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March 15, 2011

Alan Rosenberg, MD  
VP Medical Policy, Technology Assessment and Credentialing  
WellPoint, Inc.  
233 S. Wacker Drive, Suite 3900  
Chicago, IL 60606

Dear Dr. Rosenberg,

The American Gastroenterological Association is the trusted voice of the GI community. Founded in 1897, the AGA has grown to include 17,000 members from around the globe who are involved in all aspects of the science, practice and advancement of gastroenterology. The AGA Institute administers the practice, research and educational programs of the organization.

The AGA Institute is pleased to provide these comments on WellPoint Medical Policy # GENE.00019, **BRAF Mutation Analysis**. Although the policy is generally clear, we disagree with your conclusion and believe that the medical literature cited in your policy is adequate to conclude that BRAF mutation analysis is cost-effective and medically necessary in two instances: evaluation of patients with metastatic colorectal cancer; and when screening or evaluating patients for suspected Lynch syndrome prior to determining if further genetic testing is necessary.

Colorectal cancer (CRC) is the 3<sup>rd</sup> most commonly-diagnosed cancer, and third highest cause of cancer death in the United States. The American Cancer Society estimated that over 148,000 people were diagnosed with colorectal cancer in 2010, and nearly 50,000 people would die from the disease. 5-year relative survival rates are around 36% for local recurrence and 24.0% for distant metastases. 10 to 30% of colorectal cancer is familial, with identified genetic factors responsible for 5-6% of all colorectal cancers.

The BRAF V600E protein is involved in sending signals in cells and in cell growth, and specific mutations in the gene may be prognostic for disease prognosis or predictive for treatment response in advanced colorectal cancer. Approximately 10% of the colorectal tumors test positive for BRAF mutations.

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The current standard of care for metastatic colon cancer includes cytotoxic agents such as 5-FU, irrinotecan, and capecitabine. Platinum-based agents such as oxaliplatin and bevacizumab are also used, and the exact combination depends upon clinical factors, and patient/oncologist preferences. The anti-Epidermal Growth Factor Receptor (EGFR) antibodies cetuximab and panitumumab are also approved for CRC treatment.

Colorectal cancer guidelines from the National Comprehensive Cancer Network (NCCN, 2011) recommend consideration of reflex BRAF testing in patients with wild type K-ras (KRAS). The NCCN guidelines explain that several small studies suggest that patients with wild-type KRAS and a BRAF mutation are unlikely to respond to anti-EGFR therapies such as cetuximab and panitumumab. The guidelines explain that patients with a known BRAF mutation are unlikely to respond to anti-EGFR antibodies, although the data are somewhat inconsistent. Studies demonstrate that in patients with metastatic colorectal cancer, about 8 percent have mutations in the BRAF gene. If KRAS is non-mutated, BRAF testing should be considered.<sup>1</sup>

We provide some background on KRAS and the relationship and utility of BRAF testing. Investigators have established an association between some genotypes of KRAS oncogenes and response to treatment with cetuximab or panitumumab (Lievre, et al., 2006 & 2008; Di Fiore, et al., 2007; Gonçalves, et al., 2008; De Roock, et al., 2008). Patients whose tumors express specific forms of the KRAS gene exhibit considerably decreased responses to cetuximab and panitumumab. It has been theorized that cetuximab and panitumumab do not target EGFR receptors associated with these specific KRAS mutations and thus are unable to block their activation. It has been suggested that KRAS genotype be considered as a selection factor for cancer patients who are candidates for treatment with cetuximab or panitumumab.<sup>23456</sup>

The ASCO's provisional clinical opinion on testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-EGFR monoclonal antibody therapy (Allegra et al, 2009) stated that based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.<sup>7</sup>

The Blue Cross and Blue Shield Association (BCBSA, 2008) Technology Evaluation Center Medical Advisory Panel concluded that use of KRAS mutation analysis meets TEC criteria to predict non-response to anti-EGFR monoclonal antibodies cetuximab and panitumumab to treat metastatic colorectal cancer. The TEC assessment found that the evidence is sufficient to conclude that patients with mutated KRAS tumors in the setting of metastatic colorectal cancer do not respond to anti-EGFR monoclonal antibody therapy. The assessment explained that the data show that the clinical benefit of using EGFR inhibitors in treating metastatic colorectal cancer, either as monotherapy or in combination with other treatment regimens, is not seen in patients with KRAS-mutated tumors. The assessment found: "This data supports knowing a patient's tumor mutation status before consideration of use of an EGFR inhibitor in the

treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs, avoid exposure to unnecessary drug toxicities, and expedite the use of the best available alternative therapy."<sup>8</sup>

