A practical review of prognostic correlations of molecular biomarkers in glioblastoma

*Michael Karsy, MD, PhD,1 Jayson A. Neil, MD,1 Jian Guan, MD,1 Mark A. Mahan, MD,1 Howard Colman, MD, PhD,1,2 and Randy L. Jensen, MD, PhD1,2

1Department of Neurosurgery, Clinical Neuroscience Center; and 2Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah

Despite extensive efforts in research and therapeutics, achieving longer survival for patients with glioblastoma (GBM) remains a formidable challenge. Furthermore, because of rapid advances in the scientific understanding of GBM, communication with patients regarding the explanations and implications of genetic and molecular markers can be difficult. Understanding the important biomarkers that play a role in GBM pathogenesis may also help clinicians in educating patients about prognosis, potential clinical trials, and monitoring response to treatments. This article aims to provide an up-to-date review that can be discussed with patients regarding common molecular markers, namely O-6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase 1 and 2 (IDH1/2), p53, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), phosphatase and tensin homolog (PTEN), phosphoinositide 3-kinase (PI3K), and 1p/19q. The importance of the distinction between a prognostic and a predictive biomarker as well as clinical trials regarding these markers and their relevance to clinical practice are discussed.

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KEY WORDS GBM; biomarker; IDH1/2; MGMT; overall survival; progression-free survival

GLIOBLASTOMA (GBM) is a WHO Grade IV tumor with a poor prognosis, significant comorbidity, and limited therapeutic options. It was originally classified as either primary, arising de novo, or secondary, arising from low-grade glioma. Mutations important to the classification of these tumors have been shown to be important in gliomagenesis.25 Some genes critical to the understanding of GBM tumorigenesis and prognosis include O-6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase gene 1 and 2 (IDH1/2), p53, epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), phosphatase and tensin homolog (PTEN), phosphoinositide 3-kinase (PI3K), and 1p/19q. The importance of the distinction between a prognostic and a predictive biomarker as well as clinical decision making for the everyday clinician.

Recent interest in personalized medicine has spurred an investigation into individualized disease treatment through biomarker stratification.37 The US Food and Drug Administration defines a valid biomarker as “a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of test results.” Biomarkers in GBM have been investigated for their use in stratifying prognosis, guiding the development of targeted treatment, and attempting to personalize clinical treatment. More specifically, prognostic biomarkers provide information on the natural history of the disease, and tests can be designed to distinguish disease recurrence in marker-positive and marker-negative patients regardless of clinical treatment. Alternatively, predictive markers are useful in identifying prognosis as well as clinical decision making for the everyday clinician.

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ABBREVIATIONS AA = anaplastic astrocytoma; GBM = glioblastoma; MGMTm = MGMT promoter methylation; OS = overall survival; PFS = progression-free survival.


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* Drs. Karsy and Neil contributed equally to this work.
patients who may achieve a particular outcome based on a particular treatment. A predictive marker can help in the selection of patients who may be sensitive or resistant to a particular treatment, while prognostic markers can help inform patients about prognosis stratification. Several of the markers discussed in this review, including IDH1/2 and MGMT, have distinct roles as both prognostic and predictive biomarkers, which will be discussed.

The advent and spread of genomic screening technologies has expanded investigation into cancer as well as broadened the category of biomarkers. Recent investigations have added to the complexity of GBM treatment and counseling by describing 4 distinct molecular subtypes. These include the classic, mesenchymal, proneural, and neural types, which have distinct alterations in EGFR, neurofibromin 1 (NF1), PDGF, and uncharacterized gene pathways, respectively.20 The molecular fingerprint of individual GBM tumors has been associated with prognosis and treatment response. For example, further investigation has supported the association of younger patients, secondary GBM, and longer survival within the proneural subtype. In addition, the classic and proneural subtypes have shown improved prognosis with treatment, while the mesenchymal subtype correlates with a worse prognosis. However, while these findings have been an exciting avenue for research, the use of genomic data for everyday clinical prognosis and treatment remains limited. Genomic classification of tumors is not yet clinically feasible, nor do we have a strong mechanistic understanding of how these multiple genomic alterations affect clinical prognosis.

