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Refining Prognostic and Predictive Models in Glioblastoma: A Comprehensive Literature Review of MGMT Promoter Methylation and IDH1 Mutations

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive and lethal primary brain tumor in adults with limited treatment options and a median survival of 12 - 15 months. In recent years, molecular biomarkers have emerged to assist with individualized treatment and improve prognostic calculations. This narrative literature review presents a summary with findings from peer reviewed research targeting two of the most clinically significant biomarkers currently in GBM, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase 1 (IDH1) mutations. MGMT methylation has shown strong predictive value for predicting which patients will respond to alkylating chemotherapy, specifically temozolomide, which is the standard of care (SOC) in GBM. IDH1 mutations are useful and reliable prognostic biomarkers for predicting better survival and slower tumor growth in GBM patients. Importantly, research shows that, in patients with both MGMT and IDH1 mutations together, their clinical outcomes are more favorable than patients with only one or the other. While the evidence is promising, the variations between methodology and the need for standardized processes in evidence, combined with current practice, has also been a drawback for clinical utility. This review includes some emerging therapies, diagnostic technologies, as well as a perspective on future research aiming to improve the usage of MGMT and IDH1 in personalized treatment approaches of glioblastoma. These examples built upon the understanding of biomarkers in GBM represent a necessary instrument towards further positioning glioblastoma management from a general approach to individualized approach.

Keywords

Glioma, Glioblastoma Multiforme (GBM), Isocitrate Dehydrogenase 1 (IDH1), O6-Methylguanine-DNA Methyltransferase (MGMT)

1. Introduction

Gliomas are tumors of the CNS that originate from the glial cells, primarily the astrocytes and oligodendrocytes. The most aggressive and deadly primary brain tumor in adults is glioblastoma multiforme (GBM), which is distinguished by its poor prognosis, rapid growth, and resistance to treatment [1] [2]. Even with improvements in radiotherapy, chemotherapy, and surgery, the standard survival period for GBM patients is still between 12 and 15 months [1]. This has prompted scientists to investigate the genetic and molecular indicators that may direct more individualized and successful therapeutic approaches [3] [4].

Isocitrate dehydrogenase 1 (IDH1) mutations and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation are two of the most researched biological indicators; both have demonstrated promise in forecasting patient outcomes and adaptability to radiation therapy [5]-[7]. The discovery of these genetic markers has piqued interest since they can differentiate glioblastoma subtypes and give a molecular-level understanding of tumor behavior [2] [8].

Secondary glioblastomas will have more IDH1 mutations, which usually correlate with better prognosis [5] [9], and the methylation of the MGMT promoter is associated with responding better to alkylating agents such as temozolomide [1] [6] [10]. Understanding how these genetic markers influence therapy response and survival continues to increase the potential for precision medicine in the treatment of glioblastoma [3] [4]. Prognostic biomarkers provide information about the overall outcome regardless of treatment, while predictive biomarkers indicate the benefit from a specific therapy. In this context, MGMT promoter methylation is primarily predictive, while IDH1 mutations are prognostic.

Although these biological markers are being employed in practice, there remain unanswered questions about their combined predictive power, their diagnostic accuracy, and their role in guiding treatment selection [2] [7]. The goal of this paper is to review the literature regarding IDH1 and MGMT as prognostic and predictive biomarkers in the context of glioblastoma and to explore their potential to inform care decisions and improve patient outcomes.

2. Literature Review

2.1. Introduction to Glioblastoma and Associated Biomarkers

Glioblastoma multiforme (GBM) is a World Health Organization (WHO) designated grade IV glioma and is the most common and most aggressive primary malignant brain tumor in adults that accounts for nearly half of all gliomas with an

annual incidence of about 3.2 per 100,000 people in the world [11]. GBM is characterized by rapid growth, diffuse infiltration, resistance to treatment, and inevitable recurrences. After achieving maximal surgical resection and chemoradiotherapy, the median survival is still quite dismal, usually between 12 to 15 months [12]. Tumor heterogeneity and GBMs ability to quickly adapt to treatment makes most standard treatments ineffective.

This dismal picture has placed acute importance on identifying new markers, which can better predict prognosis and help guide treatment decisions. In the age of precision medicine, prognostic biomarkers provide essential information about the progression of the disease, and predictive biomarkers can inform on the likelihood of response to therapies. Introducing molecular markers into the clinical pathway could lead to improved survival outcomes by tailoring treatment to the unique properties of each individual tumor [13] [14].

