Glioblastoma is the most common primary brain tumor in the United States and despite aggressive multimodal therapy with maximum safe resection, radiotherapy in combination with concurrent and adjuvant temozolomide, the median survival of glioblastoma in clinical trial populations is 16 months. While the introduction of temozolomide into first-line standard of care (1) achieved some survival improvement, nearly all patients relapse and treatment options for recurrent disease remain limited and largely ineffective. Even under optimal circumstances with use of ‘state of the art’ diagnostic and therapeutic interventions, less than 15% of patients will survive 5 years (2-4).

Recently, there has been growing recognition for the need for novel, effective therapies for glioblastoma. Vice President Joseph Biden in a January 15, 2016 roundtable at the Abramson Cancer Center stated a goal of catalyzing greater investment, coordination, and collaboration in cancer therapy including a specific focus on advances in the treatment of glioblastoma. Currently validated treatments for glioblastoma and other central nervous system tumors are few in number and short on proven effectiveness. These treatments are also often toxic, threaten neurological function and hamper the quality of remaining life. The Brain Tumor Center at the MD Anderson has defined their Glioblastoma Moon Shot goal as an aim for better, safer therapeutics along with quadrupling the 5-year survival rate, from 10% to 40% over the next decade (5).

The ability to measure response to a treatment is a critical component in evaluating the efficacy of new therapies and identifying patients who require salvage therapy in a timely manner. Unfortunately, current diagnostic neuroimaging paradigms fail to reliably evaluate treatment response for glioblastoma. The initial landmark imaging evaluation guidelines—the Macdonald criteria—were established in 1990 and was based solely on the assessment of contrast-enhancement as a surrogate for tumor size. Contrast-enhancement is non-specific and simply reflects the degree of extravasation of a contrast agent across a disrupted blood brain: changes in contrast-enhancement may be attributable to true progression, imaging technique, treatment (surgery, radiation, or chemotherapy), steroids and parenchymal changes unrelated to the tumor (postsurgical changes, ischemia, seizures). Particularly with the use of multimodal therapy with radiation and temozolomide and new systemic therapies such as bevacizumab, new radiological phenomena including pseudoprogression and pseudoresponse have added further challenges to assessing treatment response.

In the context of clinical trials, accurate response assessment is essential. Misclassification of patients may lead to premature discontinuation of an actually effective agent, thereby withholding a potentially active treatment from the patient or inappropriate continuation of an inactive treatment that may have associated toxicities. Moreover, such misclassification may confound the data obtained in such studies and may lead to false conclusions with regards to the efficacy (or safety) of an investigated drug. An effort to address this challenge to accurately evaluate brain tumor response resulted in the formation...
of the Response Assessment in Neuro-Oncology (RANO) working group. In 2010, this group published updated guidelines for response assessment of high-grade gliomas incorporating additional MRI and clinical considerations, which addressed the recognized and accepted limitations of the Macdonald Criteria (6).

While these new criteria help standardize our approach for evaluating conventional MR images, the challenges of accurately assessing treatment response versus failure remain unaddressed. “Advanced” magnetic resonance based imaging techniques have the potential to provide anatomical, physiological, functional, metabolic and even genomic information that reflect treatment response evaluation and prognosis. Techniques including diffusion-weighted imaging (DWI), diffusion tensor imaging, perfusion MRI, and magnetic resonance spectroscopy (MRS) allow tumor assessment at the metabolic and physiologic level, but they have not yet been able to reliably differentiate tumor recurrence from radiation necrosis or pseudoprogression (7-12).

There has been general optimism for various advanced MR techniques to better characterize gliomas and differentiate tumor progression from pseudoprogression or radiation necrosis. For example, integration of the 2-hydroxyglutarate metabolite by MRS for the evaluation of IDH mutation status (13), T1ρ imaging (14), advanced diffusion imaging techniques including kurtosis (15), and “texture” based MR imaging analysis (16) have not yet been validated as being ready for routine clinical utilization.

Despite years of scientific work resulting in thousands of publications, there are very limited advanced MR features that have enough validated evidence to support clinical implementation to assist in evaluating tumor response. A major challenge in the field of MRI has been the ability to meaningfully compare findings across studies and institutions due to wide variability in image acquisition, post-processing, analysis and interpretation. Even for conventional MRI, a standardized recommended protocol has only recently been published in 2015 and implementation across clinical trials have only begun (17).

Functional molecular imaging with positron emission tomography (PET) has been in clinical use for the evaluation of brain tumors for over thirty years (18) providing complementary non-invasive metabolic imaging information about gliomas beyond current MR-based capabilities. Functional molecular imaging uses various tracers to visualize biological processes such as cell proliferation, membrane biosynthesis, glucose consumption, and uptake of amino acid analogs. Hence, PET provides additional insight beyond MRI into the biology and treatment response of gliomas and shows potential to be used as an adjunctive tool for noninvasive tumor grading, guiding surgical and radiotherapy treatment through improved tumor detection and delineation, evaluating treatment response, and prognostication.

