Neuro-Oncology
20(9), 1162–1172, 2017 | doi:10.1093/neuonc/nox242 | Advance Access date 23 December 2017

The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology

Daniel N. Cagney, Joohee Sul, Raymond Y. Huang, Keith L. Ligon, Patrick Y. Wen, and Brian M. Alexander

Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, Massachusetts (D.N.C., B.M.A.); Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (J.S.); Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (R.Y.H.); Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (K.L.L.); Center For Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, Massachusetts (P.Y.W.)

Corresponding Author: Brian M. Alexander MD, Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, 75 Francis Street, Boston, MA 02115 (Brian_Alexander@dfci.harvard.edu).

Abstract

In early 2016, the FDA and the National Institutes of Health (NIH) published the first version of the glossary included in the Biomarkers, EndpointS, and other Tools (BEST) resource.[1] The BEST glossary was constructed to harmonize and clarify terms used in translational science and medical product development and to provide a common language used for communication by those agencies. It is considered a "living" document that will be updated in the future. This review will discuss the main biomarker and clinical outcome categories contained in the BEST glossary as they apply to neuro-oncology, as well as the overlapping and hierarchical relationships among them.

Key words

BEST glossary | biomarkers | endpoints | glioma | outcomes

Biomarkers

Biomarkers play a crucial role in neuro-oncology in both routine clinical care and therapeutic development. The term "biomarker" applies to many different patient or disease assessments, and imprecise use of terms without a clear understanding of the definitions can lead to confusion. The FDA/NIH Biomarker Working Group defines a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers but a biomarker is **not** an assessment of how an individual feels, functions, or survives."[1] Biomarkers can refer to characteristics that are measured anywhere along the clinical continuum from prediagnosis of disease, to pretreatment (as the basis for precision medicine), to the posttreatment phase (outcomes and endpoints). A summary of biomarker categories placed along this continuum is illustrated in Fig. 1 and listed in Table 1. Ideally, biomarker tests intended for use in patient care would undergo rigorous evaluation prior to introduction into the clinic. Following biomarker discovery, this evaluation process would first include *analytical validation* to assess the accuracy and reliability of the proposed test to measure the candidate biomarker. Accuracy is a measure of how often a test is correct in a given population, ie, the number of true positives and true negatives divided by the number of overall assessments. Accuracy is related to the *sensitivity* and *specificity* of a test, and the prevalence of the target marker in the studied population. The *sensitivity* of a test is the measure of true positives divided by true positives plus false negatives—in other words, the intrinsic ability of the test to "find" a true positive when it exists. Conversely, *specificity* is the measure of true negatives divided by true negatives plus false positives, or the intrinsic ability of the test to distinguish a true negative. Testing for

clinical validity entails testing within a clinical trial appropriately designed to enable a sufficient understanding of how well the proposed biomarker and test performs. Much of the following discussion outlines the evidence for clinical validation for various biomarkers by BEST-defined categories; however, most of the clinical use of biomarkers in neuro-oncology may be based on specific testing without established clinical or analytical validity, and instead relies on extrapolation of clinical data from other testing of a common biomarker.

Susceptibility/Risk Biomarkers

A susceptibility/risk biomarker indicates the potential for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease.[1] In neuro-oncology, these biomarkers could refer to measurements of exposures or identification of patient factors that are associated with increased risk for developing a CNS neoplasm. For example, exposure to ionizing radiation (IR) has been linked to the development of both meningioma and glioma,[4] so risk biomarkers that correlated with the absorbed dose of IR (ie, "biodosimeters") may also be linked to the risk of developing such tumors.[2] Inherited genetic disorders marked by germline mutations of the p53 tumor suppressor gene (Li–Fraumeni syndrome), DNA mismatch repair gene mutations (Turcot syndrome), neurofibromatosis type 1 (NF1) gene and NF2 gene alterations, alterations in RB1 or MYCN (retinoblastoma), and tuberous sclerosis 1 (TSC1) and TSC2 mutations are each associated with increased risk of glioma.[3,4] DNA repair gene polymorphisms such as excision repair cross-complement 1 (ERCC1), ERCC2, and X-ray repair cross-complement 1 (XRCC1) (higher risk) and O^6-methylguanine-DNA methyltransferase (MGMT) and poly(ADP-ribose) polymerase 1 (lower risk) have also been associated with risk of developing glioma.[5] Additionally, there have been significant efforts undertaken to characterize specific single-nucleotide polymorphisms that may portend genetic susceptibility to developing brain tumors.[6,7] Finally, an association between increased risk of allergy and decreased risk of glioma has been described; indicators of atopy, such as serum immunoglobulin E levels, have been correlated with this decreased risk.[8,9]