The two most researched and clinically valid biomarkers of glioblastoma have been O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and isocitrate dehydrogenase 1 (IDH1) mutations. MGMT methylation limits the DNA repair mechanism of glioma cells leading to enhanced sensitivity to alkylating agents such as temozolomide [14]. IDH1 mutations occur in secondary glioblastomas and, therefore, are associated with increased survival and result in varying metabolic effects [15].

2.2. The Role of MGMT Promoter Methylation

The O6-methylguanine-DNA methyltransferase (MGMT) gene codes for a DNA repair enzyme that removes mutagenic and cytotoxic adducts from the O6 guanine position. The gene's ability to perform this function protects cells from being damaged by alkylating agents, the most common example being temozolomide (TMZ), which is administered as a first-line treatment for glioblastoma multiforme. When the MGMT promoter is methylated, the expression of the gene is silenced, reducing the tumor's ability to repair DNA and making it more susceptible to damage from TMZ [13] [14].

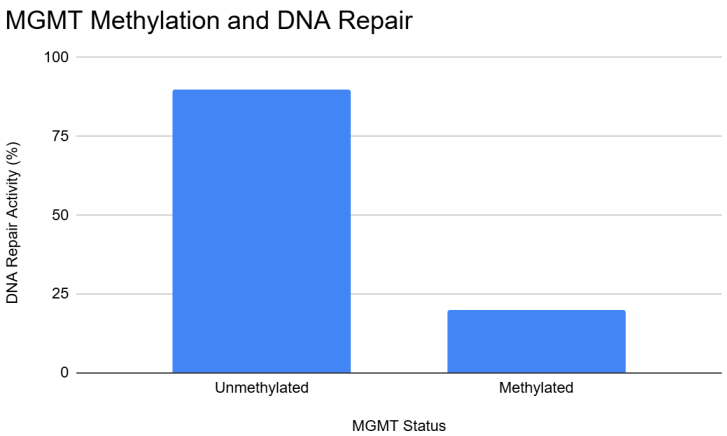

Figure 1. MGMT methylation and DNA repair.

Figure 1 demonstrates how MGMT methylation suppresses DNA repair activity, increasing the tumor's sensitivity to alkylating agents like temozolomide.

Esteller *et al.* (2000) further presented evidence that MGMT silencing is associated with increased sensitivity for alkylating agents, starting the journey toward clinical relevance. The clinical use of MGMT testing is complicated by lack of uniformity in assays and interpretation. A review presented by Wick *et al.* (2012) outlined significant variation in methodology and lack of standardization and called for global reports. Wick *et al.* (2012) concluded that standards will ensure the accuracy and consistency of the use of the MGMT biomarker.

Multiple reports have validated the predictive ability of MGMT methylation. A cohort of individuals published in 2023, which looked at cohort data, strongly established methylation as correlated with longer overall survival and response to therapy [16]. Patients with significant levels of methylation experienced a 40% relative reduction in mortality risk from those without methylation. Another study published in Acta Neuropathological Communications looked at methylation patterns in long and short-term GBM survivors and demonstrated that long-term survivors exhibited also demonstrated pattern with dense and stable methylation of the MGMT promoter region [17].

2.3. The Role of IDH1 Mutations

Alterations in the isocitrate dehydrogenase 1 (IDH1) gene have revolutionized both the classification and understanding of gliomas, particularly glioblastomas. IDH1 alterations are most found in low-grade gliomas and secondary glioblastomas in younger patients. They are considered an early and defining event in glioma genesis, with major implications for prognosis, tumor biology, and therapeutic targeting [18].

IDH1 mutations are prognostic rather than predictive, like MGMT promoter methylation, suggesting longer overall survival independent of treatment. Patients with IDH1-mutant gliomas also have slower tumor progression, better therapy responses, and better outcomes compared to IDH1 wild-type tumors [19]. This evidence has contributed to IDH1 status being central to the 2021 WHO CNS tumor classification guidelines for glioma subtyping.

IDH1 mutations act mechanistically by producing the oncometabolite, D-2-hydroxyglutarate (2-HG), resulting in changes to cellular metabolism, epigenetic regulation, and cellular differentiation. One of the first to establish the metabolic effects of IDH1 mutation was Dang *et al.* via backside inhibition of 2-HG before moving toward targeted 2-HG inhibition but lost this mechanism when using competitive inhibition [20].

As shown in Figure 2, IDH1 mutations significantly elevate 2-HG levels, which disrupt chromatin structure and cellular differentiation pathways.

