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REVIEW ARTICLE

Glioblastoma: Prognostic Factors and Predictive Response to Radio- and Chemotherapy

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Abstract: Glioblastoma multiforme (GBM) is characterized by poor prognosis despite an aggressive therapeutic strategy. In recent years, many advances have been achieved in the field of glioblastoma biology.

Here we try to summarize the main clinical and biological factors impacting clinical prognostication and therapy of GBM patients. From that standpoint, hopefully, in the near future, personalized therapies will be available.

Keywords: Glioblastoma, prognostic factor, predictive response, Glioblastoma multiforme (GBM).

1. INTRODUCTION

Glioblastoma multiforme (GBM) is the most common histological form of a primary malignant brain tumor in adults. It accounts for approximately 60–70% of gliomas and 15% of primary brain tumors.

The incidence peak normally occurs in individuals aged 65 years or more, and its incidence has substantially increased in recent years [1].

GBM is characterized by the ability to infiltrate surrounding normal brain parenchyma and by a tendency to recur after gross total resection. That being so, the prognosis of these patients is extremely poor, of just 12-15 months following standard therapy, with only 3-5% of patients surviving up to 5 years after diagnosis [2].

To date, gliomas are classified largely based on their histopathological characteristics.

GBM is characterized by uncontrolled cellular proliferation, robust angiogenesis, intense resistance to apoptosis, diffuse infiltration, propensity for necrosis and genomic instability [3].

However, GBM exhibits a high degree of intra- and inter-tumor heterogeneity both at the cellular and molecular level, despite similar tumor morphology, that might explain why the clinical course of these patients is heterogeneous and why it is very hard, today, to provide a prognosis in individual patients.

Classical prognostic factors include age at diagnosis (longer survival for young patients <50 years), Karnofsky Performance Score (higher status of at least 70 points correlates with an improved outcome) and tumor size and location (eloquent areas of the brain carry better prospects) [4].

However, it is essential to elucidate the genetic and molecular mechanisms underlying these tumors to obtain new robust molecular prognostic factors and effective treatments.

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The aim of this article is to review new prognostic and predictive biomarkers of GBM and discuss their implications for clinical practice.

2. PRIMARY AND SECONDARY GLIOBLASTOMA

"From a biologic and clinical point of view, the secondary glioblastomas developing in astrocytomas must be distinguished from "primary" glioblastomas. They are probably "responsible for most of the glioblastomas of long clinical duration" [5]. Those were the words that Scherer, in 1940, used to describe two entities of GBMs, for the first time.

But only decades later, after the introduction of immunohistochemistry, the characterization of GBM was unequivocally established.

Traditionally, GBM is distinguished as primary and secondary.

Primary GBM are defined as presenting without a known clinical precursor, instead, secondary GBMs as a lesion aroused from lower-grade lesions.

Clinically, they develop two tumor forms with different epidemiology and prognosis.

Primary GBMs occur mostly in the elderly population, whereas secondary GBMs are more common in the relatively younger middle-aged population and they are associated with a longer clinical history (16.8 versus 6.3 months) and a better prognosis in terms of survival (7.8 versus 4.7 months) [6].

Unfortunately, these two forms are histologically largely indistinguishable, but it is demonstrated that they constitute two distinct disease entities, which develop through the acquisition of different genetic alterations [7], indicating distinct molecular signatures.

Primary GBM is remarkable for loss of heterozygosity (LOH) of 10q (70%), epidermal growth factor receptor (EGFR) amplification (36%), PTEN mutation (25%) and CDKN2A-p16^{INK4A} deletion (31-78%) [6].

Secondary GBM most frequently demonstrates a mutation of the TP53 tumor suppressor gene (65%) and O6-methylguanine DNA methyltransferase (MGMT) promoter methylation (75%).

This differentiation is important for patient's prognosis and is correlated to traditional prognostic factors, since secondary GBM as well younger age at diagnosis or presence of MGMT promoting methylation are predictive factors having a better prognosis.

A biologic explanation for this clinical categorization is given by mutations of genes encoding isocitrate dehydrogenase (IDH1 and IDH2). Since the mutational profiles of these metabolic enzymes are present in the vast majority of WHO grade II or III gliomas and in the secondary glioblastomas that develop from these precursors [8], IDH1 and 2 mutations can be used as molecular markers of secondary glioblastoma.