Diagnostic Biomarkers

A diagnostic biomarker is used to identify individuals with a disease or condition or to define a subset of the disease.[1] Diagnostic biomarkers are frequently used in neuropathology and are increasingly vital for classification of brain tumors. The 2016 World Health Organization (WHO) classification[10] incorporated several molecular parameters in addition to histopathology. This represented a major restructuring of the diffuse gliomas, medulloblastomas, and other embryonal tumors and incorporated new molecularly defined entities such as those characterized by isocitrate dehydrogenase (IDH) mutations. Diagnostic clarity is vital to ensure optimal management and is essential for defining clinical trial populations. The ability to clearly define patient populations through diagnostic biomarkers would not only increase the chances that those markers could function as predictive or prognostic markers to support precision medicine but would also decrease patient heterogeneity and make therapeutic signals easier to detect. In 2015 three studies advanced our understanding of the molecular heterogeneity of gliomas[11–13] and informed their reclassification into different clinical groups based on codeletion of chromosome arms 1p/19q, IDH mutations, and telomerase reverse transcriptase (TERT) promoter mutations. The groups had different patient characteristics, natural histories, and associations with germline variants, implying that they were characterized by distinct mechanisms of pathogenesis.[11–13]

The Cancer Genome Atlas (TCGA) Research Network[11] and investigators from Japan[12] classified lower-grade gliomas into 3 prognostically different subtypes, according to the presence or absence of *IDH* mutations and 1p/19q codeletions. Among patients with low-grade gliomas, those with *IDH* mutations (80%) had improved prognosis compared with patients without an IDH mutation, while a subset with an *IDH* mutation and 1p/19q codeletion (30%) had

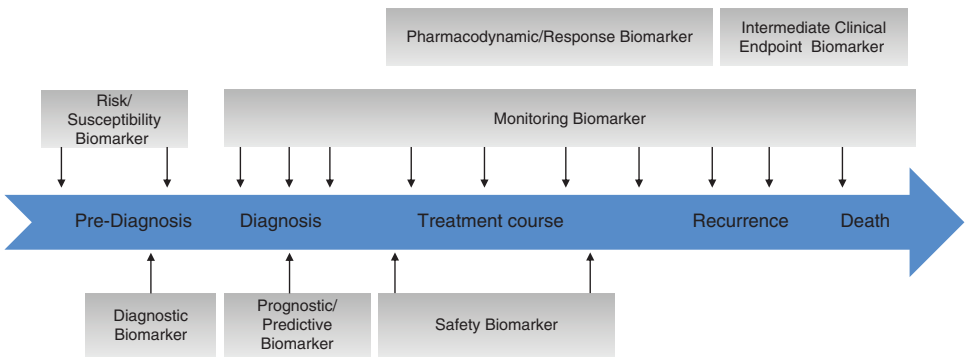

Fig. 1 Biomarkers along the clinical continuum.

Table 1 Biomarkers in neuro-oncology

Types of Biomarkers	Definition	Examples in Neuro-oncology
Susceptibility/risk biomarker	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.	Inherited genetic disorders History of ionizing radiation DNA repair gene polymorphisms Single-nucleotide polymorphisms Atopy
Diagnostic biomarker	A biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.	Histology MGMT promoter methylation 1p/19q codeletion IDH1/2 mutation TERT promoter mutation
Monitoring biomarker	A biomarker measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.	Contrast enhanced MRI brain Complete blood count Circulating tumor cells Circulating exosomes Circulating microRNAs
Prognostic biomarker	A biomarker used to identify likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest.	MGMT promoter methylation 1p/19q codeletion IDH1/2 mutation
Predictive biomarker	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.	MGMT promoter methylation 1p/19q codeletion IDH1/2 mutation
Pharmacodynamic/response biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.	Contrast enhanced MRI brain Reduced malignant cell count in CSF cytology/flow cytometry
Safety biomarker	A biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.	Complete blood count Genetic polymorphisms: A allele of NQO1 (rs1800566) G allele of MGMT (rs2308327)

the most favorable clinical outcome. Lower-grade gliomas harboring *IDH* mutations without 1p/19q codeletion had intermediate outcomes and those without *IDH* mutations (20%) had a clinical course similar to that of glioblastoma (GBM). Additionally, mutations in CIC (capicua transcriptional repressor) and FUBP1 (far upstream element-binding protein 1) were found in 1p/19q codeleted tumors while inactivation of ATRX (alpha thalassemia/mental retardation syndrome X-linked protein) and p53 mutations were associated with 1p/19q intact tumors; these associations further aid in classification of tumors.[11] The third study classified lower-grade gliomas by *IDH* mutation status and codeletion of 1p/19q, as well as including TERT promoter mutation status.[13] This classification created 5 molecularly defined subgroups; triple-positive (mutations in both *TERT* and *IDH* plus 1p/19q codeletion), mutations in both *TERT* and *IDH*, mutation in *IDH* only, triple-negative, and mutation in *TERT* only. The results corroborated the 3 main subgroups described earlier. These studies[11–13] have important implications for patients, allowing more accurate determination of diagnosis and prognosis and informing selection of the most appropriate therapies.

