COLLEGE of AMERICAN PATHOLOGISTS

December 30, 2021

Dr. Miguel Brito
Chief Medical Officer
Palmetto GBA

Letter submitted electronically to B.Policy@PalmettoGBA.com

Re: Request for LCD Reconsideration, Lab: Special Histochemical Stains and Immunohistochemical Stains L35922.

Dear Dr. Miguel Brito,

The College of American Pathologists appreciates the opportunity to request reconsideration of the Palmetto GBA Local Coverage Determination (LCD) for Lab: Special Histochemical Stains and Immunohistochemical Stains L35922 (hereinafter referred to as "special stains"). This request is made in accordance with CMS IOM, Publication 100-08, Medicare Program Integrity Manual, Chapter 13 and with Section 1869(f) of the Social Security Act.

As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

This letter highlights several provisions of the LCD where the evidence cited by Palmetto to support its coverage position is outdated and does not adhere to current clinical practice guidelines for the reasonable and necessary use of immunohistochemistry (IHC) stains and special stains. We offer evidence aimed at addressing the outdated information that would inappropriately deny or limit coverage for special stains in the areas of GI and prostate pathology. We respectfully ask that you consider these comments, which were prepared by subject matter experts representing the aforementioned areas of pathology.

1. Special Stains and/or IHC for GI Pathology

LCD statement: "Lynch Syndrome tumor screening for DNA mismatch repair (MLH1, MSH2, MSH6 and PMS2) by qualitative IHC and/or microsatellite instability (MSI) is considered medically necessary and covered by Medicare for the following indications:

- All individuals with colorectal cancer diagnosed at age ≤70 years of age, and those > 70 years of age who meet the revised Bethesda guidelines OR
- Individuals with endometrial cancer"

CAP position: NCCN now recommends universal MMR or MSI testing on all newly diagnosed patients with colorectal cancer regardless of age[6,7]. This includes testing for suspected or proven metastatic adenocarcinoma (if not previously done). In recent years the purpose of MMR IHC and/or MSI testing has expanded beyond merely identifying patients with Lynch syndrome, with the dMMR/MSI-H phenotype now representing the single best predictor of response to checkpoint inhibitor therapy. As such, age-based and clinical-criterion-based selection is outmoded, and universal testing with MMR IHC or MSI is now NCCN-recommended for all patients with newly diagnosed colorectal cancer[6,7]. Universal testing is also NCCN-recommended in endometrial cancer and should be considered in sebaceous neoplasms and adenocarcinomas of the small intestine, stomach, pancreas, biliary tract and in brain, urothelial, and adrenocortical tumors[6].

Several other groups have endorsed universal testing including the Centers-for-Disease-Control-and-Prevention-sponsored Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group[9] and the Association for Molecular Pathology (AMP) Mismatch Repair-Defective CRC Working group[2] A subsequent cost-effectiveness analysis from the EGAPP demonstrated an incremental cost-effectiveness ratio for universal testing similar to that seen with screening colonoscopy.[5]

It is well established that clinical criteria (i.e., revised Bethesda guidelines) fail to detect a large proportion of patients with Lynch syndrome. Many laboratories have appropriately shifted to universal testing of colorectal and endometrial cancers to detect Lynch syndrome.[10] This shift will impact clinical management in a manner already demonstrated in the peer-reviewed published literature to improve patient outcomes.

CAP request: We request that the first bullet in this section be amended to state, "All individuals with newly diagnosed primary or metastatic colorectal cancer."

2. Special Stains and/or IHC for Prostate Pathology

A. LCD statement: "The accuracy of the pathologic diagnosis of prostate cancer is critical for optimal patient care. The diagnosis can usually be made on morphologic features such as growth pattern, nuclear atypia and the absence of basal cells. However, it may be difficult to reach a firm diagnosis by routine H&E stain for small foci of cancer in needle biopsies because many benign conditions can mimic prostate cancer.