Recently, new targeted therapies are developing to try to take advantage of this weakness. Inhibitors such as vorasidenib and ivosidenib appear to limit disease progression and lower 2-HG [21] [22]. Although these inhibitors are still in early-

or mid-trial development, the forward movement of these products adds to the body of information that the IDH1 mutation serves as a prognostic marker as well as a druggable target.

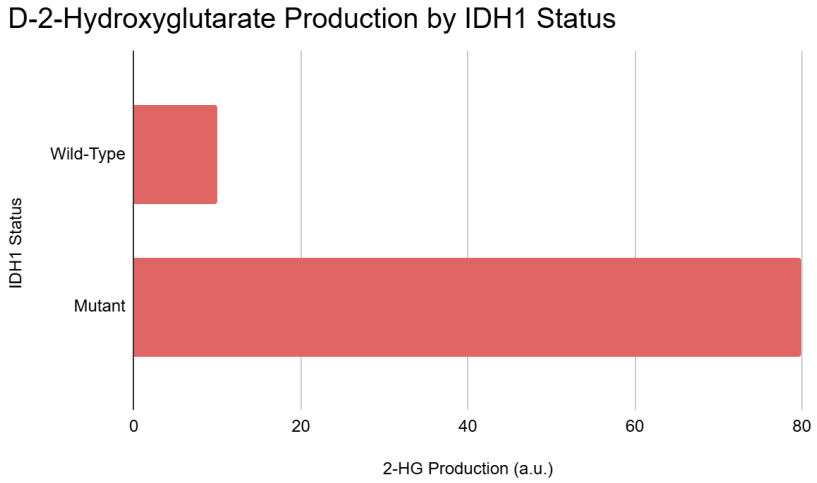

Figure 2. D-2-Hydroxyglutarate production by IDH1 status.

2.4. Comparative Studies of MGMT and IDH1

MGMT promoter methylation and IDH1 mutations have primarily been studied in glioblastoma as independent markers; however, the most recent studies have considered their relationship. It may be clinically more informative to combine both biomarker measures, as overlap (both biomarkers) may provide better estimates of prognostic predictability and treatment than if either biomarker were assessed independently.

A 2023 multicenter study by Chen *et al.* found that patients harboring both MGMT promoter methylation and IDH1 mutations had the most favorable progression-free and overall survival. This dual biomarker model demonstrated stronger prognostic performance than either marker alone.

Significant results have been obtained by Molenaar *et al.* (2014) [4], who conducted a major study to examine the survival effects of fMGMT promoter methylation and IDH1 mutations in three cohorts of patients. Their study revealed that patients with tumors that contained both mutations had significantly better survival outcomes than patients with either a single mutation or neither mutation. Their results imply that combining biomarkers would allow for more meaningful decision-making in clinical treatment and stratified designs that are more amenable to use in clinical trials.

As shown in **Figure 3**, combined MGMT methylation and IDH1 mutation status is associated with the most favorable survival outcomes.

This conclusion has further support from Weller *et al.* (2009), who conducted a large prospective trial with the German Glioma Network. They concluded that both MGMT and IDH1 were associated with survival, in an independent manner, and recommended that they be included in the model for clinically analyzing the

study's participants. The prospective nature of the study significantly strengthened the entire literature base for the clinical utility of biomarkers.

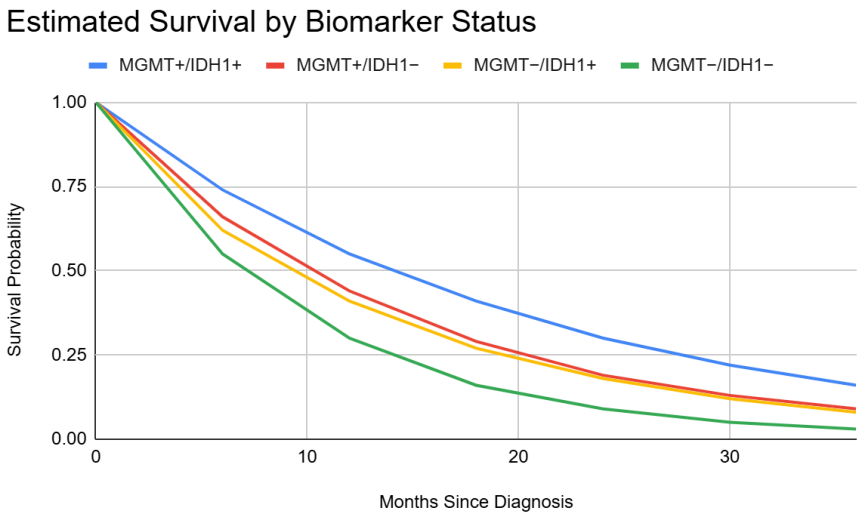

Figure 3. Estimated survival by biomarker status.