A new approach termed "imaging genomics" links specific imaging properties to genomic alterations.[14,15] Some imaging approaches also capitalize on our increasing knowledge of the metabolic alterations predominating in gliomas (such as those associated with *IDH* mutations) and involve adaptations of PET technology.[16] PET using radiolabeled amino acids such as L-methyl-11C-methionine (11C-METH), is an additional tool for the characterization of primary brain tumors. Lopci et al[17] performed a semiquantitative evaluation of the 11C-METH PET images in patients with newly diagnosed glioma. They reported that the maximum standardized uptake value (SUVmax) and SUVratio were inversely correlated with the presence of *IDH1* mutation ($P < 0.001$) and were higher in patients with primary GBM (*IDH1* wild type) than in those with other gliomas ($P < 0.001$). While promising, the linkage of imaging characteristics to specific molecular alterations in tumors is in the early stages and requires further prospective clinical validation.

Monitoring Biomarkers

Monitoring biomarkers are those that are measured serially and used to detect a change in the extent of disease (eg, imaging), to assess safety and toxicity (eg, platelet and blood count), or to provide evidence of exposure (eg, drug serum levels), including exposures to medical products.[1] Monitoring biomarkers may also overlap with safety biomarkers that aid our understanding and management of toxicities associated with treatments.

Imaging technologies are appealing tools for monitoring biomarker assessment, as they allow for non-invasive

visualization of tumor and adjacent tissues in their entirety. MRI is the most commonly used modality to monitor disease status, and recent consensus guidelines have been developed for utilizing imaging endpoints in GBM clinical trials, including a standardized MRI protocol for multicenter studies.[18] In recent years, mounting clinical experience has shown that tumor progression and treatment-related changes (eg, pseudoprogression, delayed radiation necrosis) can be indistinguishable at a single time point using conventional contrast-enhanced structural brain imaging[19–21]; however, this distinction is crucial to assess the activity of a treatment and dictates subsequent clinical management, including whether a change in therapy or repeat surgery is warranted. Over the past decade, physiological imaging techniques have been explored to address the challenges of accurate interpretation of imaging.[20,22,23] Perfusion-weighted MRI imaging approaches, utilizing dynamic susceptibility contrast enhanced perfusion[23] or dynamic contrast enhanced perfusion,[24,25] are promising tools for distinguishing between treatment effect and tumor progression but have not been rigorously validated in clinical trials.

Blood is the most easily accessible tissue source for monitoring biomarkers and is frequently used to assess disease status in malignancies such as prostate and ovarian cancer using serum biomarkers of prostate-specific antigen and cancer antigen 125, respectively. In neuro-oncology, blood-based monitoring biomarkers are primarily used to assess toxicity and safety to continue administering treatment. For example, because myelosuppression is a common risk associated with temozolomide (TMZ) and radiotherapy (RT), standard practice dictates a weekly complete blood count with differential and platelets during the 6 weeks of definitive chemoradiotherapy.[26] However, blood-based tumor monitoring biomarkers may be more problematic due to the blood–brain barrier, which blocks reliable shedding of tumor-related biomarkers into circulating blood.

Although potentially challenging, the potential large benefits have supported areas of research into blood-based biomarkers in neuro-oncology, including monitoring circulating tumor cells, exosomes, and microRNAs. As these blood-based biomarkers may have utility for monitoring disease, they could also be useful as response biomarkers or in the pretreatment space as diagnostic, prognostic, or predictive markers. Circulating tumor cells have been identified in many tumor types and may be detected in GBM patients.[27] These circulating tumor cells, enriched for the mesenchymal gene expression signature, may represent a more aggressive glioma phenotype showing overlapping functionality as a prognostic marker.[28] However, this more aggressive glioma phenotype has not been demonstrated in prior TCGA datasets.

Circulating GBM exosomes have been used to analyze primary brain tumor mutations and to monitor treatment-related changes.[29] Some groups have utilized CSF exosomes as a diagnostic and monitoring aid. The use of microRNAs in blood as a monitoring or response biomarker is of ongoing interest in glioma. Qiu et al[30] have shown that certain up- and downregulated microRNAs may be associated with long overall survival (OS) in GBM patients. Additionally, Akers et al[31] showed that CSF miR-21 levels in exosomes of GBM patients were upregulated and could represent a potential monitoring biomarker.