The identification of these molecular signatures has begun to introduce new concepts in tumor classification. The World Health Organization (WHO) incorporated IDH mutation and 1p/19q co-deletion into an "integrated diagnosis" in the 2016 revised 4th edition of the classification of tumors of the central nervous system [9].

3. CLINICAL PROGNOSTIC FACTORS

3.1. Age of Patient

Age at diagnosis is considered an important predictive factor. Indeed, secondary GBM most commonly affects younger patients prior to the age of 50 years and it has a better prognosis [6]. Besides this group, , the majority of patients are individuals aged 62 years or more. In these patients, age is a controversial predictive factor, because it is not so clear if different survival is related to a different biology of GBM in the elderly or to a nihilistic approach arising from the incorrect opinion that chronological age is a real limit to cancer treatment [10].

A SEER (Surveillance Epidemiology and End Results) study [11] demonstrated that only 65% of individuals aged more than 65 years with GBM received adjuvant radiotherapy, to confirm the tendency to undertreat elderly patient.

It is necessary to go beyond chronological age and obtain a stratification of patients with biological age (Fig. **1**) [12].

3.2. Performance Status

Performance status (PS) -according to the Eastern Cooperative Oncology Group (ECOG) or Karnofsky is the marker with the greatest relevance.

Standard GBM treatment has been shown to be effective for patients with a good functional status [13]. Patients with low performance score have low median survival and so the benefit of therapeutic interventions, surgery, radiotherapy, and chemotherapy, can be not useful.

The majority of current studies exclude patients with a KPS score below 70, and so randomized controlled trials.

A better neurological status at diagnosis has been associated with longer survival [14]. Furthermore, it has been demonstrated that the absence of a major neurological deficit prior to surgery is associated with a better prognosis (Fig. **1**) [15].

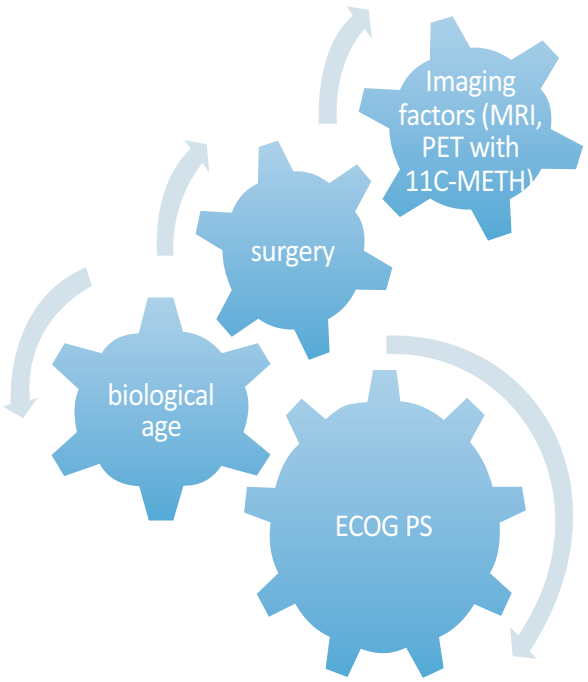

Fig. (1). Clinical prognostic factors in GBM.

3.3. Surgery

Surgical resection is an important part of the treatment strategy for primary glioblastoma in adults with an adequate performance status regardless of patient age. Surgery reduces 1-year relative risk of dying by about 45% and the risk of progression by about 37% [16].

Noorbakhsh *et al*. conducted a Surveillance, Epidemiology, and End Results (SEER)-based analysis of 20,705 adult patients with GBM, and the results indicated that resection of the gross tumor is associated with improved survival, even in elderly patients [17]. Obviously, if gross tumor removal was obtained, then patients had higher KPS scores. Furthermore, a residual tumor volume was a more accurate and meaningful predictor of survival, especially in those patients with larger preoperative tumor size [18].

However, data from hospitals with a high volume of GBM patients indicate how surgical resections do not seem to be a prognostic factor (Fig. **1**) [19].

3.4. Imaging Prognostic Factors

Magnetic resonance imaging (MRI) is routinely used for initial diagnosis and monitoring of treatment response in patients with GBM [20].