BRAF mutations have been associated with poorer disease prognosis and decreased treatment response to anti-EGFR antibodies. In the CAIRO2 trial (Tol, 2010), patients with metastatic colorectal cancer were randomized to either standard treatment (capecitabine, oxaliplatin, and bevacizumab), or to standard treatment + cetuximab. In the trial, overall there was no difference in overall survival between the treatment groups (20.3 months vs. 19.4 months,  $p=0.16$ ). Subgroup results based on BRAF status showed that BRAF was associated with poorer outcomes for both treatment arms. There did not appear to be a significant difference in response to cetuximab based on BRAF status.<sup>9</sup> In another study (Laurent-Puig, 2009), out of 110 tumor samples collected retrospectively in patients treated with cetuximab as a 2<sup>nd</sup> line or later therapy, 5 tumors tested positive for BRAF mutations. These patients exhibited significantly lowered overall survival compared to those without BRAF mutations, with an HR of 6.6 [2.4-18.2,  $p<0.001$ ].<sup>10</sup> Leveraging the PETACC-3 adjuvant trial (Stage II to III colon cancer), Roth et al. conducted a prospective collection and DNA extraction from tumor samples ( $n=1,404$ ), and examined the impact of BRAF mutations. They found that in tumors with a low degree of microsatellite instability ( $MSI <3$ ), BRAF mutations ( $n=103$ ), were prognostic for a reduction in overall survival (HR=2.2 [1.4-3.4,  $p=0.0003$ ]) (Roth, 2010)<sup>11</sup>

The most immediate and obvious benefit of BRAF testing, as suggested by the NCCN guidelines, is to avoid anti-EGFR antibody therapy in patients who are unlikely to benefit, thus avoiding unnecessary treatment toxicities. Beyond this immediate implication, BRAF mutation-positive patients could either be directed to clinical trials for experimental treatments, or aggressive chemotherapeutic regimes, which may offer these patients improved survival outcomes.

BRAF mutation analysis is especially beneficial for those with suspected Lynch syndrome with an incomplete or unknown family history. This highly specific and relatively inexpensive test can eliminate a number of those who would otherwise require genetic testing. Bessa, et al. (2008) performed a prospective, multi-center, population-based analysis of BRAF mutation analysis for Lynch syndrome screening. The aim of this study was to evaluate the contribution of *BRAF* V600E mutation analysis in the identification of *MSH2/MLH1* gene mutation carriers in newly diagnosed CRC patients. *BRAF* V600E mutation was analyzed in CRC patients with mismatch repair (MMR) deficiencies (microsatellite instability and/or lack of *MLH1/MSH2* protein expression) in the EPICOLON population-based study. The effectiveness and efficiency of different strategies were evaluated with respect to the presence of *MSH2/MLH1* germline mutations. MMR deficiencies were detected in 119 of the 1222 CRC patients with tumors showing either microsatellite instability ( $n = 111$ ) or loss of protein expression ( $n = 81$ ). *BRAF* mutation was detected in 22 (18.5%) of the patients. None of the patients with unambiguous germline mutation had *BRAF* mutation. Regardless of the strategy used to identify *MSH2/MLH1* gene carriers, the introduction of *BRAF* analysis in these patients slightly

improves their effectiveness. The introduction of *BRAF* mutation analysis as a step before germline genetic testing in patients with MMR deficiencies achieved a significant reduction in costs per mutation detected. Detection of *BRAF* V600E mutation could simplify and improve the cost effectiveness of genetic testing for hereditary nonpolyposis colorectal cancer, especially in patients whose family history is incomplete or unknown.<sup>12</sup>

Nakagawa et al. (2009) studies the use of MLH1 or BRAF testing in combination with high-frequency microsatellite instability (MSI-H) for Lynch syndrome screening. The authors performed a comprehensive study to evaluate the methylation status of whole MLH1 promoter region by direct bisulfite sequencing of the entire MLH1 promoter regions on Lynch and non-Lynch colorectal cancers (CRCs). They established a convenient assay to detect methylation in key CpG islands responsible for the silencing of MLH1 expression. They studied the methylation status of MLH1 as well as the CpG island methylator phenotype (CIMP) and immunohistochemical analysis of mismatch repair proteins on 16 cases of Lynch CRC and 19 cases of sporadic CRCs with high-frequency microsatellite instability (MSI-H). Sensitivity to detect Lynch syndrome by MLH1 (CCAAT) methylation was 88% and the specificity was 84%. Positive likelihood ratio (PLR) was 5.5 and negative likelihood ratio (NLR) was 0.15. Sensitivity by mutational analysis of BRAF was 100%, specificity was 84%, PLR was 6.3 and NLR was zero. By CIMP analysis; sensitivity was 88%, specificity was 79%, PLR was 4.2, and NLR was 0.16. Although the assay for CIMP status also showed acceptable sensitivity and specificity, it may not be practical because of its rather complicated assay. The authors concluded that BRAF mutation or MLH1 methylation analysis combined with MSI testing could be a good alternative to screen Lynch syndrome patients in a cost effective manner.<sup>13</sup>