Prognostic Biomarkers

Prognostic biomarkers are used to identify the likelihood of a clinical event, disease recurrence, or progression based on the natural history of the disease.[1] As such, these biomarkers generally demonstrate an association with a specific outcome such as progression-free survival (PFS) or OS. Some examples of prognostic biomarkers in neuro-oncology include MGMT promoter methylation status,[32] 1p/19q codeletion status,[11,33] and IDH1/2 mutations.[11,34]

MGMT

Hegi et al[35] retrospectively determined MGMT promoter status from tumors of patients who enrolled in the European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada (EORTC/NCIC CE.3) randomized study of concomitant and adjuvant TMZ + RT versus RT alone. Regardless of treatment, MGMT promoter methylation emerged as a favorable independent prognostic factor. Similar results were described in the EORTC/NCIC/TROG (Trans Tasman Radiation Oncology Group) study of hypofractionated RT ± TMZ in elderly patients,[36] and a meta-analysis[37] of 20 studies indicated that MGMT gene silencing was associated with a longer survival in patients undergoing treatment for high-grade gliomas. The prognostic significance of MGMT promoter methylation status has also been investigated in lower-grade gliomas. In a post hoc analysis of EORTC study 26951, MGMT promoter methylation was associated with longer survival in patients with anaplastic oligodendroglial tumors treated with RT and adjuvant procarbazine/CCNU/vincristine (PCV) or radiotherapy alone.[38]

1p/19q codeletion

Unbalanced whole-arm translocation between chromosomes 19 and 1 with the loss of the derivative chromosome t(1p;19q) occurs in oligodendrogliomas and is used to define this subset of gliomas.[39] Codeletion of 1p/19q is a consequence of this unbalanced whole-arm translocation.[40] The prognostic impact on OS of 1p/19q codeletion has been shown in large clinical trials.[41,42] The Radiation Therapy Oncology Group (RTOG) 9402 trial compared chemotherapy (PCV) and RT versus RT alone in patients with low-grade gliomas. Regardless of treatment arm, patients with codeleted tumors had longer OS compared with those with intact tumors (PCV plus RT: 14.7 vs 2.6 y, hazard ratio [HR] = 0.36, 95% CI: 0.23 to 0.57; RT: 7.3 vs 2.7 y, HR = 0.40, 95% CI: 0.27 to 0.60).[41] Similar results were demonstrated in EORTC 26951, a study comparing chemotherapy plus RT versus RT alone. Both PFS and OS were significantly longer in the patients with codeleted tumors compared with the patients with intact tumors (PFS, 76 vs 11 mo, HR = 0.39, 95% CI: 0.28 to 0.53; OS, 123 vs 23 mo, HR = 0.36, 95% CI: 0.26 to 0.50).[42]

IDH1/2

Mutations in *IDH1* or *IDH2* are relatively uncommon in cancer but are a frequent genetic alteration of grade II and III diffuse gliomas and secondary GBMs.[43] Many next-generation sequencing panels assess for these mutations, and in clinical practice immunostaining using an antibody against the most common mutant protein (ie, IDH1-R132H) has been developed.[44,45] Patients with GBM harboring *IDH1/2* mutations have a better prognosis compared with patients without *IDH1/2* mutations.[46–49] Although patients with IDH1 mutations are generally younger, numerous studies have confirmed that IDH1 mutation is a favorable independent prognostic marker in grades III and IV gliomas.[50,51]

Imaging

In recurrent GBM, baseline contrast enhancing tumor volume has shown promise as a prognostic biomarker.[52] Ellingson et al[52] evaluated the prognostic significance of baseline contrast enhancing tumor prior to second- or third-line therapy in recurrent GBM for OS. They noted that tumors dichotomized into large (≥15 cc) and small (<15 cc) tumors were significant predictors of OS ($P < 0.0001$), independently of age and treatment. The evaluation of this biomarker is in the early stages and needs further exploration in clinical trials.

