

Glioblastoma Multiforme and Cognitive Decline: Towards A More Precise Prognostic Assessment

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ABSTRACT

Glioblastoma multiforme (GBM) is the most prevalent, fast-growing, and lethal form of primary brain tumor in adults. As GBM grows, it infiltrates different lobes, decreasing cognitive function in a pattern-like manner. This decrease remains crudely tracked, and if it were to be studied more in depth, the inaccurate prognoses of GBM patients could be more accurate. This paper reviews how GBM affects cognitive function (specifically via frontal/temporal lobe involvement), evaluates current cognitive assessment tools, and proposes cognitive tracking as an underused prognostic marker. PTEN loss and EGFR amplification, molecular markers that indicate a worse prognosis, are associated with tumor aggressiveness that in turn contributes to cognitive decline. Furthermore, retrospective analysis of GBM cases where cognitive function was tracked found that in past cases, poor cognitive function was directly related to a shorter life-expectancy. Due to their deficient nature, this paper addresses the limitations of current tools currently used to measure cognitive function such as education bias, cost, validity, or time. Moreover, it discusses future solutions to the problem, touching on better cognitive prognostic tools like separate tests, add-ons to current tests, and the use of artificial intelligence to properly measure cognitive function.

INTRODUCTION

Brain tumors are relatively rare, making up less than 1.9% of all yearly cancer diagnoses worldwide (Ilic & Ilic, 2023). Glioblastoma multiforme (GBM) is the most aggressive, lethal, and prevalent form of primary brain tumor in adults, accounting for 48% of all malignant brain tumors and about 15% of all primary brain tumors (Ostrom et al., 2019). GBM incidence is 3.2 per 100,000 individuals annually (Ostrom et al., 2019). GBM tumors originate from astrocytic glial cells, a major supportive cell type of the central nervous system. These star-shaped glial cells function to stabilize the blood-brain barrier from within the brain and spinal cord (Thakkar et al., 2024). When cancerous, tumors arising from astrocytic glial cells are commonly categorized as a grade IV tumor by the World Health Organization due to their aggressive nature, widespread infiltration, and resistance to conventional therapies. The tumor occurs more commonly in older adults (between 45–70) and has a slight male predominance, reflecting patterns observed in large-scale epidemiological studies (Wei & Morrison, 2023).

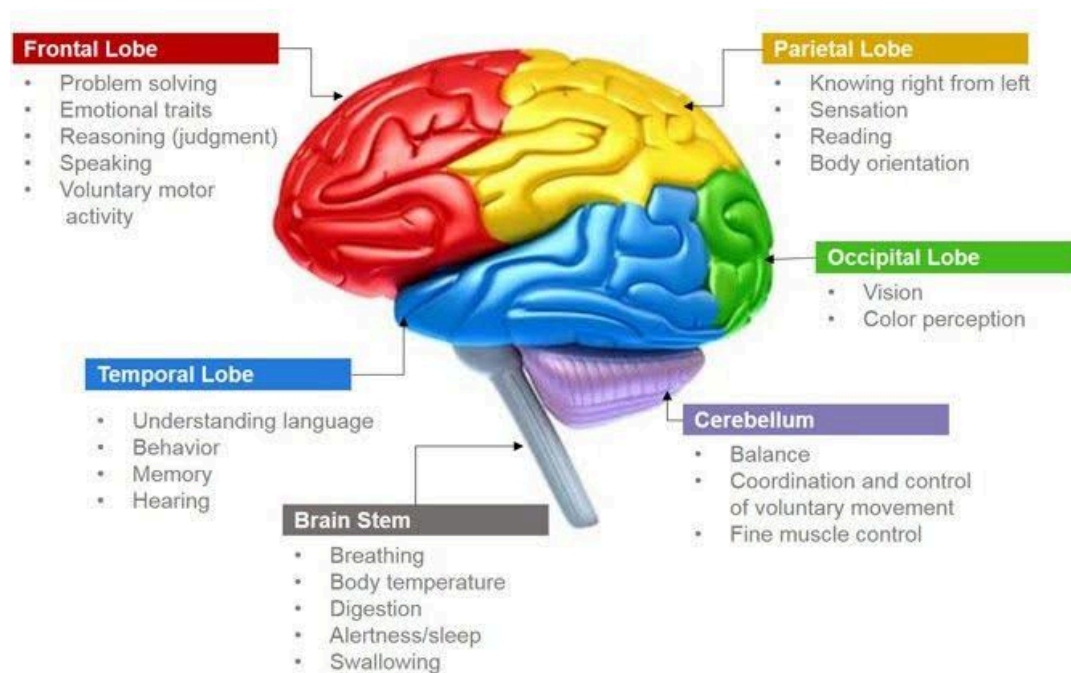
Understanding where GBM most commonly develops in the brain helps explain its symptoms and cognitive effects. The brain is the control center of the body and is responsible for all cognitive functions.