Some investigators attempted to identify MRI characteristics of GBMs that correlate with patient outcome. Preoperative tumor volume, the extent of edema, the degree of necrosis, and the degree of contrast enhancement are statistically significant prognostic indicators [21-23].

Histologically similar tumors often demonstrate highly distinct imaging profiles on MRI [24].

The degrees of contrasted area, edema surrounding the tumor, and intensity in T2-weighted imaging were correlated with the survival of patients with GBM [22].

Diehn *et al*. also demonstrated that with MRI, it is possible to obtain a radiophenotype, and activation of specific gene-expression programs can be inferred from imaging traits, thus providing insights into tumor biology on a tumor-by-tumor basis (Fig. **1**) [25].

A recent study analyzing CT perfusion parameters showed that these data were predictive of survival and could be useful in assessing early response and in selecting an adjuvant treatment to prolong survival [26].

Furthermore, imaging obtained with PET with radiolabelled amino acids: methionine (11C-METH), has proven to be a valuable tool for the characterization of primary brain tumours [27].

High METH uptake had a worse outcome than patients with low MET uptake (Fig. **1**) [28].

4. BIOLOGICAL PROGNOSTIC FACTORS

4.1. Methylguanine-DNA Methyl Transferase

O6-methylguanine-DNA methyltransferase is a cellular DNA-repair protein, a key repair enzyme that rapidly reverses alkylation at the O6 position of guanine.

Epigenetic silencing MGMT gene by promoter methylation, results in decreased MGMT expression.

It is found in approximately 40 % of primary GBM patients [29]. Hegi *et al*. [30] reported a correlation between MGMT methylation and longer survival of patients treated for GBM with radiotherapy and concomitant TMZ.

Silencing of the MGMT protein by promoter methylation may suppress this repair mechanism, consequently increasing cytotoxicity of chemotherapy and radiotherapy.

Low levels of MGMT protein are associated with a higher therapeutic effect of TMZ and longer OS in GBM patients [31, 32]

A meta-analysis evaluated the prognostic impacts of MGMT promoter methylation on both OS and progression-free survival (PFS) in GBM patients, suggesting its value as a predictive biomarker in GBM cases (Fig. **2**) [33].

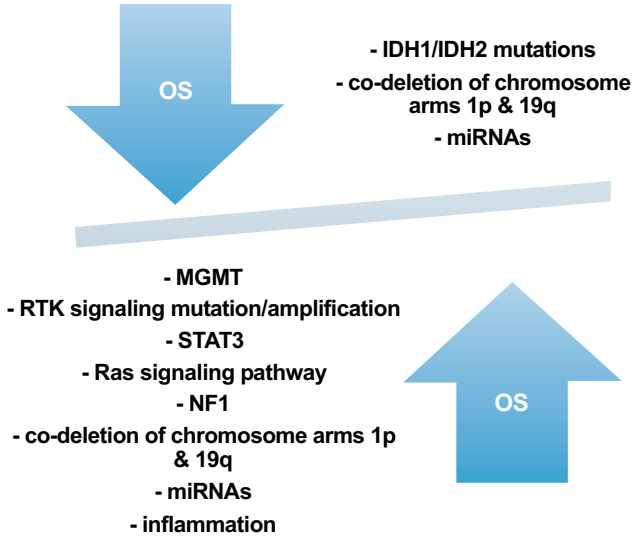

Fig. (2). Biological prognostic factors in GBM.

4.2. RTK Signaling Mutation/Amplification

Mutations or amplifications of receptor tyrosine kinase (RTK) signaling including EGFR, PDGFRA, basic fibroblast growth factor receptor 1 (FGFR-1), and insulin-like growth factor receptor (IGFR-1) are present in more than 80% of primary GBM (Fig. **2**) [34].

4.2.1. EGFR

EGFR amplification is observed in about 40% of primary glioblastomas and is very rare in secondary GBMs. Approximately 50% of these EGFR amplifications harbor a mutation in this gene that codes for EGFRvIII, an active variant of EGFR that is supposed to promote tumor growth and is potentially associated with a worse clinical outcome [35].