Some authors are suggesting that there should be a more explicit distinction between the prognostic versus predictive roles of a biomarker that is associated with clinical outcome. In an analysis of anaplastic oligodendroglial tumors, Van den Bent *et al.* (2010) reported that IDH1 mutation was prognostic for longer survival time, but not predictive for response to certain therapeutic regimens. This illustrates the difficulty in correctly categorizing a biomarker's role and confirms that our specification of predictive and prognostic utility was not blurred in treatment selection.

Additional analysis describes that the combination of MGMT and IDH1 provides more clearly defined divisions of glioblastoma subgroups for oncologists to understand, allows for a better prediction of outcomes, and improves the ability to develop personalized approaches for delivering comprehensive care.

2.5. Controversies, Challenges, and Limitations in Literature

While substantial progress has been made in MGMT promoter methylation and IDH1 mutations, there continue to be barriers to the universally applicable clinical utility of these biomarkers. One of the frequently cited barriers is the lack of standardized protocols for testing, particularly for MGMT. As Wick *et al.* (2014) note, the methylation status depends differently on the techniques and threshold values employed by different laboratories and practices, complicating the interpretation of results and clinical decisions regarding the use of those results. The variability of testing provides waning reliability and predictive value to utilize MGMT as a predictive biomarker and serves to limit comparisons of clinical cohorts across studies.

Recent advances in assay comparison, such as the multicenter validation by Liu

et al., highlight the discrepancies between methylation-specific PCR and pyrosequencing platforms for MGMT testing [23]. These inconsistencies underscore the need for standardization.

Adding additional nuance, the European Society for Medical Oncology (ESMO) biomarker factsheet on MGMT methylation also points out that, while methylation may invoke a complete gene silencing state, sometimes intermediate methylation may be a state of partial activity, which is likely to affect the response to temozolomide in an unpredictable manner [24]. These factors suggest that there is a need for rigorous quantitative assessment measures instead of a simple yes/no binary model.

Concerning IDH1 mutations, while they are widely regarded as strong prognostic markers, some groups have suggested that their predictive ability with respect to the response to therapy is marginal. For instance, Van den Bent *et al*. (2010) showed that IDH mutations did not predict the efficacy of chemotherapy in their cohort of anaplastic oligodendroglial tumors, leading to some significant questions regarding their functional relevance when making treatment decisions in glioblastoma. Furthermore, emphasis on IDH1 alone may be shortsighted, as co-mutations and the presence of other epigenetic changes, such as G-CIMP, represent a larger context that could be influencing tumor behavior [8].

A significant limitation consistently across much of literature is the retrospective nature of studies. It was pointed out by Molenaar *et al*. (2014) [4] that selection bias could influence their study sample cohorts; preferring to study smaller sample cohorts in a prospective way. Thus, we recommend that larger, prospective, randomized trials are necessary to substantiate the proposed synergistic predictive capabilities of MGMT and IDH1, and across different clinical populations.

2.6. Future Directions and Implications for Precision Medicine

The combination of MGMT promoter methylation and IDH1 mutation status in glioblastoma into a new biomarker-based diagnosis changes the practice of precision oncology towards individualized biomarker-driven care. However, while there is promise here, research and development are still needed to develop the full potential of these discoveries in precision oncology. One distinct possibility is using targeted therapies that leverage molecular vulnerabilities in IDH1-mutant tumors. For example, the INDIGO trial—a Phase 3 clinical study—found evidence that vorasidenib—an oral IDH1/2 inhibitor—delayed disease progression in patients with low-grade gliomas that have an IDH mutation [22]. IDH1 is a potential predictive biomarker in addition to being prognostic.

Another option is to pharmacologically modulate MGMT activity. In patients with tumors without MGMT promoter methylation (whereby temozolomide chemotherapy would be resistant), researchers are pursuing MGMT inhibitors that may transiently inhibit distal DNA repair and enhance the efficacy of chemotherapy [14]. While still in early development, this approach (and some others) may expand treatment options for a larger subset of glioblastoma patients.

Beyond single biomarkers, future diagnostic models will incorporate multiple diagnostic markers in a "multi-marker panel", including MGMT, IDH1, G-CIMP status, 1p/19q codeletion, and TERT promoter mutations. By using a systems-level approach, tumor heterogeneity could be better considered to allow more accurate therapeutic stratification [18].