This paper focuses on two lobes: frontal and temporal (Tamimi & Juweid, 2017). While GBM can arise in any lobe, this paper focuses on the frontal and temporal lobes due to their leading roles in the executive and memory-related cognitive functions most affected by GBM. The frontal lobe helps with decision making, personality, movement, and problem solving. The temporal lobe helps with memory, hearing, and understanding language. GBM typically develops in the cerebral hemispheres, particularly in the frontal and temporal lobes. These areas are critical for regulating higher-order functions such as reasoning, memory, and behavior, which is why the tumor often results in cognitive and neurological deficits.

This paper explores how the development of Glioblastoma Multiforme (GBM) impairs cognitive function in individuals and how this can be assessed. Cognitive decline in GBM patients reflects disease progression while also impairing quality of life, impacting treatment adherence, and worsening overall prognosis. The next sections discuss clinical presentation and symptoms of GBM, followed by diagnostic methods including imaging and molecular markers. The paper then describes how cognitive function is assessed, reviewing multiple diagnostic methods before finally suggesting that cognitive function could be a significant marker in GBM prognosis if tracked precisely. As of now, prognoses of GBM are limited in accuracy. If cognitive function were to be measured adequately, prognoses could become significantly more accurate, leading to better patient treatment.

Figure 1.

Regions of the brain and their functions (Anatomy Info, n.d.)



METHODS

Sources for this review were found using google scholar, PubMed, and StatPearls using keyword combinations such as ‘glioblastoma multiforme cognitive decline,’ ‘GBM cognitive assessment,’ ‘glioblastoma prognosis,’ and ‘neurocognitive testing.’ An initial number of approximately 26 articles were screened for relevance, of which 22 articles were selected for inclusion.

GBM Clinical Presentation

Symptoms - Symptoms of GBM vary based on tumor size, location, and rate of tumor growth. Early symptoms are typically subtle and non-specific, such as headaches or changes in personality. As the tumor progresses, those affected may experience cognitive impairment, memory loss, confusion, and difficulty concentrating. Due to the tumor’s ability to interact with and disrupt normal electrical activity in the brain, seizures are common, and may be a presenting symptom for medical attention. Focal neurological defects such as language difficulties, weakness on one side of the body, and visual disturbances are also frequent. Symptoms such as nausea, vomiting, and drowsiness can also develop as a result of increased intracranial pressure due to tumor growth (Thakkar et al., 2024). A collection of these symptoms in an individual often prompts neuroimaging studies, leading to the diagnosis of GBM.