O-6-Methylguanine-DNA-Methyltransferase (MGMT)

MGMT encodes a repair protein that removes alkylation at the O6 position of guanine, a common site altered by alkylating chemotherapy. Temozolomide commonly alkylates DNA at the N7 or O6 position of guanine to disrupt DNA replication and trigger cell death. Hypermethylation of this gene promoter (MGMTm) results in reduced MGMT expression and thus an impaired ability for cells to repair from damage induced by chemotherapeutic agents and radiation. In the original trial by Stupp et al. evaluating temozolomide, MGMTm significantly impacted response to temozolomide with radiotherapy.17,46 Of the 206 cases available, 45% showed MGMTm and resulted in an independently favorable prognostic factor with a median overall survival (OS) of 21.7 months after radiochemotherapy treatment compared with 15.3 months for the nonmethylated MGMT samples that received treatment.

More recent randomized trials have supported the prognostic and predictive roles of MGMTm. In the NOA-04 randomized clinical trial of anaplastic astrocytoma (AA;
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<td>Hegi et al., 2005; Gorlia et al., 2008; Wick et al., 2009; Wick et al., 2012</td>
<td>O-6-methylguanine-DNA-methyltransferase (MGMT)</td>
<td>Removes alkylation at O6 position of guanine</td>
<td>Methylation silences gene transcription to improve tumor response to alkylating agents (e.g., temozolomide)</td>
<td>Improved OS (11.9–21.7 mos); improved PFS; improved response to radiochemotherapy</td>
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<td>Labussière et al., 2014; Stacheva et al., 2014; Beiko et al., 2014; SongTao et al., 2012</td>
<td>Isocitrate dehydrogenase 1 and 2 (IDH1/2)</td>
<td>Enzyme in the Krebs cycle that produces CO2 &amp; α-ketoglutarate through oxidative decarboxylation of isocitrate</td>
<td>IDH1R132H &amp; IDH2R172 increase D-2-hydroxyglutarate production, which may alter DNA methylation &amp; reduce oxidative stress</td>
<td>Improved OS (4–147 mos, mean 30 mos); improved PFS; improved response to radiochemotherapy; improved resection</td>
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<td>England et al., 2013; Malkoun et al., 2012; Ruano et al., 2009; Rich et al., 2005; Stancheva et al., 2014; Felsberg et al., 2009; Houllier et al., 2006</td>
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<td>Loss of function: endogenous growth-inhibitor effects of wild-type p53 are lost. Gain of function: mutant p53 upregulates a distinct subset of genes from wild-type p53. Dominant negative: mutant p53 tetramerizes with wild-type p53 to downregulate activity.</td>
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<td>Phillips et al., 2013; Felsberg et al., 2009; Donato et al., 2007</td>
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WHO Grade III), MGMT<sub>m</sub> was effective in predicting longer OS (11.9 vs 8.2 months) and progression-free survival (PFS; 8.4 vs 4.6 months), as well as improved response to chemotherapy (procarbazine, lomustine, and vincristine or temozolomide) compared with non-MGMT<sub>m</sub> controls.\textsuperscript{52} Interestingly, in patients who received only radiotherapy, a longer PFS was seen without MGMT<sub>m</sub> (3.3 vs 4.6 months), but the reason for this counter-intuitive effect is unclear. In the NOA-08 trial, 584 patients with GBM or AA were recruited for treatment with temozolomide alone or with radiotherapy.\textsuperscript{53} MGMT<sub>m</sub> was seen in 73 of 209 tested patients (35\% of samples) and was associated with significantly longer OS (11.9 vs 8.2 months). Furthermore, event-free survival, defined as survival from surgery to first disease progression or death, was greater in patients with MGMT<sub>m</sub> who had chemotherapy than in non-MGMT<sub>m</sub> patients (8.4 vs 4.6 months). This result suggests that patients with MGMT<sub>m</sub> showed a greater response to chemotherapy; however, MGMT status was not distinguished between patients with GBM and those with AA, limiting interpretation of the study. The European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981 National Cancer Institute of Canada (NCIC) trial showed that MGMT<sub>m</sub> also predicted improved responsiveness to temozolomide.\textsuperscript{15} Researchers in this study evaluated 573 patients with GBM who had been assigned to radiotherapy with or without temozolomide. Extent of tumor resection, younger patient age, Mini-Mental Status Examination score > 27, and lack of corticosteroid treatment at baseline were all prognostic of better outcomes. The MGMT<sub>m</sub> status was identified in 96 of 206 samples (47\%; 367 samples did not have MGMT results) in which MGMT<sub>m</sub> was associated with an improved OS (HR 2.10, 95\% CI 1.54–2.85). Furthermore, response to radiochemotherapy was improved with MGMT<sub>m</sub>, although this result was not statistically significant. While this study lacked complete evaluation of MGMT status in all patients, a useful predictive nomogram was presented and could be used for everyday clinical activity (www.eortc.be/tools/gbmcalculator). Some have advocated the use of MGMT<sub>m</sub> as a standard marker for GBM prognosis as well as to identify patients for clinical trials in evaluating alkylating therapies and/or radiation therapy.