More options for biomarker assessment, enabled by available or emergent technologies, further strengthens this transition. Liquid biopsies and real-time methylation assays are in the works to ease dependence on invasive tissue biopsy [21].

As science advances, the coalescence of molecular diagnostics and targeted therapies will play a key role in reshaping glioblastoma care from a one-size-fits-all approach to one that considers the genetic and epigenetic design of the tumor.

3. Methodology

The research of this review used a narrative literature review approach to summarize and critically assess available data regarding the prognostic and predictive properties of MGMT promoter methylation and IDH1 mutations in glioblastoma (GBM). The research was systematically searched PubMed, Scopus, and Google Scholar for peer-reviewed research articles from 2008 through April 2024 using combinations of the words, "glioblastoma," "MGMT methylation," "IDH1 mutation," "biomarkers," "prognostic," and "predictive." The research was sought studies that presented original data, systematic reviews, and clinical trials. This did not involve new experimentation but an evaluation of previously published peer-reviewed studies, clinical trials and expert consensus statements linking diagnostic molecular biomarkers patterns to clinical assessments. The first search resulted in around 182 records. Once inclusion and exclusion criteria were applied, 58 full-text articles were examined. Of those, 38 met the criteria for inclusion in final synthesis. The second search was completed and concluded with discussion of, by rationale, excluding a remainder of studies, either for relevance or methodology clarity (of the studies) or clinical focus. The aim was to improve our understanding of how genetic and epigenetic modifications are associated with survival, treatment response—specifically to alkylating agents fairly like temozolomide and disease progression. This is the first step in summarizing the considerable investigation conducted over the last 15 years demonstrated by synthetic identification of the alterations in MGMT and IDH1 and their relatives and combined prognostic and predictive value and as part of the ongoing impact of precision oncology in the management of GBM. By synthesizing this information from multiple institutions and time periods, knowledge development may be facilitated about the clinical significance of MGMT and IDH1 and their independent or synergistic impacted paths in GBM and their association with temporal conditionalities in the evolution of the biology of GBM.

3.1. Inclusion Criteria

To uphold a high academic quality assurance, peer-reviewed articles were the only

included sources for this literature review. Peer-Reviewed articles offered an important filter to assess quality, including factors such as validity and reliability, scientific contribution, others, etc. The objective was to mostly use confirmed findings that have undergone quality scrutiny from experts in the fields (oncology, neurobiology, and molecular medicine).

This review was scoped at published studies that focused specifically on the context of glioblastoma and their relationship with MGMT promoter methylation (MGMTp) or IDH1 mutations. Studies focusing on general classifications of glioma or other unrelated molecular markers were not included. This narrow scope allowed for a stronger and more meaningful synthesis of clinical evidence and implications for the treatment of glioblastoma.

For study types, this review emphasized original research, meta-analyses, systematic reviews, and clinical trials, as these demonstrate strong methodologies, larger sample sizes, and statistically significant findings. The reviewer felt that using studies that include these types would produce a fair and representative overall impression of what is currently understood, as well as tentatively indicate emerging ideas.

Lastly, each study selected was required to provide some information related to MGMT and/or IDH1, specifically regarding the diagnostic, prognostic, or predictive roles of MGMT and/or IDH1. They needed to address how these biomarkers were used to classify disease, assess patient prognosis or outcomes, or inform treatment decisions. This focus on clinically relevant information was central to understanding the potential implications of molecular testing on patient care, and the prospects to continue developing pathways towards personalized medicine and glioblastoma care.

3.2. Exclusion Criteria

To maintain a concentration on clinically focused studies, we omitted research that examined only pediatric subjects or gliomas that were not GBM's, regardless of relevance. These studies may provide valuable insight into brain tumor biology, but the mutations, treatment, and progression of the disease differ significantly from adult glioblastoma. Including these studies may have caused discordance resulting in confounding variations, making it impossible to derive appropriately accurate conclusions regarding MGMT and IDH1 in the adult GBM population.

We also omitted studies that either had no consideration of their clinical relevance or did not evaluate whether MGMT or IDH1 was a useful biomarker. This review sought to see how these markers were considered to help in diagnosis, prognosis, or treatment. Since this review was devoted to translating clinical relevance into practice, studies that were purely mechanistic in nature or only provided explanations of platforms that did not connect findings to clinical relevance were eliminated.