Cognitive Decline - Cognitive function refers to the mental abilities like memory, problem-solving, and language that the brain uses to acquire knowledge and understanding through experience, the senses, and thought. GBM most commonly occurs in the frontal lobe and temporal lobe, regions necessary for executive cognitive tasks (Tamimi & Juweid, 2017). As the tumor grows, it invades these critical areas, leading to memory loss, difficulty concentrating, speech problems, and personality changes (Hanif et al., 2017; Lee & Chaloner Winton Hall, 2019). These symptoms frequently appear as the earliest clinical manifestations of GBM. The cognitive effects of GBM are not only due to the tumor’s physical presence, but also to surrounding edema, increased intracranial pressure, and disruption of neural pathways (Hanif et al., 2017). Additionally, treatments including radiotherapy and chemotherapy may have side effects leading to impaired attention, processing speed, and executive functioning (Hanif et al., 2017).

Diagnosis

Imaging and Molecular Markers - Diagnosis of GBM involves neuroimaging techniques such as contrast-enhanced MRIs, which typically reveal a ring-enhancing lesion with central necrosis and surrounding edema, raising clinical suspicion for a high-grade glioma. However, definitive diagnosis requires histopathological confirmation through surgical biopsy or tumor resection. Tissue samples allow for molecular analysis and classification under the updated World Health Organization (WHO) guidelines.

Molecular markers also play a key role in the diagnosis of GBM. Molecular markers are measurable indicators whose presence, absence, or altered expression can provide diagnostic or prognostic information. Typically, they are genes or gene products. Two of the most important molecular markers in

GBM are isocitrate dehydrogenase (IDH) mutation status and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. IDH encodes an enzyme involved in cellular metabolism; its mutation leads to oncometabolite production and is a key prognostic marker in gliomas. IDH status is a significant prognostic factor in GBMs, as IDH-wildtype GBMs have a significantly worse prognosis than IDH-mutant tumors (Hanif et al., 2017). The IDH gene is mutated in about 10% of GBM cases.

When the MGMT promoter is methylated, a process that adds a methyl group (CH₃) to the gene, it is silenced, which improves tumor sensitivity to alkylating agents. About 40–45% of GBM cases show MGMT promoter methylation, and these patients tend to have improved survival outcomes (Morandi et al., 2010).

Another important gene is Phosphatase and tensin homolog (PTEN), a tumor suppressor involved in regulating cell growth. A loss of this gene allows GBM to proliferate unchecked (National Library of Medicine, n.d.-a). PTEN is mutated in 30-40% of GBM cases. The tumor can also be characterized by heterogeneous features, including necrosis, microvascular proliferation, and genetic mutations such as epidermal growth factor receptor (EGFR) amplification and PTEN loss. EGFR is a cell-surface receptor that binds epidermal growth factors, triggering signaling pathways that drive cell proliferation. It is amplified or mutated in about 40-50% of GBM cases. An amplification of these genes will lead to increased tumor proliferation in GBM (National Library of Medicine, n.d.-b). While IDH, MGMT, PTEN, and EGFR status are not themselves direct measures of cognitive function, they can contribute significantly to tumor aggressiveness and rate of progression. These two factors influence the extent of cortex infiltration and, in turn, the severity of cognitive decline.

Cognitive Function

Cognition level is often measured in cognitive performance status (PS), which is deduced through patients' performance in different tests of cognition. Cognitive PS has recently emerged as a meaningful prognostic indicator in GBM. Its positives include its extensive validation and straightforward utilization, with tests that can be administered by non-clinicians.

To assess cognitive impairment, clinicians use standardized neuropsychological tests such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Wechsler Adult Intelligence Scale (WAIS) (Table 1). These tests evaluate numerous factors, including short-term memory, attention span, verbal skills, and problem solving (Hanif et al., 2017). In previous times, cognitive function over the development of the condition was poorly tracked or not assessed at all in a majority of GBM patients. However, more recent studies have begun to observe the matter more closely. In one study, 80 patients were tested for their cognitive function using Karnofsky's test. Clinical investigators have found that patients with observed lower cognition have a lower chance of survival (Günerhan et al., 2023). Retrospective analysis of patient data supports this: GBM patients with lower cognitive function were found to have a consistently shorter life expectancy than those with a higher cognitive function. This discovery established PS as a reliable tool that can accurately predict the life expectancy of GBM patients.