Predictive Biomarkers

Predictive biomarkers are used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure.[1] As diagnostic and prognostic markers define subsets of disease with different natural histories, these biologically relevant subsets may also be expected to correlate with response to various therapies or confound interpretation of response data. In some cases in neuro-oncology this relationship clearly holds, while in others, the data are more ambiguous. To determine whether a particular biomarker is predictive, a test for interaction is frequently performed. A statistically significant Treatment × Biomarker interaction term in a multivariate model provides evidence that the treatment effect differs by biomarker subpopulation.[53]

MGMT

Esteller et al reported an association of MGMT promoter methylation and response of high-grade astrocytomas to alkylating agents.[54] The results from the EORTC/NCIC trial provided some evidence for an association of MGMT status and magnitude of response to TMZ. Even though the test for interaction of MGMT status and TMZ was not statistically significant in an underpowered retrospective analysis, the HR for death was less in patients treated with TMZ for methylated (HR 0.51) versus unmethylated tumors (HR 0.69).[35] However, it is unclear in the predictive value of MGMT in patients with longer follow-up.[55] The relative difference between TMZ effects on methylated and unmethylated tumors may also translate to greater absolute differences based on the prognostic utility of methylation. In both the NOA-04[56] and the Nordic[57] trials, patients with methylated MGMT promoters had significantly longer survival with the addition of TMZ but not with RT, demonstrating that MGMT promoter methylation status predicted response to TMZ. Most recently, the EORTC/NCIC/RTOG randomized trial of hypofractionated RT ± TMZ for elderly patients with GBM showed similar results to the EORTC/NCIC CE.3 study. While all patients had a survival benefit from the addition of TMZ (HR 0.67), the magnitude of the benefit for unmethylated patients (HR 0.75) was less than that of patients with tumors harboring methylated MGMT promoters (HR 0.50).[36]

1p/19q codeletion

Multiple retrospective studies have revealed that the chemosensitivity of oligodendroglial tumors is related to 1p/19q codeletion.[58] The possible predictive capacity of 1p/19q codeletion was investigated in the setting of 2 large randomized trials—RTOG 9402 and EORTC 26951.[41,42] Like MGMT promoter methylation status in GBM, 1p/19q codeletion seems to have some predictive capacity for PCV effect (but not sure that intact tumors do not benefit) that is magnified by the prognostic value in absolute benefit terms. For example, in the RTOG 9402 study, codeleted tumors treated with PCV plus RT had an HR for OS of 0.59 (95% CI: 0.37–0.95; $P = 0.03$) and an HR for PFS of 0.47 (95% CI: 0.30–0.72; $P < 0.001$) compared with those treated with RT alone.[41] The HRs for OS and PFS for the addition of PCV in patients with intact tumors are higher at 0.85 (95% CI: 0.58–1.23, $P = 0.39$) and 0.81 (95% CI: 0.56–1.16, $P = 0.24$), respectively. While tests for statistical significance were negative for patients with intact tumors, it is important to note that the trial is significantly underpowered to detect treatment effects in subsets, especially if the potential true HR is higher than expected for the intact group. Furthermore, for both groups of patients, OS curves started to split around the median and test for interaction between codeletion status and PCV effect was negative. In the EORTC 26951 study, very similar results were found. For patients with 1p/19q codeleted tumors, HR for OS (0.56, 95% CI: 0.31–1.03) and PFS (0.42, 95% CI: 0.24–0.74) were lower for the addition of PCV than for patients with intact tumors (0.83, 95% CI: 0.62–1.10; 0.73, 95% CI: 0.56–0.97, respectively).[42] Tests for interaction were similarly negative, likely owing to the underpowered analysis and the incomplete predictive nature of the biomarker.

IDH1/2

A similar reanalysis of RTOG 9402 and EORTC 26951 related to IDH1/2 mutational status. In the EORTC 26951 trial, the HRs for OS (0.53; 95% CI: 0.30–0.95) and PFS (0.49; 95% CI: 0.29–0.84) were lower for the PCV arm for IDH1/2 mutated patients compared with wild-type (0.78; 95% CI: 0.52–1.18 and 0.56; 95% CI: 0.37–0.86, respectively). In RTOG 9402 reanalysis, however, there was a starker predictive association. Patients with tumors harboring *IDH1/2* mutations had a survival benefit from PCV (HR 0.59; 95% CI: 0.40–0.86), while those without a detectable mutation by immunohistochemical R132H profiling or IDH2

sequencing did not (HR 1.14; 95% CI: 0.63–2.04).[59] Notably, patients with 1p/19q intact tumors in association with IDH mutations had a survival benefit from PCV (HR 0.56; 95% CI: 0.32–0.99), a possible explanation for the likely small PCV benefit in 1p/19q intact tumors and subsequent incomplete predictive ability previously reported.

Gene signatures

Developing gene signatures for predictive or prognostic purposes is challenging due to the need to first develop the signature in a clinically annotated tissue dataset and then validate in others. One example is the development of a 9-gene signature based on quantitative real-time PCR analysis of formalin-fixed paraffin-embedded tumor tissue that showed a significant association with outcome during development[60] but which was not associated with outcome in either the control or experimental arms in RTOG 0825, providing no evidence for either prognostic or predictive capacity.[61] Assay variability and other technical challenges may lead to interrater differences in addition to the informatics challenges, showing the importance of analytical validation.