Opinion articles, editorials or pieces of commentary were necessarily excluded on the grounds that they themselves presented no original data. Opinion articles,

editorials and commentary pieces may provide expert opinions or summarize emerging trends or themes, but they do not have the evaluative research evidence necessary for a systematic scientific literature review. Including these documents would have lessened the rigor of the review conclusions by including judgements or subjective opinions without sufficient evidentiary data.

Finally, studies that did not demonstrate minimal clarity or transparency of methodological processes were excluded. For example, articles that did not provide a complete account of their experimental design, unclear about the sample population, or the methods regarding data analysis were excluded. The rationale for excluding studies that did not demonstrate clarity regarding methodological processes was to ensure a valid and comparable corpus of reviewed literature, and to ensure the conclusions drawn were conducted on the basis that high quality, evidence-informed research was identified.

3.3. Data Extraction and Analysis

Data for this review were manually extracted from each article selected for analysis independently to maintain specificity and reliability from study to study, when assessing the clinical relevance of MGMT promoter methylation and IDH1 mutations in glioblastomas. Each article was thoroughly read and reviewed for specific elements related to the biomarkers, to contribute to understanding the roles of the biomarkers in diagnosis, prognosis, and treatment response. Extraction by hand provided the researcher with the opportunity to tailor study-specific details into the extraction process that identified the details and nuance of the findings from each study with respect to consideration of MGMT status and/or IDH1 mutation status, while removing other less relevant material for the analysis.

A key part of data extraction involved identifying the study design used in each article. Depending on the study, this included a prospective, retrospective, observational, or randomized design. Recognizing the design of the study is critical to understanding the strength of the evidence, since, in general, prospective and randomized controlled trials provide more reliable and valuable information than retrospective studies which are limited by factors that often cannot be controlled (e.g., bias, confounding factors).

The extracted data reported survival outcomes (e.g., median overall survival and progression-free survival), treatment response rates, and the authors' conclusions related to the prognostic and predictive role of MGMT and IDH1. We compared these findings across studies to look for illuminating trends and marked differences. We emphasized studies that evaluated biomarkers independently and in combination, as these studies provided an avenue to look for possible synergistic roles of the biomarkers when managing patients and applying precision medicine principles.

During the analysis phase, studies were organized and compared based on biomarker category, first examining MGMT promoter methylation and next IDH1 mutations. Then, studies looking at individual markers were compared along with

studies investigating the combined prognostic or predictive value of both markers. This investigation determined whether dual biomarker analysis added value of clinical knowledge than either marker separately evaluated. Further, the degree of clinical validation was considered for each study with emphasis on prospective studies and studies that applied large cohort analysis or standardized testing protocols. This also considered methodological similarities, testing constraints, and potential for clinical trials that exist or in the progress of investigating therapeutics targeting these biomarkers. In summary, we noted the direction of any current research activity, and the reliability of this research direction using the templates identified above for the identification and assessment of meaningful clinical knowledge.

3.4. Limitations

While we acknowledge these limitations, this review has several limitations because of the increased variability across studies when determining the methodology employed, when identifying and reporting MGMT methylation and IDH1 mutation. This review did not use a formal risk-of-bias assessment tool such as ROBIS or Cochrane's risk-of-bias checklist. This is a limitation in the critical appraisal of the included studies. Variability of assay and interpretation method, threshold filament to define biomarker positivity, introduced some inconsistencies between studies which limited direct comparison. Furthermore, much of the existing literature is based on surgery and treatment regimens that retrospectively abstract data may ordinarily introduce selection bias, but this may potentially limit the strength of conclusions as well. This review does not constitute a formal meta-analysis with true statistics; however, it was established to summarize key findings, highlight patterns, and identify gaps in the current literature that could lead to future directions for clinical applications, efforts to reduce and standardize approach, and interventions based on biomarker-directed treatment strategies for glioblastoma.

4. Results

The literature review showed that there was consistent evidence that MGMT promoter methylation was a clinically important indicator of greater outcomes in patients treated with alkylating agents such as temozolomide. Multiple independent studies have shown that patients treated with temozolomide whose tumors were tested for MGMT promoter methylation had significantly greater overall survival (OS) and progression-free survival (PFS) if positive for MGMT promoter mutations. For example, in the Oxford Glasgow study cohort (2023) among people with methylated tumor bases, there was a 40% relative reduction in mortality when compared to those with unmethylated tumor bases. These findings underscore the association of MGMT methylation with susceptibility of tumor cells to DNA-damaging/exogenous agents by effacing their intrinsic DNA glycosylation potential.

