



November 27, 2017

Palmetto GBA
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Re: Draft Local Coverage Determination: MoIDX: Genetic Testing for Lynch Syndrome (DL35024)

Dear Dr. Almas:

Thank you for this opportunity to respond to your draft local coverage determination regarding MoIDX: Genetic Testing for Lynch Syndrome (DL35024). The Association for Molecular Pathology (AMP) is an international medical 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 and commercial clinical laboratories, community hospitals, and the in vitro diagnostics industry.

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.

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.

Proposed Coverage for Comprehensive Genomic Profiling

AMP and CAP applaud Palmetto for proposing to allow Immunohistochemistry (IHC)/Microsatellite Instability (MSI) testing in other disease states where there is a high clinical probability of Lynch Syndrome (LS), and the overall tenor of the draft LCD. However, we believe that this proposal contains language that will be unduly restrictive in certain clinical scenarios negatively impacting patients, and we would appreciate the opportunity to work with you to improve this coverage policy.

As drafted, AMP and CAP believe this policy unnecessarily restricts coverage to either IHC or MSI testing instead of allowing both. There are several clinical scenarios with a high index of suspicion where a patient would benefit from the second method when the first is negative. **This is due to the fact that the two methodologies are complementary in that each method will detect evidence of mismatch repair protein dysfunction in a small number of cases that are negative by the other methodology, as was referenced in the dLCD.**

Therefore, it is in the best interest of patient care to perform a second methodology when one is negative and a diagnosis of Lynch Syndrome cannot be completely excluded. Such an approach would reduce the chances of false negative and will optimize patient care.

For example, the recent approval of PDL-1 checkpoint inhibitors Nivolumab and Pembrolizumab for the treatment of microsatellite instability – high (MSI-H)/mismatch repair (MMR) deficient metastatic colorectal cancer indicates that a false negative or false positive result produced by one methodology can adversely affect therapeutic decision making. A false negative result could prevent cancer patients from receiving an effective therapy. Conversely, an equivocal MMR IHC result, which may be associated with tissue fixation artifacts (i.e., false positive) or tumor heterogeneity (i.e., true positive) should be verified by MSI testing. Although targeted therapy is increasingly being considered the new “standard of care”, unfortunately, these therapeutic options tend to be very expensive, and may cost thousands of dollars per month. With so many therapeutic options available, preventing administration of a PDL-1 inhibitor due to a false positive result also protects the patient and the entire healthcare system from the financial toxicity of an ineffective treatment.

We advocate allowing both IHC and MSI testing for patients eligible for PDL-1 inhibitors and recommend expanding the policy statement to include this provision. This approach is consistent with other scenarios listed in the policy, i.e., “If IHC test results are normal, there remains a small chance of high levels of microsatellite instability (MSI-H), so both IHC and MSI should be performed to rule out LS in a clinically suspicious setting such as meeting a Revised Bethesda guideline. Additionally, some individuals with MSH6 germline mutations do not manifest the MSI-H phenotype. This finding supports the diagnostic strategy to screen suspected LS patients with CRC by both MSI and IHC.”

Recommendations Regarding the Proposed Coverage Requirements

AMP and CAP are supportive of Palmetto’s proposal to allow IHC/MSI testing to all patients with colorectal cancer (CRC) and endometrial cancer regardless of age, or a multi-gene NGS or other multi-analyte methodology that is inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes, recognizing that LS tumor screening with IHC or MSI is considered medically necessary for all patients with colorectal and endometrial cancer. We recommend that **these criteria be slightly** revised to allow for both testing methods, when clinically indicated and appropriate.

The policy states the following:

For patients with unresectable or metastatic solid tumors, either MSI or IHC or a multigene NGS or other multi-analyte methodology panel inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes is medically reasonable and necessary.

AMP and CAP recommend that the following sentence be added in order to eliminate any potential coverage restrictions:

“If IHC is normal, MSI by PCR testing may be considered. If MSI by PCR is normal, testing by IHC may be considered.”

In addition, it is important to note that BRAF testing is medically necessary outside of recommended Lynch Syndrome screening protocols. BRAF testing in colon cancer is recommended by the most recent ASCO/ASCP/CAP/AMP guidelines for molecular biomarker testing in colorectal cancer (Sepulveda AR, Hamilton SR, et al). This guideline highlighted multiple systemic reviews, which revealed that patients with colon cancer that contain a BRAF mutation have a worse outcome relative to nonmutation patients.

A BRAF mutation identifies a molecular subtype of colon cancer with a particularly dismal prognosis, especially in those cases that do not demonstrate evidence of mismatch repair protein dysfunction. Such patients have a high likelihood of disease relapse and failure of standard line therapies and stand to benefit from novel therapeutic strategies such as

FOLFIRINOX (folinic acid [leucovorin calcium], fluorouracil, irinotecan hydrochloride, and oxaliplatin) followed by placement in a clinical trial. Emerging clinical data suggest that the combination of BRAF and EGFR inhibitors appears to be effective in this population.

The policy states the following:

“Steps 3 and/or 4 apply only for tumors that are negative for MLH1 protein expression by IHC.

Step 3: BRAF V600E (BRAF) Mutation Testing

BRAF mutation testing and MLH1 promoter methylation studies distinguish between sporadic dMMR and LS dMMR. This is because BRAFM mutation and MLH1 PHM are very seldom seen in LS. BRAF mutation testing of the CRC tumor is associated with the presence of an epigenetic alteration (i.e., hypermethylation of MLH1) and either finding excludes germ-line MMR gene mutation (e.g., LS).“

Limiting BRAF testing to only those cases that are MLH1 negative would limit patient access to medically necessary laboratory testing of the BRAF gene. We recommend this dLCD be revised to incorporate the above AMP and CAP comments. Consideration may also be given to producing a new dLCD for BRAF testing in colon cancer that is aligned with national guideline recommendations.

CPT Coding

Palmetto proposes a list of twenty covered CPT codes for cancer and molecular pathology. The criteria for LS tumor screening can also be fulfilled with additional CPT codes that Palmetto did not include in their draft policy proposal. The inclusion of appropriate CPT codes for IHC are paramount to ensuring that this policy covers all services that may possibly be reported in treating patients. **We recommend inclusion of additional CPT codes for IHC that would fulfill criteria for this policy. The additional codes include, but may not be limited to, those listed below:**

088342 IHC, Per Spec, First Antibody Applied to a Slide
088341 IHC, Per Spec, Additional Single Antibody Applied to a Slide
088344 IHC, Per Spec, Each Multiplex Antibody Procedure

We respectfully ask that you consider these comments, which were prepared by members of AMP and CAP and who provide services to Medicare beneficiaries covered by Palmetto. 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 Tara Burke, AMP Director of Public Policy and Advocacy, 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:

Sepulveda AR, Hamilton SR, et al. J Mol Diagn. Molecular Biomarkers for the Evaluation of Colorectal Cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. 2017 Mar;19(2):187-225.