**Isocitrate Dehydrogenase 1 and 2 (IDH1/2)**

IDH1/2 encode an enzyme in the Krebs cycle that produces CO<sub>2</sub> and α-ketoglutarate through oxidative decarboxylation of isocitrate. IDH1 encodes a cytosolic protein, while IDH2 encodes a mitochondrial protein. Identified in 2008 after a collaborative genomics study by Parsons et al.,\textsuperscript{36} IDH1/2 was shown to be mutated in approximately 5\% of primary gliomas and 60\%–80\% of secondary gliomas. In fact, IDH1/2 mutation may serve as an early driving mutation of GBM.\textsuperscript{10} IDH1<sup>R132H</sup> and IDH2<sup>R172H</sup> mutations are the most common types of IDH mutations seen in GBM (>90\% samples with IDH1/2 mutation) and result in increased production of the oncometabolite D-2-hydroxyglutarate, which may alter DNA methylation patterns in GBM and alter gene transcription on a wide number of targets.\textsuperscript{33} IDH1/2 use nicotinamide adenine dinucleotide phosphate (NADP+) as a cofactor in NADPH production. Thus, mutations may decrease NADPH formation, resulting in increased oxidative stress, DNA oxidation, overwhelming of DNA repair mechanisms, and eventual induction of DNA damage.\textsuperscript{28}

Multiple studies have validated both the prognostic and predictive benefit of IDH1/2 mutation. IDH1/2 mutations have been shown to improve OS from 4 months to as much as 147 months (mean 30 months), depending on the study.\textsuperscript{1,29,44,45} A recent study of 395 GBM samples showed IDH1/2 mutations in 30 samples were associated with a significant improvement in OS (26.6 vs 14.5 months).\textsuperscript{29} Another recent study of 106 GBM samples, with 14 samples containing mutated IDH1/2, also showed a significant improvement in OS (30.9 vs 7.7 months).\textsuperscript{45} Currently, multiple clinical trials are evaluating the use of IDH1/2 as biomarkers for stratifying patients during targeted therapy in GBM (clinicaltrials.gov).

Several studies have shown a predictive effect for IDH1/2 in treatment efficacy. In a study of 88 cases of secondary GBM, IDH1/2 mutations correlated with improved PFS as well as response to temozolomide.\textsuperscript{44} An interesting study of 355 malignant astrocytomas (128 WHO Grade III, 207 WHO Grade IV) showed that an IDH1 mutation correlated with improved MRI-defined enhancing disease and greater gross-total resection (93\% vs 67\%) and longer median OS (163.4 vs 16.2 months).\textsuperscript{1} Several clinical factors correlated with IDH1 mutation, which may have improved resection, including younger patient age and frontal location of tumors; however, additional survival benefit (median survival 97.5 years) was gained from greater tumor resection (<5 cm residual) in IDH1 mutants but not IDH1 wild type. In addition to improved overall patient prognosis, IDH1/2 mutation results support enhanced therapeutic efficacy with chemoradiotherapy and greater resection.

**p53**

The p53 protein is encoded by the TP53 tumor suppressor gene, which is involved in regulation of the cell cycle, apoptosis, cell differentiation, and other mechanisms of cell regulation during exposure to DNA-damaging agents (for example, ultraviolet radiation, toxins). This gene is the most common mutation in GBM, found in 28\% of primary GBMs and 65\% of secondary GBMs.\textsuperscript{34} Three patterns of mutation occur with p53 dysfunction, namely loss of function, where endogenous growth-inhibitor effects of wild-type p53 are lost; gain of function, where mutant p53 upregulates a distinct subset of genes from wild-type p53; and dominant-negative effects, where mutant p53 tetramerizes with wild-type p53 to downregulate activity.\textsuperscript{12} Other mechanisms of p53 inactivation include mutations of its modulators including inhibitor MDM2 or deletion of p14ARF.\textsuperscript{2,32} Results from The Cancer Genome Atlas show that alterations in the p53 pathway (ARF/MDM2/MDM4/p53) are found in 78\% of GBMs,\textsuperscript{7} making it a common and important mutation in GBM.