MGMT methylation was also associated with better responses to treatment besides survival; response was defined as patients who received standard of care therapy with radiation and chemotherapy components and demonstrated either tumor shrinkage or delayed recurrence of their tumors. Patients with methylated tumors were more likely to exhibit shrinkage and late recurrence of their tumors while they were on therapy. There are multiple studies that replicated these findings in various population-based studies that support the reproducibility and potential clinical relevance of MGMT as a predictive biomarker. Furthermore, the extent of likelihood to improve outcomes and response varied depending on the degree of MGMT methylation suggesting a need to use quantitative rather than binary analysis.

A review of the literature pertaining to IDH1 mutations consistently indicated their prognostic biomarker role. Patients with IDH1-mutant glioblastomas were typically younger individuals with a secondary tumor and had clinical courses that were more favorable by a wide margin when compared to those with wild-type IDH1. Survival benefits occur across treatment approaches suggesting that IDH1 status is an inherent feature of tumor biology instead of a treatment effect. These results contributed to IDH1 being included among the criteria for diagnosis and risk stratification in the 2021 International Association of Cancer Registries WHO Glioma Classification scheme.

In addition, the literature suggested that IDH1-mutant tumors had distinct metabolic and epigenetic characteristics that may be responsible for their favorable outcomes. The oncometabolite 2-hydroxyglutarate (2-HG) alters chromatin regulation and prevents cellular differentiation leading to opportunities for therapeutic exploitation. Clinical trials with IDH inhibitors (e.g., vorasidenib, ivosidenib) are already underway; early findings suggest that progression and quality of life may be improved in those affected.

When MGMT and IDH1 were analyzed together, a combined biomarker strategy used for survival predictions was found to be even more effective than using a singular biomarker. Molenaar *et al.* (2014) [4] and Weller *et al.* (2009) showed that patients with both MGMT methylation and IDH1 mutation achieved the longest post-surgery survival times and the best therapeutic responses, which supports the theory that having both biomarkers yields a greater result than either one used alone. The combination of biomarkers can offer more precise prognoses and make it easier to tailor treatment, particularly when the standard of care for glioblastoma is nonspecific.

5. Discussion

The results of this review support the growing agreement in the literature that MGMT promotes methylation and IDH1 mutations are critical biomarkers in glioblastoma. MGMT promoter methylation is predictive of a patient's sensitivity to temozolomide, and therefore this biomarker is beneficial in guiding chemotherapy treatment decisions. By inactivating MGMT through promoter methylation,

the tumor loses the ability to repair damaged DNA and allows temozolomide to work effectively. Therefore, testing MGMT methylation status is a standard consideration when deciding on chemotherapy treatment in clinical oncology settings when alkylating agents are considered.

Another contributing factor to biomarker reliability is intra-tumoral heterogeneity. The spatial variability of GBM tumors means that tumor tissue sampled in a single biopsy may not represent the tumor's true molecular status. Inconsistencies in biomarker detection may also be attributable to intra-tumoral heterogeneity—along with individual variability in sampling protocols—and further consideration should be given to this in the interpretation of the results.

In contrast, IDH1 mutations are diagnosed as prognostic than predictive biomarkers, as the presence of IDH1 mutations indicates a secondary glioblastoma, with a longer overall survival beyond therapy. These tumors have a slower growth rate and respond better to standard therapies than IDH1 wild-type glioblastomas. Although IDH1 status does not currently inform decision-making treatment choices directly as MGMT does, the growing association with better tumor outcomes makes it a significant aspect of tumor classification and evolving long-term management.

Despite these benefits, using these biomarkers clinically is not without challenges. One primary limitation is that there may not be a standardized testing process. For instance, determining MGMT methylation differs based on the detection method (bisulfite converted methylation specific PCR versus pyrosequencing), and there is variability in cutoff thresholds at different institutions. This variability in biomarker testing impacts the ability to compare studies and limits the capacity to generalize findings across populations. Furthermore, there is an urgent need for some guidelines with clear definition of assay procedures and criteria for interpretations.

Moreover, the predictive function of IDH1 is less well-established than its prognostic function. Some studies have suggested that IDH1 mutations do not meaningfully alter the effectiveness of chemotherapy or radiation, leaving the rationale for the algorithm selection unclear. The distinction between prognostic and predictive biomarkers is vital, as the misinterpretation of either can lead to inappropriate or ineffective therapies. These roles need to be clearly communicated in clinical reports and in research studies, to avoid the misapplication of the evidence.

