March 24, 2017

Olatokunbo Awodele, M.D, MPH
2525 No. 117th Avenue
Suite 200
Omaha, NE 68164
policycomments@wpsic.com

RE: Draft Local Coverage Determination – MGMT Promoter Methylation Analysis (DL37001)

Dear Dr. Awodele:

Thank you for the opportunity to comment on DL37001. As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the College of American Pathologists (CAP) serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

The Association for Molecular Pathology (AMP) is an international medical and professional association representing approximately 2,300 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private and hospital-based clinical laboratories, and the in vitro diagnostics industry.

Members of both AMP and CAP are experts in molecular pathology, and the implementation of this coverage policy will directly impact their practices. We are submitting joint comments because at this time both of our organizations share the same concerns regarding this draft LCD, and we request that WPS consider implementing the consensus recommendations outlined in this letter.

First, we thank you for your decision to cover MGMT Promoter Methylation Analysis under limited circumstances. We agree with your determination that this test is medically necessary, but believe that a certain critical clinical indication, namely the conundrum of tumor pseudo-progression, as detailed below, has been overlooked.

MGMT Testing for Glioma Patients with Pseudoprogression

The neuro-oncology community has recently come to recognize the concept of pseudo-progression in the treatment course of high grade gliomas. In particular, pseudo-progression is a radiographically-identified, apparent post-treatment disease progression followed by subsequent improvement or stabilization without any additional treatment. Pseudo-progression is a transient phenomenon that likely represents a local tissue reaction to the therapy, and its presence has actually been shown to improve overall survival (DaCruz LCH Am J Neuroradiol 32:1978 – 85, 2011).

Pseudo-progression is, therefore, a radiographic mimic of true tumor-specific disease progression and its distinction is thus critical, given that the best treatment option for pseudo-progression is to continue the current therapy, while a different glioma therapy is the best treatment option for true disease progression. Current radiographic imaging methods cannot distinguish (DaCruz LCH Am J Neuroradiol 32:1978 – 85, 2011) these two disparate diagnoses with radically different treatment ramifications, and a brain biopsy is the classic option to distinguish these two conditions. However, it has recently been determined that gliomas with MGMT promoter methylation have a significantly higher prevalence of pseudo-progression than non- methylated tumors (Brandes J Clin Oncol 26:2192-2197, 2008). In this study, 91% of patients whose original biopsies demonstrated methylated MGMT had pseudo-progression (versus 41% of patients without methylated MGMT, P = .0002), and were best managed by continuing the current therapy.

The retrospective determination of MGMT promoter methylation status in the pre-treated, original biopsies can be critical in the distinction of this post-treatment effect in patients with imaging consistent with progression/pseudo-progression to ensure that effective therapies are not inappropriately terminated under the false assumption of disease progression (versus the alternative diagnosis of transient good-prognosis pseudo-progression).

It is also critical in true recurrence/tumor progression that these new biopsies of treated tumors be retested for MGMT methylation status as methylation of MGMT in tumor cells renders these cells sensitive to alkylating chemotherapy. Often, but not always, recurrent tumors will exhibit altered methylation status with significant implications for therapeutic decision making (Brandes AA, et el., Neuro Oncol. 2010 Mar;12(3):283-8.)

Request: We request that MGMT testing be covered for all glioma patients, including retrospective testing of MGMT status in patients with a post-treatment imaging study suggesting progression/pseudo-progression and that any ICD-10 codes relating to this progression or pseudoprogression be added to this policy to cover both retrospective (new) testing of the original biopsies and retesting of recurrent tumors.

We respectfully ask that you consider these comments, which were prepared by a consortium of providers in the WPS jurisdiction as well as other members of CAP and AMP who provide service to Medicare beneficiaries covered by WPS. We are happy to be of assistance in providing additional clinical information, references, contacts, or whatever is needed to assist you with this draft LCD. Please direct your correspondence to Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@amp.org or
Tara Burke, AMP Policy Analyst, at tburke@amp.org

Sincerely,

College of American Pathologists
Association for Molecular Pathology