The role of EGFR amplification, as a prognostic biomarker, is not so clear. In fact, clinical studies have conflicting results. Reports show no association with overall survival in patients, instead, others show a negative impact, and some even indicate a favorable impact on patient survival.

4.2.2. PDGFR

Nearly 30% of human gliomas show expression patterns that are correlated with PDGFR signalling [36]. Amplification of PDGFR seems to promote aggressive glioma growth [29]. PDGF expression leads to tumor formation through both autocrine and paracrine signaling mechanisms, driving the evolution of heterogeneous malignant gliomas [37].

4.2.3. IGFR

Human epidemiological studies suggest that the IGF system is implicated in the development of malignancies, including GBM [38]. Approximately 20% of the GBMs showed positivity for the IGF ligands (IGF receptors) [39]. IGF-IR expression has a prognostic value, being negatively associated with cancer-specific survival in GBM [39, 40].

4.2.4. FGFR

FGF signaling has been considered as a pro-oncogenic pathway in GBM cells, and is crucial for the proliferation and survival of GBM cells [41]. FGFR1 expression levels have been shown to be a poor predictive marker of overall survival and time to progression in patients treated with chemo-radiotherapy in glioblastoma.

5. ISOCITRATE DEHYDROGENASE 1 AND 2 (IDH1/IDH2) MUTATIONS

Isocitrate dehydrogenase (IDH) is an enzyme that catalyzes the oxidative decarboxylation of isocitrate and produces α -ketoglutarate. Approximately 70% to 80% of secondary glioblastomas have somatic mutation in the isocitrate dehydrogenase 1 (IDH1) gene, which are rare in primary GBMs [42].

Mutations in IDH1 are proposed as an early event during glioma tumorigenesis, occurring preferentially in younger patients [8]. IDH1/2 mutations cause both loss of function and gain of function of the enzyme, so there is not the degradation of hypoxia-inducible factor 1α (HIF-1α) by α -ketoglutarate -dependent prolylhydroxylases. HIF-1α is an important transcription factor involved in crucial aspects of cancer biology, including angiogenesis, cell survival, glucose metabolism and invasion [43].

A meta-analysis examining the association of isocitrate dehydrogenase (IDH)1/2 mutations with overall

survival (OS) and progression-free survival (PFS) in patients with glioblastomas, showed that the presence of IDH1/2 mutations is associated with longer OS and PFS. This result was seen in both patients treated with surgery and those treated nonsurgically (*e.g*. radiotherapy), as well as in patients with IDH1 and IDH1/2 mutations (Fig. **2**) [44, 45].

6. STAT3

STAT3 is a member of the STAT (Signal Transducers and Activators of Transcription) family of transcription factors [46]. It is known that transcription factor STAT3 plays a central role in neural stem cell and astrocyte development [47].

Recent studies have uncovered that STAT3 plays distinct and opposing tumor suppressive and oncogenic roles in glioblastoma tumor pathogenesis depending on the genetics of PTEN and EGFRvIII status of the tumor [48]. STAT3 plays a critical tumor-suppressive role in PTEN-deficient human glioblastoma and IL8 is upregulated in PTEN-deficient human, in EGFRvIII-expressing cells. Instead, STAT3 promotes the survival of GBM cells (Fig. **2**) [49, 50].

7. RAS SIGNALING PATHWAY

The Ras signaling pathway is critical in the malignant phenotype of glioblastoma and has e been shown to govern proliferation and survival [51], invasiveness, and radiation resistance [52].

Ras gene mutations have not been found in the glioblastoma, hence Ras protein seems to be activated by the stimulation of surface receptors and other abnormal signaling events [53].

Activated intermediates of the Akt pathway and MAPK are associated with decreased overall survival in glioblastoma. Furthermore, it is probable that high expression of p-MAPK is associated with increased tumor resistance to radiotherapy in patients with glioblastoma (Fig. **2**) [51, 54].

8. NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 (NF1) is a genetic tumor-predisposing syndrome caused by germline mutations in the NF1 gene [55]. NF1 loss generally leads to increased activity in a variety of pro-tumorigenic pathways, particularly the mitogen-activated protein kinase pathway [56]. NF1 loss was associated with worse survival in GBMs (Fig. **2**) [56, 57].

