April 15, 2016

Cahaba Government Benefit Administrators, LLC
Attn: Dr. Thom Mitchell
Senior Contractor Medical Director
P.O. Box 13384
Birmingham, AL 35202-3384

Re: Proposed Draft Local Coverage Determination (LCD): K-RAS Testing Prior to Treatment of Colorectal Cancer (DL36582)

Dear Dr. Mitchell,

Thank you for the opportunity to comment on Draft DL36582. 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.

The College of American Pathologists (CAP) is a national medical specialty society representing 18,000 physicians who practice anatomic and/or clinical pathology. College members practice their specialty in clinical laboratories, academic medical centers, research laboratories, community hospitals and federal and state health facilities.

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, as such, we request that Cahaba consider the joint recommendations outlined in this letter.

Coverage Indications, Limitations and/or Medical necessity

We appreciate that the draft proposal highlights the clinical utility of KRAS mutation testing for colorectal cancer that also includes limited coverage for partial genomic profiling. However, the policy's coverage indications and limitations do not align with the current standard of practice. More recent published findings indicate that patients whose tumors have mutations in the KRAS gene beyond those in exon 2, or those with mutations in the NRAS gene in exons 2, 3 and 4, are also unlikely to benefit from anti-EGFR directed monoclonal therapies. This expanded testing of additional RAS exons would identify an additional 15 percent of patients with colorectal cancer (CRC) with identifiable RAS-mutated tumors who would derive no benefit from EGFR inhibitors. Instead, the weight of current evidence supports a new standard of care to extend RAS testing to include the KRAS exons 3 and 4 and NRAS exons 2, 3, and 4. We believe these extended KRAS and NRAS exon targets should be included in the LCD policy.

1. The National Comprehensive Cancer Network (NCCN) guidelines have recognized this new standard of care and now recommend expanded RAS testing. The package inserts that accompany the anti-EGFR directed drugs cetuximab and panitumumab also indicate the need for expanded RAS testing. Whether the treatment choice is an anti-EGFR therapy, up front or in a later line of treatment, determines how quickly the test needs to be completed.[1,2]

2. The American Society of Clinical Oncology (ASCO), has recommended extended RAS testing as a predictive biomarker of response for anti–EGFR monoclonal antibodies, further stressing the importance of

broader molecular analyses for patients with metastatic colorectal cancer (mCRC), according to a joint provisional statement published in the *Journal of Clinical Oncology*.[3] The endorsement was based on findings from 15 analyses that evaluated outcomes with expanded testing in phase II and III clinical trials for the EGFR antibodies cetuximab (Erbitux) and panitumumab (Vectibix). The evidence overwhelmingly showed that patients with RAS-mutated mCRC had inferior outcomes with anti–EGFR therapy.

3. The AMP/CAP/ASCO and ASCP are currently completing CRC Molecular Marker Practice Guidelines that will reflect the ASCO guidance that tumors of patients with stage III and IV disease who are candidates for anti EGFR therapy should be tested for an expanded panel of mutations in KRAS and NRAS.

4. Genomic Testing (eg, Next Generation Sequencing): A patient who presents with Stage III or IV CRC or suffers recurrence of disease is a potential candidate for anti-EGFR therapy. In these cases, the available tissue for testing is typically very limited. Small cancer biopsy samples are often insufficient for repeated or sequential single gene tests and can hamper timely access to the initiation of therapy, which is critical in diseases such as cancer. Repeat procedures to acquire sufficient tissue put patients at unnecessary risk of complications. Efficient use of limited tumor tissue and timeliness in producing results both would support the use of NGS as an acceptable methodology in the practice of testing for all relevant mutations. The clinical need to assess multiple genetic regions within the KRAS, NRAS, and BRAF genes for the appropriate treatment of colon cancer patients indicates the appropriateness of genomic sequencing procedures in this setting.

Summary statement:
As noted above, we believe all clinically relevant analytes (eg, KRAS exons 2, 3 and 4 and NRAS exons 2, 3, and 4) should be acknowledged in the LCD policy. We also believe that both clinically appropriate and efficient use of limited patient tumor tissue and timeliness in producing results would support the use of up-front NGS as an acceptable methodology in the practice of testing for all relevant mutations.

Thank you again for the opportunity to comment on this draft coverage policy. We would be happy to provide you with additional clinical information or references to assist with this draft LCD. Please direct your correspondence to Tara Burke, AMP Policy Analyst, at tburke@amp.org or Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org

Sincerely,
Association for Molecular Pathology
College of American Pathologists

References

1. Benson AB 3rd, Venook, AP, Bekaii-Saad T, et al. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw v2, 2016.

2.. Benson AB 3rd, Venook, AP, Bekaii-Saad T, et al. NCCN Clinical Practice Guidelines in Oncology: rectal cancer. J Natl Compr Canc Netw v1, 2016.

3. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS Gene Mutation Testing in Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015 [Published online October 5, 2015]. *J Clin Oncol.* doi: 10.1200/JCO.2015.63.9674.