Much of the literature is based on retrospective cohort analyses, which are inherently limited by selection bias and missing data. There are a handful of prospective randomized controlled trials which have rigorously examined the independent and combined effects of MGMT and IDH1 on survival and treatment response, but more robust trial designs are warranted to verify these biomarkers are truly suitable for routine clinical practice and establish causal relationships, rather than associations.

6. Future Directions

As neuro-oncology advances towards personalized treatment approaches, glio-

blastoma treatment in the future will depend on the uptake of molecular biomarkers such as MGMT and IDH1 into clinical care. A promising direction is the development of comprehensive biomarker panels that include not only MGMT and IDH1, but also molecular features such as 1p/19q codeletion, TERT promoter mutations, ATRX status and G-CIMP profiles. These types of panels provide a multi-dimensional perspective regarding tumor biology and allow oncologists to develop treatment approaches based on a patient's tumor molecular characteristics.

New treatment modalities are also being developed based on these molecular biomarkers. For MGMT-unmethylated tumors, which are resistant to temozolomide, MGMT inhibitors are under investigation to see if they can transiently inhibit DNA repair and improve chemotherapy. Although this is still in early-stage clinical development or preclinical studies, these options could provide additional treatment pathways for patients who do not benefit from standard treatment. There are also ongoing clinical trials using IDH inhibitors such as vorasidenib, which target IDH-mutant tumors, even in advanced disease. In clinical trials, these IDH inhibitors are demonstrating promises to slow disease progression and potentially increase survival in IDH-mutant tumors.

Improvements in diagnostic technologies are also likely to be a substantial driver. The emergence of non-invasive liquid biopsies and in vivo methylation assays may lead to an ability to continuously monitor tumor molecular status. In this case, the need for repeat surgical biopsies would be removed, with clinicians having real-time information about how a tumor is responding to treatment. Such monitoring could support new paradigms for adaptive therapeutic strategies where therapy is altered in a timely manner based on molecular feedback.

The standardization of the biomarker assay process is another necessary step. If we can establish a set of standardized protocols to assess MGMT methylation, including specific assay type and threshold values, we will ensure some consistency in the interpretation of the biomarker across clinical centers. Education programs to teach oncologists and pathologists about molecular diagnostics will also need to take place to move these tools quickly into our everyday clinical practice.

Current and future research must continue and expand on prospective, multicenter studies of MGMT and IDH1 together. Given the difficulty of achieving an acceptable level of empirical rigor, these studies should have a variety of patients and ideally control for other variables that may confound the variables of interest. The included factors should be the implications of these variables on treatment decisions and consequently patient outcomes. Conducting such rigorous studies will be critical for turning the promise of precision oncology into actual benefit for glioblastoma patients.

7. Conclusions

Biomarkers for MGMT promoter methylation and IDH1 mutations continue to be two of the most clinically relevant molecular biomarkers for glioblastoma.

MGMT methylation acts as a predictive biomarker and provides information regarding the patient's response to alkylating chemotherapy, while IDH1 mutations are further prognostic biomarkers, indicating more favorable outcomes and slow disease progression. The combined use of these markers improves our understanding of tumor behavior and allows for a more personalized approach to treatment.

Currently, literature represents a compelling evidence base for the clinical relevance of both biomarkers. There have been many retrospective studies and large cohort studies demonstrating significant association between biomarker status and relevant clinical outcomes such as overall survival and therapy response. However, despite the evidence and utility of these biomarkers, it should be noted that there remain some formidable challenges, particularly variability in testing methodology, and standardization in clinical laboratories.

This predictive value of IDH1 is still uncertain. While its prognostic role is appropriate, it is important to understand the interpretation of this biomarker's role in deciding "would a specific therapy be appropriate". This would be a misinterpretation of this biomarker's role and could result in incorrect treatments if the predictive value is accepted. A clear distinction should be made in clinical practice and research literature to avoid this confusion.

The application of precision medicine in glioblastoma care will depend on overcoming these limitations with additional research and clinical innovation. The first step to enabling biomarker-guided treatment is to develop standardized testing based on prospective clinical trials and develop multi-marker panels. If this is accomplished, glioblastoma patients may receive increasingly accurate, more effective, and less toxic treatments.

The integration of MGMT and IDH1 represents noteworthy progress toward improving outcomes in this devastating disease within routine clinical workflows. The incorporation of these biomarkers will only continue to expand as tumor biology becomes more fully understood and technology advances to discover, validate, and incorporate biomarkers into practice for the diagnosis, treatment, and long-term management of glioblastoma.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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