9. CO-DELETION OF CHROMOSOME ARMS 1P & 19Q

Complete 1p/19q co-deletion is interconnected with better therapeutic sensitivity to chemotherapy [58] and radiotherapy [59] in patients with anaplastic oligodendroglioma. Results of the study with GBM are conflicting. Complete 1p/19q co-deletion is associated, for some author, with longer survival; for others, with a shortened survival (Fig. **2**) [60, 61].

10. mIRNA

Different studies confirmed that also small non-coding RNA molecules (miRNAs) have key roles in various pathogenic events in glioblastoma. MiRNAs could represent putative target molecules, considering their role in tumorigenesis, cancer progression and their specific tissue expression [62].

For example, miR-24 and miR-21 are highly expressed in GBMs favoring invasion and proliferation [63, 64]. Furthermore, upregulated miRNAs such as miRNA-326 and miRNA-130a, and down-regulated miRNAs such as miRNA-323, miRNA-329, miRNA-155 and miRNA-210 were associated with a long overall survival in GBM patients and could serve as prognostic and predictive markers for survival (Fig. **2**) [65, 66].

11. INFLAMMATION AS PROGNOSTIC FACTOR

Mounting evidence suggests an important role for inflammation in the pathogenesis and progression of cancer. The development of an inflammatory microenvironment has long been considered important in the initiation and progression of glioblastoma (Fig. **2**) [67].

A panel of cytokines and angiogenic factors, whose levels were significantly higher and strongly correlated with clinical aggressiveness in GBMs was found. Inflammatory cells and cytokines present in GBM are more likely to contribute to tumour growth, progression, and immunosuppression, rather than in building an effective antitumour defence [68]. IL-1 is a major neuroinflammatory cytokine in the brain that is released in response to injury or a growing tumor [69]. Moreover, IL-1 regulates survival and invasiveness of glioblastoma cells, increases Sphingosine kinases (SphK1) activity and intracellular concentration of S1P, a potent lipid mediator of various cell processes, including cell proliferation, differentiation, survival, and migration [70].

Il-6 and IL-8 are related to the expansion of GBM, IL-6 mitogenic for tumour cells. IL-8 amplifies the inflammatory microenvironment and also has chemotactic and angiogenic properties [71].

Instead, anti-inflammatory cytokines IL-4 and IL-12 appear at a lower level. IL-4 is involved in the inhibition of cell proliferation, regulation of adhesion molecules, and induction JAK/STAT signalling, IL-12 is a powerful anticancer factor, which can inhibit the growth of implanted glioblastoma and the increase in survival time [68]. Furthermore, serum levels of angiogenic factors were considerably elevated in glioblastoma patients, while VEGF and bFGF were significantly overexpressed [68].

VEGF-VEGFR2 signalling is maintained by continuous secretion of VEGF ligand and promotes tumour growth, invasiveness and enhanced resistance to some treatments [72].

The same presence of systemic inflammation is a predictor of outcomes in various types of malignancies including GBM. Neutrophil-to-lymphocyte ratio (NLR) and PLRs (platelet-to-lymphocyte ratio) are two emerging markers of systemic inflammatory response easily calculated from routine complete blood counts (CBCs) in peripheral blood.

NLR and PLR reveal an imbalance between tumorigenic inflammatory processes and anti-tumor cellular immunity. An elevated neutrophil count could promote

Table 1. Prognostic and predictive response therapy factors in GBM.

Biological Prognostic Factors	Positive	Negative
Methylguanine-DNA Methyl transferase.	Silencing of the MGMT protein (promoter methylation) may suppress repair mechanism, and increase cytotoxicity of CT and RT.	-
RTK signaling mutation/amplification		
EGFR	-	Amplification promotes tumor growth and is potentially associated with a worse clinical outcome.
PDGFR	-	Amplification seems to promote aggressive glioma growth.
IGFR	-	IGF-IR expression has a prognostic value, being negatively associated with cancer-specific survival.
FGFR	-	FGFR1 expression levels have been shown to be a poor predictive marker of overall survival.
Isocitrate Dehydrogenase 1 and 2 (IDH1/IDH2) mutations.	presence of IDH1/2 mutations is associated with longer OS and PFS.	-
STAT3	tumor suppressive role in PTEN-deficient human glioblastoma.	EGFRvIII-expressing cells, instead, STAT3 promotes the survival of GBM cells.
Ras signaling pathway.	-	Activated intermediates of the Akt pathway and MAPK are associated with decreased overall survival. High expression of p-MAPK is associated with increased tumor resistance to radiotherapy.
Neurofibromatosis type 1.	-	loss was associated with worse survival.
Co-deletion of Chromosome Arms 1p & 19q.	Complete 1p/19q co-deletion is associated, for some author, with longer survival.	-
miRNA	miR-24 and miR-21 are highly expressed in GBMs favoring invasion and proliferation.	upregulated miRNAs such as miRNA-326 and miRNA-130a were associated with long overall survival.