Pharmacodynamic/Response Biomarkers

Pharmacodynamic/response markers aim to show that a biological response has occurred in an individual who has received an intervention or exposure.[1] These biomarkers may be endpoints of earlier-phase, proof-of-concept trials and tend to be experimental therapy specific based on the mechanism of action. Pharmacodynamic or response biomarkers that are proven to correlate with more clinically meaningful endpoints could theoretically be developed along the surrogate endpoint pathway, though therapeutic specificity might limit the utility ultimately for broad application. Blood-based pharmacodynamic biomarkers are probably the most common example of this in neuro-oncology to date, examples being measurement of peripheral blood mononuclear cells by western blot to determine inhibitor of targets such as pAkt and pS6 after small-molecule Akt inhibitor treatment.[62]

Radiographic response for high-grade gliomas is generally assessed by contrast enhanced MRI. Historically, the Macdonald criteria measured contrast enhancing on imaging to determine disease status, separating response into 4 categories: complete response, partial response, stable disease, and progressive disease.[63] In 2010, the Response Assessment in Neuro-Oncology (RANO) criteria were developed[64] to reform and improve upon the Macdonald criteria. The main change was to include evaluation of non-enhancing tumor progression. The RANO criteria included definitions of measurable and nonmeasurable disease; guidelines to determine progression for patients being considered for enrollment into clinical trials; strategies to address pseudoprogression, pseudoresponse, and equivocal imaging changes; mandated instructions of confirmatory scans for response; and the recommendation to perform follow-up imaging to assess equivocal imaging changes. Conventional MRI enables structural evaluation of tumor size, anatomic position, and pattern of contrast enhancement but is limited in the ability to evaluate pathophysiologic properties such as microscopic tumoral infiltration, microvascular characteristics, early response changes, and the relationship of tumor to eloquent cortical areas. These limitations have led to the development of advanced MRI techniques that can evaluate the cellular, hemodynamic, metabolic, and functional properties of gliomas. Response biomarkers may require modifications based on therapeutic class. This is illustrated by RANO and variations of RANO.[65] Pharmacodynamic biomarkers are generally related to the biology of the experimental therapy and therefore are more therapy-specific than response biomarkers. In some cases, an impact on a pharmacodynamic marker may be thought of as a necessary (if not sufficient) result for an experimental therapy to ultimately be clinically effective. In these cases, pharmacodynamic markers may be important early phase clinical trial endpoints as signals of biologic activity.[66] Evidence of an impact on a pharmacodynamic marker may provide confidence in further testing or suggest candidates for combinations when later stage endpoints are not met. An example utilizing both imaging and molecular pharmacodynamic biomarkers was the Adult Brain Tumor Consortium study of cediranib plus cilengitide for patients with recurrent GBM.[67] The trial included MRI and blood biomarkers to evaluate tumor infiltration and explore the association of biomarker candidates with response. While no survival benefit was found, the combination of cediranib and cilengitide had imaging-defined antivascular effects associated with corresponding increases in hypoxia-inducible (vascular endothelial growth factor, stromal cell derived factor 1α, and carbonic anhydrase IX) and proinflammatory molecules (interleukin [IL]-6 and IL-8).

Safety biomarkers

Safety biomarkers are used to indicate the presence or extent of toxicity related to an intervention or exposure.[1] The most commonly used safety biomarker in neuro-oncology is weekly complete blood counts in patients receiving chemoradiation for glioma to monitor for myelosuppression.[26] Armstrong et al[68] sought to evaluate clinical factors and genetic polymorphisms as predictors for myelotoxicity and noted that the presence of the A allele of *NQO1* (rs1800566) resulted in a 70% reduction in risk of myelotoxicity (95% CI: 0.11–0.85). Patients carrying the G allele of the *GSTP1* 105(rs1695) polymorphism also experienced a 72% reduction in risk of toxicity (95% CI: 0.10–0.75). However, patients carrying the G allele of *MGMT* (rs2308327) exhibited a 240% increase in risk of toxicity (95% CI: 0.99–5.84), These data are hypothesis generating, and the utility of them may be applied to individualized dosing regimens in the future.

Outcomes and Endpoints

The BEST glossary describes an *outcome* as a measurable characteristic that is affected by an individuals' baseline

state or an intervention, while *an outcome assessment* is an evaluation of an outcome that results in recorded data points. Outcomes may refer to *clinical outcomes* (described below) or to *biomarkers* (described previously). The definition of an *endpoint* is distinguished from that of an outcome in that an endpoint is a "precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined."[1] Endpoints, in that sense, exist only in the context of research questions, whereas outcomes are a more general distinction.