However, PS cannot be the sole identifier because PS tests fail to account for cognitive impairments patients experience due to factors unrelated to GBM. Symptoms caused by treatment side effects, medication effects, and even associated conditions like fatigue and sleep disturbances are common contributors to cognitive decline that are unrelated to GBM itself (Günerhan et al., 2023). There are numerous neuropsychological tools available to assess cognitive function in GBM patients. With these tools come their respective limitations.

LIMITATIONS OF CURRENT TOOLS

All the listed tests are tests of cognition that are administered to observe changes in cognitive function over time in GBM patients. Each has their own drawbacks that can lead to misdiagnosis or missed cognitive symptoms in patients.

Firstly, the **MMSE** test is used often when a test is needed to observe cognitive decline due to its typically accurate results. Results can be skewed by the education of the individual tested, as early symptoms are commonly missed in individuals with higher education. It is insensitive to mild cognitive impairment and often overlooks a person's ability to control their thoughts, emotions, and behaviors, where symptoms commonly occur early on in GBM located in the frontal lobe (D'Ignazio et al., 2025). Patients who experience early GBM-related decline might be diagnosed as normal if scored directly off this test.

The **MoCA** test is broader and more comprehensive than the MMSE and comparable tools. It checks for cognitive decline more sensitively, rarely overlooking it. Results can test cognition inaccurately due to the level of education of the patient. It is suited to find memory deficits rather than the variety of impacts GBM can have, and the test requires a skilled administrator. The test may inaccurately suggest cognitive impairment in individuals with limited education or high anxiety (Ciesielska et al., 2016). This could result in an inaccurate assessment of disease progression.

The **WAIS** is a test that has had multiple versions adapted and improved over generations with the most recent test being the **WAIS-IV**. The test has 10 core subtests with 5 additional subtests, and yields detailed and accurate results on the following four indexes: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed (Strategic Psychology Canberra, n.d.). The test is limited by the expensive cost for patients to take the test, its time intensive nature, and that it requires trained neuropsychologists to administer, restricting its use in clinics that lack resources or urgent care clinics. Patients who have been fatigued by treatments or illness may perform significantly worse than expected. This can falsely convey long term deficits in patients, leading to a misdiagnosis of GBM progression.

Karnofsky's test is a test commonly administered in patients with GBM to assess their general functional status. The test is easy and fast to administer, and is a validated prognostic tool. Limitations include the fact that Karnofsky's test is not a cognitive test, rather a test for functional status. It misses subtle signs of cognitive symptoms and possibly symptoms in the frontal lobe (Physiopedia, 2025). This can lead to critical misdiagnosis as patients can score high on this test while experiencing severe executive dysfunction. Its common usage in GBM patients is largely due to its validity as a prognostic tool and a

predictor of survival, and because cognition was not a commonly tested factor of GBM diagnosis. Overall, tests used to track cognition in GBM should be able to diagnose GBM specifically by testing for the wellness of the frontal and temporal lobes rather than the patient's overall ability to live. New tools are in development to address this issue.

Table 1.

Advantages and Limitations of Different Tests of Cognition Administered

Test	Year Developed	Length of Test	Advantages	Limitations
MMSE	1975	5-10 min	- Quick to administer - Widely used - Accurately checks for moderate to severe decline	- Poor to identify mild cognitive issues - Bias towards higher education
MoCA	2005	10-15 min	- Broader cognitive coverage - Free - Checks for moderate cognitive impairment - Useful to detect Alzheimer's	- Requires basic training - Education-sensitive - Less suited for tracking in the long-term
WAIS-IV	2008 (org. 1955)	60-90+ min	- Highly comprehensive - Standardized - Detailed subscales - The norm to determine IQ	- Prolonged testing time - Requires experts' administration - Expensive
Karnofsky's	1949	1-5 min	- Very quick and efficient - Simple to understand scoring - Useful in busy clinics	- Not a cognitive test. - Measures physical function and independence. - Is unable to detect specific cognitive

			- Helpful in prognosis and treatment planning - Used in GBM patients before.	- defects. - Scoring is variable between clinicians.
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Better Cognitive Prognostic Tools

In recent times, new prognostic tools that track cognition have been developed. The Cogstate (computerized neurocognitive testing) is one of these tools, and its use in GBM patients has shown promising results.