Recently, both the Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology have collaborated towards a highly progressive and pragmatic step in the non-invasive evaluation of glioma patients by making formal recommendations on the use of PET in the management of glioma patients (19). The new guidelines define the recommended application of the most validated PET radiopharmaceuticals (18F-FDG, 11C-MET, 18F-FET, and 18F-FDOPA) in the assessment of tumor grading, delineation of glioma extent, evaluation for treatment planning including biopsy and resection, and assessment of treatment response including differentiation of progression from pseudoprogression. A series of trials has suggested that PET imaging is superior to MR imaging for each of these diagnostic paradigms (Table 1, from Alberts paper).

With the promise of PET as a key non-invasive imaging tool for glioma management and the support of the Neuro-Oncology community, it is time for the imaging community to collaboratively pursue rigorous multi-center clinical trials to generate stronger data that quantitatively demonstrates the clinical benefit of incorporating PET into glioma management. Recognizing the limitations and shortfalls of advanced MR imaging studies to-date, efforts now being pursued within the MR imaging community should be integrated into PET studies. This would entail a coordinated effort to implement standardized PET imaging protocols and to establish quality metrics that will enhance our ability to generate reproducible findings which would in turn support the need for PET utilization in clinical care in order to improve the outcomes of patients with glioblastoma.
**Table 1** Diagnostic performance of different amino acid tracers compared with conventional and advanced MRI

<table>
<thead>
<tr>
<th>Clinical problem</th>
<th>MET</th>
<th>FET</th>
<th>FDOPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation of glioma from non-neoplastic lesions</td>
<td>Numerous studies, higher diagnostic accuracy than MRI alone</td>
<td>Higher diagnostic accuracy than MRI alone</td>
<td>Not available for the initial diagnosis</td>
</tr>
<tr>
<td>Glioma grading (including detection of anaplastic foci)</td>
<td>Higher diagnostic accuracy than MRI, but still limited accuracy due to high overlap between WHO grades</td>
<td>Higher diagnostic accuracy than MRI, in particular for dynamic PET</td>
<td>No studies available comparing directly PET with MRI; in the pure PET studies, conflicting results reporting high and low performance</td>
</tr>
<tr>
<td>Delineation of glioma extent</td>
<td>Metabolically active tumor larger than contrast enhancement in LGG and HGG at diagnosis and recurrence</td>
<td>In newly diagnosed glioblastoma, metabolically active tumor larger than CE pre- and postoperatively</td>
<td>In glioma, metabolically active tumor larger than rCBV, ADC and contrast enhancement</td>
</tr>
<tr>
<td></td>
<td>Delineates metabolically active tumor in non-enhancing anaplastic glioma</td>
<td>In WHO grades II/IV gliomas metabolically active tumor larger than rCBV</td>
<td></td>
</tr>
<tr>
<td>Differentiation of glioma recurrence from treatment-induced changes (e.g., pseudoprogression, radionecrosis)</td>
<td>Higher diagnostic accuracy than MRI</td>
<td>Higher diagnostic accuracy than MRI</td>
<td>Higher diagnostic accuracy than MRI</td>
</tr>
<tr>
<td>Assessment of treatment response (including pseudoresponse)</td>
<td>Superior to MRI; metabolic response to TMZ predictive for survival</td>
<td>Superior to MRI; metabolic responses to TMZ, RT, and BEV occurred earlier and/or were associated with improved survival</td>
<td>Superior to MRI; metabolic response to BEV occurred earlier and was predictive of improved survival</td>
</tr>
<tr>
<td>Assessment of prognosis in gliomas</td>
<td>Metabolically active tumor volume is prognostic in WHO grade IV glioma</td>
<td>Higher prognostic value of time-activity curves in dynamic PET than MRI within WHO grade II and WHO grades III/IV glioma</td>
<td>Superior to MRI in WHO grade II glioma; maximum uptake is an independent predictor of progression</td>
</tr>
<tr>
<td></td>
<td>In contrast to pretreatment CE volumes, metabolically active tumor volumes are prognostic in HGG</td>
<td>FET uptake in combination with specific MRI findings is prognostic for WHO grade II gliomas</td>
<td></td>
</tr>
</tbody>
</table>

LGG, low-grade glioma; HGG, high-grade glioma; CE, contrast enhancement; rCBV, relative cerebral blood volume; ADC, apparent diffusion coefficient; TMZ, temozolomide; RT, radiotherapy; BEV, bevacizumab.

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**Footnote**

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