Surrogate Endpoints

A *surrogate endpoint* is defined as "an endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."[1] Ideally, a true surrogate endpoint captures the entire relationship between an experimental therapeutic and the ultimate clinically relevant endpoint of interest. Because they capture this relationship at an earlier time point, reliable surrogate endpoints could significantly speed therapeutic development. The FDA/NIH working group defined endpoints that have potential to be surrogates along a development continuum with increasing levels of supportive evidence (Fig. 1). A *candidate surrogate endpoint* is an endpoint still under evaluation for its ability to predict clinical benefit, while a *reasonably likely surrogate endpoint* is one that is supported by clear mechanistic and/or epidemiologic rationale but with insufficient clinical data to show that it is a validated surrogate endpoint.[1] Finally, a validated surrogate endpoint is supported by a clear mechanistic rationale and clinical data providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit.[1] Validated surrogate endpoints can be used to support traditional approval without the need for additional efficacy information.

In general, PFS and objective response rate (ORR) are considered valuable endpoints in clinical trials given their earlier time to event, more proximal relationship to an experimental therapy, and impact on treatment decision making.[69] While impact on OS is considered the gold standard for determining the value of an experimental therapy in GBM, identifying a true therapeutic signal may be challenging. For example, OS has more natural variation that is at least in part explained by other factors (eg, age, performance status) than an endpoint such as ORR, where any responses are likely directly attributable to therapy. Additionally, a direct positive effect on a tumor leading to a delay in progression may not translate to a detectable OS benefit if there is crossover to effective therapies after progression or if survival post progression (SPP) is long even in the absence of effective therapies.[70] Complications from crossover and long SPP are not significant factors for using OS in clinical trials for GBM at present, however, so the utility of surrogates is questionable.[71] A compelling ORR was used to support the accelerated approval of bevacizumab in GBM,[72] but there has been little evidence to link a therapeutic effect on ORR with an impact on OS.[73] While correlation has been shown between the therapeutic impacts on PFS and OS for TMZ,[35,73] the experience with bevacizumab[61,74] and the anticipated issues of pseudoprogression with immunotherapy[65] limit the confidence of the generalizability of this finding. As more therapies are proven effective for GBM and as survival times extend, the importance of PFS will only increase; therefore, more scrutiny of its value as an endpoint is needed.

Intermediate Clinical Endpoints

Intermediate clinical endpoints (generally referenced in a regulatory context) are clinical outcomes that are considered reasonably likely to predict the medical product's effect on irreversible morbidity and mortality or other clinical benefit.[1] In contrast to the endpoints on the surrogacy spectrum, intermediate clinical endpoints are based on clinical outcomes (not biomarkers) and don't necessarily rely on specific data supporting a link to a more clinically meaningful endpoint. Intermediate clinical endpoints may receive full FDA approval if the clinical effect is considered meaningful in and of itself, otherwise they may be the basis of accelerated approval.[1]

Clinical Outcomes and Clinical Outcome Assessments

Patients with malignant gliomas may experience progressive deterioration of neurological function that impacts physical, cognitive, emotional, and social domains. Given the poor prognosis of these patients, the lack of effective therapies, and the challenges of evaluating disease response, a clinical outcome assessment could be a vital component to inform the value of an investigational therapy. *Clinical outcome assessments* (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions.[1] COAs can be used to determine whether or not a drug has demonstrated treatment benefit, including a safety benefit compared with other treatments.[1] Assessment of a clinical outcome can be made through report by a clinician, the patient, or a non-clinician observer or through a performance-based assessment.

Clinician-reported outcomes (ClinROs) are measurements based on a report that comes from a trained health care professional after observation of a patient's health condition.[1] Reports of events such as death would be included in this category, as would outcomes that are combinations of clinical observations and biomarker data such as PFS or ORR.

ClinRO measures, including Karnofsky performance status (KPS), Eastern Cooperative Oncology Group performance status, and the WHO performance scale, are extensively used in the clinical assessment of malignant gliomas. These scales quantify a patient's functional capacity for activities of daily living from the clinician's perspective. KPS is the ClinRO most commonly used across clinical trials for malignant gliomas and has been validated as a prognostic factor for OS in this population.[75] However, a number of studies have shown that the interrater reliability of the KPS is relatively poor.[76,77] The Neurologic Assessment in Neuro-Oncology (NANO) scale is a recently developed ClinRO[78] that includes clinical evaluation of 9 pertinent neurologic assessments conducted during routine office visits. The scale was noted to provide a high interobserver agreement by utilizing these clinician-reported outcomes. The scale is intended to complement existing patient-reported outcomes and may be used in combination with radiographic assessment to provide an overall assessment of outcome for neuro-oncology patients. While NANO is currently being evaluated in clinical trials, clinical validity and utility have yet to be firmly established.

