tumors. Her research interests center on understanding the molecular and histopathological aspects of CNS neoplasms, with the goal of improving diagnostic accuracy and contributing to the development of targeted therapeutic strategies.

**Elena Splendiani**, Ph.D., researcher with expertise in clinical and laboratory projects, and multiple publications in renowned journals. The main research projects involve molecular pathology, precision medicine, and innovative technologies such as spatial transcriptomics.

**Dr. Sabrina Rossi** is a pathologist specializing in neuropathology, skin pathology, and pediatric diseases. She earned both her M.D. and Ph.D. from the University of Rome "La Sapienza." Dr. Rossi has obtained National Scientific Habilitation as an Associate Professor. She currently works at Bambino Gesù Children's Hospital and teaches at Campus Bio-medico University. Her research focuses on molecular diagnostics in brain tumors, sarcomas, and inherited skin conditions.

**Laura Masuelli**, M.D., Ph.D., full professor of General pathology and fisiopathology, with publications in renowned journals. She has experience on the analysis of the in vitro and in vivo biological effects of drugs for target therapy in cancer, including cancer vaccines, on ultrastructural pathology and on the morpho-molecular and immunological characterization of microvesicles and exosomes as novel biomarkers in in vitro experimental preclinical models and in patients' liquid biopsies.

**Angela Mastronuzzi** is the Head of the Neuro-Oncology Unit at Bambino Gesù Pediatric Hospital, specializing in central nervous system tumors in pediatric patients. She has extensive experience in innovative treatments, including Phase I studies, targeted therapies, and cancer predisposition

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**Franco Locatelli** is a renowned Italian pediatric onco-hematologist and researcher, serving as a professor at the Catholic University of the Sacred Heart and director of the Division of Hematology, Oncology, and Cell Therapy at Bambino Gesù Children's Hospital. His research focuses on stem cell transplantation, pediatric leukemias, and immunotherapy, aiming to improve outcomes for children with hematological malignancies. Professor Locatelli has authored numerous publications and is actively involved in national and international research networks. A leader in advancing personalized therapies and clinical trials in pediatric oncology, his work continues to shape the future of pediatric cancer treatment.

**Giuseppina Catanzaro**, MD, PhD; Associate Professor at Link Campus University (Rome). The research interests underline her expertise in the field of brain cancer cells, microRNAs, signaling pathways biology, circulating biomarkers and nano delivery systems. Other research interests are linked to metabolic diseases.

**Elisabetta Ferretti**, MD, PhD; Full Professor at Sapienza University (Rome). Her research interests connect with several fields of molecular oncology. Specifically, she is involved in the characterization of the molecular events involved in tumorigenesis as well as of microRNAs involved in the deregulation of signaling pathway sustaining tumors. She focused on the development of approaches for large-scale analysis of gene expression and epigenetic networks, including microRNAs and Long noncoding RNAs. Finally, Prof. Ferretti's projects involve analysis and discovery of circulating biomarkers (e.g. microRNAs and cfDNA) in cancer.

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