In the CABARET clinical trial that tested 120 GBM patients, Cogstate showed itself to be more sensitive to neurocognitive decline than the MMSE. Furthermore, early decline in Cogstate scores was associated with a shorter life expectancy (Field et al., 2021). A 2026 review specifically on cognitive impairment in gliomas covers specialized tools that supplement the MoCA and MMSE. These tools include the HVLIT-R, TMT, and COWAT. They aid the MoCA and MMSE in identifying cognitive impairment by testing specific domains such as verbal memory, processing speed, and verbal fluency. Furthermore, these tools are already considered one of the core components of many neuro-oncology assessment batteries (Piec et al., 2026). This tool stands as a prime example of what improved testing could look like beyond the four tools previously mentioned.

In the case of the application of artificial intelligence, new studies show promising developments in tracking cognition with AI tools. Natural language processing (NLP) is a branch of artificial intelligence that focuses primarily on empowering computers to understand and generate human language (IBM, n.d.). A recent study indicated that NLP with acoustic analysis is able to identify subtle changes in speech linked to cognitive decline (Diaz-Asper et al., 2025). A related article systematically reviewed explainable AI techniques for speech-based detection of cognitive impairment, and similarly found that AI models analyzing speech provided remarkable promise for identifying cognitive decline. Although AI tools are promising, the obscurity behind AI processing limits its clinical adoption, as clinical tools require transparency (Tbahriti et al., 2025). Through these tools, cognitive decline could be accurately tracked and used as a prognostic tool, offering GBM patients significantly more accurate prognoses than current methods allow.

CONCLUSION

Glioblastoma Multiforme is the most frequently diagnosed malignant brain tumor due to its symptoms developing late in progression and its incurable nature at the time of diagnosis. Because of its invasive nature, it is difficult to develop a prognosis for GBM. Recent studies have suggested that cognitive

function could provide a much more accurate prognosis, as severity in cognitive decline has been found to have a direct correlation to prognosis. However, this relationship has been measured through tools such as the MMSE and Karnofsky's test in the past, both of which carry significant limitations.

Of note, a study done by G. Günerhan, *et al.*, through retrospective analysis, concluded that GBM patients with worse cognitive function had consistently shorter life expectancies than those with better cognitive function. Similarly, a narrative review conducted by Ghadimi, *et al.* found that multiple studies have demonstrated that poorer cognitive performance is linked to reduced survival, concluding that cognitive assessments should be integral to GBM management and aiding prognosis. Cases reviewed by G. Günerhan, *et al.* used the MMSE to measure cognitive ability, while Ghadimi, *et al.* reviewed studies using Karnofsky's test, both significantly flawed in accurately determining true cognitive ability (Günerhan *et al.*, 2023; Ghadimi *et al.*, 2025). Cognitive function has shown observable indications of path of prognosis, but it has not yet been accurately defined. In future research, cognitive function should have strong operational definition and should then be measured as GBM progresses in patients to determine a more accurate correlation.

Newly emerging tools offer a path towards this goal. Computerized testing methods like Cogstate have already shown a greater sensitivity to cognitive function than traditional screening tools in GBM specifically, and AI based approaches, like NLP-driven speech analysis in particular, have demonstrated high accuracy in detecting and tracking cognitive decline in other populations. Applying this method to GBM could improve prognosis by allowing for more precise, continuous cognitive tracking than current periodic clinical testing permits, though the interpretability limitations of AI models remain as a barrier to clinical adoption. If a significant correlation is established, cognitive function could be revolutionary in developing more accurate prognoses in GBM.

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