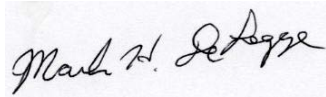
Palomaki et al. (2009) stated that BRAF mutation testing would result in important cost savings as it is relatively inexpensive in comparison to direct sequencing of MLH1. According to their analysis, the base cost of MLH1 sequencing was \$808 while the base cost of BRAF mutation testing was \$100, based on 2007 Medicare reimbursement rates.<sup>14</sup>

A 2010 Hayes analysis estimates a cost of \$275 for BRAF testing, noting that the strategy of Immunohistochemistry (IHC) ->BRAF ->MMR gene testing was the most cost-effective strategy, compared to IHC->MMR, MSA->MMR, or MMR testing alone in patients with suspected Lynch syndrome. Thus, BRAF mutation analysis has been proven to be a cost-effective tool and can assist practitioners in determining if further genetic testing is necessary in screening or evaluating patients with suspected cases of Lynch syndrome. This analysis can potentially lead to exclusion of Lynch syndrome, changes in treatment plans and eventually improved health outcomes.<sup>15</sup>

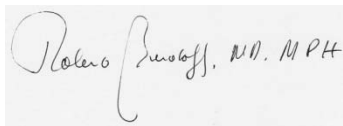
In conclusion, the AGA believes that BRAF mutation analysis is medically necessary in the evaluation of patients with metastatic colorectal cancer and screening for, and/or suspected cases of, Lynch syndrome.

Thank you for the opportunity to review and comment on this draft assessment. Please do not hesitate to contact Adam R. Borden, MHA, Manager of New Technologies and Reimbursement at the AGA Institute, at [aborden@gastro.org](mailto:aborden@gastro.org) or 301-654-2055 should you have any questions.

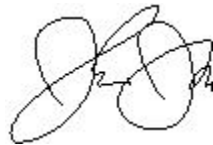
Sincerely,



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<sup>1</sup> NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. From National Comprehensive Cancer Network. [http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf) (Accessed March 7, 2011).

<sup>2</sup> Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol.* 2009;27:2091-2096.

<sup>3</sup> Di Fiore F, Blanchard F, Charbonnier F, et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. *Br J Cancer.* 2007;96:1166-1169

<sup>4</sup> De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. *Ann Oncol.* 2008;19:508-515.

<sup>5</sup> Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res.* 2006;66:3992-3995.

<sup>6</sup> Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol.* 2008;26:374-379.

<sup>7</sup> Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: Testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict

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response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol* 2009;27:2091-2096.

<sup>8</sup> KRAS Mutations and Epidermal Growth Factor Receptor Inhibitor Therapy in Metastatic Colorectal Cancer. From Blue Cross Blue Shield Association Technology Evaluation Center.

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<sup>9</sup> Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. *N Engl J Med* 2009;361:98-99.

<sup>10</sup> Laurent-Puig P, Cayre A, Manceau G, Buc E, Bachet JB, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *J Clin Oncol* 2009;27:5924-5930.

<sup>11</sup> Roth AD, Tejpar S, Delorenzi M, Yan P, Fiocca R, et al. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol* 2010;28: 466-474.

<sup>12</sup> Bessa X, Ballesté B, Andreu M, et al. A Prospective, Multicenter, Population-Based Study of BRAF Mutational Analysis for Lynch Syndrome Screening. *Clin Gastroenterol Hepatol* 2008;6:206-14.

<sup>13</sup> Nakagawa H, Nagasaka T, Cullings HM, et al. Efficient molecular screening of Lynch syndrome by specific 3' promoter methylation of the MLH1 or BRAF mutation in colorectal cancer with high-frequency microsatellite instability. *Oncol Rep* 2009;21:1577-83.

<sup>14</sup> Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009; 11:42-65.

<sup>15</sup> Lea A. Genetic Testing for Lynch Syndrome. Special Presentation. From Hayes, Inc.

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