tumor growth and metastasis by remodeling the extracellular matrix, releasing reactive oxygen species, and suppressing lymphocyte activity [73]. An elevated platelet count recruited to the tumor microenvironment interacts directly with tumor cells, favoring their proliferation, and, indirectly, through the release of a wide palette of growth factors, including angiogenic and mitogenic proteins [74]. A high NLR and PLR were found to be closely associated with a poor prognosis GBMs [70, 75-77].

Furthermore, it is extremely important to understand the interaction of glioblastomas with surrounding stromal cells. A transmembrane receptor ligand, program death-ligand 1 (PDL-1) is demonstrated to have a negative regulator of T-cell signaling. Liu *et al*. evaluated PD-L1 expression in surgically resected tumors from GBM patients. In a subgroup of GBM patients, PD-L1 was highly expressed in tumor-adjacent brain tissue; in another group, PD-L1 was highly expressed in tumor cells.

The authors found that the first group (tumor-adjacent brain tissue with PD-L1) was significantly associated with a favorable prognosis. Instead, GBM patient subgroup, with PD-L1 expression in tumor cells, was associated with poor prognosis [78]. A regulatory pathway between PD-L1 expression in brain neurons and in tumor cells was conceivable, where an upregulation of PD-L1 expression in tumor cells allowed tumor cells to evade immune surveillance and correlate with GBM aggressiveness [78].

CONCLUSION

Recent studies have provided a biological basis to GBM. This new knowledge is very important to obtain biomarkers as prognostic and predictive response therapy factors and to develop new therapeutic opportunities, resumed in Table **1**.

As a prognostic value, histology-based diagnosis must be assisted by molecular diagnostic tests to allow biological classification and improve patient stratification. It is important to obtain more information by radiological imaging in order to obtain information on the complexity and heterogeneity of GBM.

As a predictive value, today it is not so clear how the biology of tumor is affected by biological factors.

A hypothesis concerns IDH mutations: the increased sensitivity of these GBM cells to chemotherapy and radiotherapy can be explained by a reduction of capacity of these GBM cells to produce nicotinamide adenine dinucleotide phosphate (NADPH) and consequently to lower the ability to scavenge oxygen species, making the tumor cells more susceptible to irradiation and chemotherapy [79].

miRNAs were found to affect the tumor response to radiotherapy. Globally, miR-26a, miR-124, miR-128, miR-145, miR-153, miR-181a/b, miR-203, miR-221/222, miR223, miR-224, miR-320, and miR-590-3p increase the radiosensitivity of GBM cells, while miR-21, miR-210, miR-212, and miR-135b decrease it [80].

The choice of the best assumption to apply in each GBM case is not an easy one and results must be evaluated by clinical data.

CLINICAL PRACTICE POINTS

- Primary GBM is remarkable for LOH of 10q (70%), epidermal growth factor receptor (EGFR) amplification (36%), PTEN mutation (25%) and CDKN2A-p16^{INK4A} deletion (31-78%).
- Secondary GBM most frequently demonstrates mutation of the TP53 tumor suppressor gene (65%) and MGMT promoter methylation (75%).
- Clinical prognostic factors are: biological age, ECOG PS, surgery and imaging factors (MRI, PET with 11C-METH).
- Biological prognostic factors are: MGMT, RTK signaling mutation/amplification (EGFR, PDGFRA, FGFR-1 and IGFR-1), IDH1/IDH2 mutations, STAT3, Ras signaling pathway, NF1, co-deletion of chromosome arms 1p & 19q, miRNAs and inflammation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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