Observer-reported outcomes (ObsROs) are measurements based on a report of observable signs, events, or behaviors related to a patient's health condition by someone other than the patient or a health professional.[1] Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (eg, infants, individuals who are cognitively impaired). An ObsRO measure does not include medical judgment or interpretation.[1] ObsROs are particularly relevant for neuro-oncology patients who may not be able to report outcomes for themselves. For example, in the assessment of a patient with a brain tumor, changes in physical functioning would be an important observation. Other examples include episodes of vomiting or a report of wincing thought to be the result of pain in patients who are unable to report for themselves.

Patient-reported outcomes (PROs) are measurements based on a report that comes directly from the patient.[1] Symptoms or other unobservable concepts known only to the patient can only be measured by PROs; however, PROs can also assess the patient perspective on other observable factors as well.[1] Numerous neuro-oncology studies have used PRO measures to investigate their performance, including: (i) the EORTC health-related quality of life (HRQoL) instruments (the 30-item Quality of Life Questionnaire [QLQ-C30]),[79] and (ii) the MD Anderson Symptom Inventory (MDASI)–Brain Tumor.[80] These PRO measures assess multiple domains of HRQoL, symptoms, and functional limitations. EORTC's HRQoL instruments are among the most widely used PRO measures. The QLQ-C30 is a general HRQoL questionnaire for patients with cancer and the QLQ-BN20 was developed specifically for people with brain cancer. The QLQ-C30 (version 3.0) produces 15 scores based on 9 multi-item scales (global health/QoL, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea/vomiting, and pain) and 6 single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact).[79] The MDASI[80] is a multisymptom PRO. The clinical utility of the MDASI is that it measures not only the severity of symptoms experienced by patients with cancer but also the interference with daily living caused by these symptoms.

Performance outcomes (PerfOs) are measurements based on tasks performed by a patient on testing that is administered by a health care professional.[1] Performance outcomes measurements include assessment of gait, memory recall, or other cognitive testing. PerfOs used in the setting of malignant glioma studies include assessments of cognitive and motor function. PerfO measures of cognitive function range from tests such as the Mini-Mental Status Examination to tests assessing specific cognitive domains. The Clinical Trial Battery, composed of several standardized PerfO tests, including the Hopkins Verbal Learning Test–Revised for memory; the Trail Making Test Part A for processing speed; the Trail Making Test Part B; and the Multilingual Aphasia Examination–Controlled Oral Word Association for executive function, has been applied in recent clinical trials for malignant glioma.[61,81] There is less experience with PerfO measures of neurologic function outside of cognition. The 6-minute walk test was shown to be feasible in people with recurrent malignant gliomas and correlated with KPS in one study but was not associated with survival endpoints.[82]

Biomarker Development

While a detailed description of biomarker development is beyond the scope of this manuscript, numerous reviews are available.[83,84] Successful development of biomarkers generally includes discovery, validation, and clinical implementation. Generation of clinical evidence and trial designs should be tailored to the specific type of biomarker. Biomarkers developed as a surrogate endpoint should be designed to show that the *effect* of a given therapy on the surrogate is associated with the therapeutic *effect* on a clinically relevant endpoint; it is not enough to show that the endpoints themselves are correlated. A predictive biomarker ideally would be evaluated in a randomized trial that includes biomarker-positive and -negative patients so that the biomarker association with therapeutic effect can be explored. While unrestricted randomization in biomarker-positive and -negative populations provides the best data to evaluate the utility of the biomarker, this may be an inefficient strategy that exposes patients to ineffective treatments, especially when existing data point to biomarker-specific effects. Study designs that incorporate existing data to direct biomarker incorporation into trials have been proposed, and there are several approaches to modifying ongoing trials to adapt to emerging biomarker data.[85] Finally, for further education and training about biomarker development, the FDA has developed resources including case studies around the Biomarker Qualification Program, which provides the framework for the development and regulatory acceptance of biomarkers for use in drug development programs.

Summary and Conclusion

Biomarkers have the potential to significantly improve and speed up the development of new therapies of patients with central nervous system tumors and form the basis for a precision approach to clinical medicine. However, the term "biomarker" and its various subgroupings are commonly used imprecisely, which can slow their adoption, proper application, and significance. The BEST glossary was developed to harmonize nomenclature and provide clarity in the biomarker field. Its regular application in neuro-oncology contexts will impact future discussions, trial planning, and clinical decision making.

Funding

No funding was required for this study.

Conflict of interest statement. The authors declare no conflicts of interest.

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