Some studies support an effect of p53 status on improving prognosis,\textsuperscript{31,39,40} while others show a limited impact on clinical outcome.\textsuperscript{13,19,45} One study of 46 patients who had received adjuvant radiochemotherapy showed im-
proved median PFS (9.3 vs 7 months) in samples without p53 overexpression; however, another study of 220 GBMs did not show a significant difference in median survival between wild-type and mutant p53 GBM tumors (17.0 vs 14.7 months).19 Mutant p53 has been shown to induce radiochemotherapy resistance in many cancer types including GBM,24 with altered p53 expression resulting in increased sensitivity to temozolomide in one experimental model.2 Reasons for the lack of a clear correlation of p53 with prognosis are many-fold, including the complexity of the p53 signaling pathway, the importance of other regulators in the p53 pathway that may be altered in GBM (for example, Rb, MDM2), and the heterogeneity of p53 mutation types and effects.12 In fact, methods to target p53 in clinical trials have also been limited by these issues.12

Epidermal Growth Factor Receptor (EGFR)

EGFR encodes a cell surface–bound receptor involved in cell proliferation with potential impacts on the clinical prognosis of GBM. Approximately 50% of primary GBMs and < 10% of secondary GBMs show EGFR mutations.54 Furthermore, 10%–60% of primary GBMs contain the EGFR variant III mutation (EGFRvIII), with a deletion of the regulator N-terminal domain (Δ6–273), which results in constitutive upregulation of mitogenic signaling pathways.14 Other mutation types of EGFR (for example, the C-terminal domain [C]-958, intergenic deletions [AS21–603], duplication-insertion mutations [664–1030 and 664–1014], and others) exist but with unclear clinical significance. EGFRvIII can be detected in the peripheral blood of brain tumor patients, opening the possibility of screening patients for anti-EGFRvIII therapies and monitoring response.41

Several studies suggest the potential of EGFR as a prognostic factor in GBM given the presence of a specific EGFRvIII mutational variant with a clear role in gliomagenesis,29 while others have not shown a clinical correlation between EGFR and survival.10 In one study, EGFR amplification resulted in significantly lower OS than did EGFR wild type (13.3 vs 26.6 months);29 however, a study of long-term survivors of GBM (> 36 months) showed that alterations in EGFR were not significant predictors.16 In a study from the German Glioma Network of 184 patients with GBM, EGFRvIII was seen in 18% of samples and did not show an effect on OS among mutant-containing and mutant-absent cases (9.6 vs 11.2 months).30 Moreover, EGFR amplification did not show an impact on OS compared with nonamplified samples (8.3 vs 6.4 months). Several current clinical trials in GBM aim to use EGFRvIII mutation to select patients for treatments, as was done for erlotinib in non–small cell lung cancer, as well as RNA-directed treatments and vaccine therapies.47 The goal of these trials is to eliminate the significant molecular variation in GBM tumor samples while using a specific targeted therapy. However, our limited understanding of how EGFR mutation changes downstream signaling pathways, such as AKT, MAPK, and STAT3, as well as differences in mutational types evaluated among various studies, complicates the clinical utility of this biomarker as well as its use for targeted treatment.

Platelet-Derived Growth Factor Receptor (PDGFR)

PDGFR encodes a cell-surface tyrosine kinase similar to EGFR, which is also involved in GBM proliferation and stem cell renewal. PDGFR exists as multiple isoforms, with the α subtype (PDGFRα) playing the most significant role in GBM. PDGFR is mutated in up to 30% of GBMs,5 and the PDGFRαA8,9 isofrom (with a deletion of exons 8 and 9) results in constitutive activation and is seen in 40% of GBMs.10 In a recent study, PDGFRα amplification was seen in 23% of GBM cases and demonstrated a significant reduction in median survival in only the IDH1 mutation subgroup (16.0 vs 72.6 months).38 Despite the importance of PDGF in GBM proliferation—as it is found upstream of important signaling pathways such as AKT, involved with in vitro growth of GBM, and used in animal models of GBM—no definitive role in predicting prognosis has been seen in clinical studies. In one study of 65 cases of GBM, PDGFRα amplification was detected in only 1 case.15 In another study of 43 cases of GBM, PDGFR overexpression was not associated with survival.16 Results from The Cancer Genome Atlas suggest that PDGFRα alteration plays a critical role in the proneural subtype of GBM, but no alteration in prognosis was seen among evaluated samples.46

Phosphatase and Tensin Homolog (PTEN) and Phosphoinositide 3-Kinase (PI3K)

The PI3K/AKT pathway plays a critical role in regulating cell proliferation, migration, and other functions.42 PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) at the cell inner membrane, resulting in recruitment and upregulation of various downstream pathways including AKT. PTEN is the second most common tumor suppressor mutation after p53 in GBM, where PTEN protein dephosphorylates PIP3 to PIP2 to suppress the downstream AKT pathway. Mutations of PTEN result in AKT upregulation and play a critical role in cell cycle regulation, apoptosis, and cell migration. Glioblastoma shows PTEN mutation or epigenetic silencing in 40% of cases, and loss of heterozygosity of chromosome 10 (LOH 10q23), where PTEN is located, is seen in 50%–90% of primary GBMs and 50%–70% of secondary GBMs.27 Furthermore, mutations in the catalytic p110α subunit of PI3K (PIK3CA) are another mechanism of AKT upregulation but are seen in only 5%–13% of GBMs.26 PTEN has been shown in combination with p53 mutation to form tumors resembling human gliomas in mouse knockout models.56

Despite the importance of PTEN in gliomagenesis, a distinct correlation with survival remains limited. Loss of heterozygosity of 10q23, where PTEN resides, has been shown to correlate with OS in some studies23,51 but not others.8,10 These findings suggest additional mechanisms govern PTEN signaling. Nevertheless, targeted treatments toward this pathway continue to be an active area of investigation.42

1p/19q

Codeletion of chromosomes 1p and 19q can result in
improved prognosis for oligodendrogliomas and has been explored in GBM. Deletion of 1p/19q improves PFS, OS, and response to chemotherapy and radiation in oligodendroglioma. Of note, a partial loss of 1p has been associated with a worse prognosis. Results from the Radiation Therapy Oncology Group (RTOG) 9402 and EORTC 26951 trials showed an improvement in OS with the addition of radiation to procarbazine/lomustine/vincristine chemotherapy in anaplastic oligodendroglioma with the 1p/19q mutation. In GBM, similar findings have been demonstrated in some studies but not in others. In several studies, codeletion of 1p and 19q is associated with IDH1 mutation and MGMT hypermethylation. Nevertheless, in a study of 491 gliomas, 28 patients with GBM showed codeletion of 1p/19q, which did not change OS. Interestingly, 1p/19q mutation was independent of IDH1 mutation, 10q loss, and EGFR alterations. A meta-analysis of 28 studies evaluating 3408 cases of glioma showed that 1p/19q codeletion correlated with improved PFS (HR 0.63, 95% CI 0.52–0.76) and OS (HR 0.43, 95% CI 0.35–0.53) regardless of the WHO grade. These results support further investigation into the effect of 1p/19q mutation and whether the mechanism accounting for improved prognosis in some tumors exists and plays a role in GBM.

Conclusions

Despite the immense pace of research to understand the molecular basis of GBM, the clinical utility of key genes and markers remains limited. Further prospective research is needed to investigate the role of biomarkers and their effect on outcomes in diverse patient populations so that such markers will be better accepted clinically. Standardized assays for evaluating markers and treatments in prospective clinical trials are also warranted for a better understanding of how biomarkers may play a role in GBM. A recent survey of neurooncologists evaluated the use of biomarkers in GBM. In the survey, MGMT (37%), EGFR (23%), 1p/19q (22%), EGRF (22%), p53 (20%), PTEN mutation or deletion (17%), EGFRIIL (12%), IDH1/2 (12%), PDGFR (5%), and PIK3CA (1%) were the most common markers for which evaluation was requested for GBM specimens. Furthermore, 11% of respondents stated that knowing the MGMTm status was “always” or “almost always” helpful in clinical decision making versus 26% who reported it was “never” or “almost never” helpful. Authors of the survey concluded that more focused testing of biomarkers should be performed to improve patient care and reduce cost. Current evidence supports a role for MGMTm and IDH1/2 mutation in predicting a mortality benefit as well as a benefit from current treatment modalities. The role of p53, PTEN, PI3K, and 1p/19q in prognostication remains limited probably because of the complexity of these signaling molecules as well as the diversity of GBM cases and clinical presentations. Glioblastoma remains a heterogeneous disease with individualized treatments, limited therapeutic options, and biomarkers to follow, as well as gaps in our understanding of its pathogenesis, but the use of biomarkers may allow better stratification of patients for clinical trials and treatment paradigms.

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References


Author Contributions
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Correspondence
Michael Karsy, Department of Neurosurgery, The University of Utah, 175 N. Medical Dr. E, Salt Lake City, UT 84132, email: michael.karsy@hsc.utah.edu.