The immunohistochemical diagnosis of prostate cancer largely depends on panels of markers because no absolutely specific and sensitive marker for prostate cancer has yet been identified. These panels usually include at least one basal cell marker, such as high-molecular-weight cytokeratin (HMWCK) or p63, and the prostate cancer-specific marker, alpha-methyl-CoA-Racemase (AMACR). Although AMACR is considered a useful IHC marker for prostate cancer, because of non-standardized immunostaining protocols, interpretation criteria and heterogeneous staining pattern, there is wide variation in the sensitivity and specificity of AMACR immunoreactivity in prostate biopsies. Furthermore, because AMACR expression has been demonstrated in high-grade PIN, atypical adenomatous hyperplasia/adenosis and nephrogenic adenoma, it is recommended that AMACR is best restricted to the evaluation of morphologically highly suspicious foci in which negative immunoreactivity of basal cell markers alone is insufficient to establish a diagnosis of cancer."

CAP position: The application of IHC to distinguish prostate cancer from benign mimickers and to confirm a diagnosis often becomes necessary, especially in equivocal cases. Prostate IHC generally requires one or two basal markers and AMACR because of the usual tiny size of the atypical focus and the fact that it is often present on only one or two profiles. As a result, it is ideal to perform these stains in combination to preserve tissue and facilitate definitive diagnosis. If the stains are performed separately, as if basal cell markers are performed first and AMACR later, the focus of interest is likely to be lost in the deeper AMACR stained sectioned. Further, it is more clear-cut and accurate to interpret and diagnose prostate cancer when these stains are done in combination.[4]

AMACR should not be restricted to the evaluation of morphologically highly suspicious foci in which negative basal cell markers are insufficient for a diagnosis of cancer. In practice, AMACR is routinely performed with HMWCK and p63 in a triple-stained slide. These stains are highly complementary and are best performed and interpreted together.[11] While it is true that these stains should not be routinely performed in all cases, stains should be used for cases in which there is a suspicion of cancer that cannot be confirmed by morphology alone.

CAP request: We request that Palmetto amend the LCD language to support coverage for AMACR in all specimens in which suspected cancer cannot be confirmed or excluded by morphology alone.

B. LCD statement: "It is not reasonable and necessary to perform IHC testing (either single antibody or antibody cocktails) on cases with morphologically negative cores. It is not reasonable and necessary to bill for IHC testing in a negative or a suspicious core biopsy when obvious prostate cancer is present in other cores. While the pathologist may choose to confirm a suspicious focus in one or more cores in a case where the diagnosis of cancer has already been made, it is not a Medicare covered service because it provides no additional actionable information to the treating physician."

CAP position: It is reasonable and necessary to perform IHC on a suspicious core biopsy even if carcinoma is obviously present in other cores. The number of involved cores influences treatment by informing the urologist as to the extent of cancer in the prostate which, in turn, can have a significant impact on patient management.[3] Or, the suspicious focus may prove to be of higher grade than that which is present in the other cores: management of a low grade carcinoma (Gleason pattern 3) may consist of active surveillance, but if an atypical focus in another core is shown to be high grade carcinoma (patterns 4 or 5), surgery or radiation would likely be recommended. In such a case, IHC testing to confirm malignancy of those foci would have a major impact on patient management. The NCCN Guidelines Version 1.2015 Prostate Cancer (10/24/2014) made clear that if a patient has only a single focus of low grade (Gleason pattern 3) carcinoma, the initial therapy may consist of active surveillance, EBRT or brachytherapy, or radical prostatectomy when expected patient survival is 20 years or more; active surveillance when expected survival is 10-20 years; and observation if expected survival is less than 10 years. These guidelines were updated in 2021 (NCCN Guidelines Version 2.2021)[8], but the criteria for inclusion in the very low risk group remains unchanged, so for pathologists and patients it is of great importance to determine the number and fraction of cores involved.

CAP request: We request the LCD language be amended to allow for coverage for IHC staining of any suspicious core biopsy, irrespective of carcinoma in other cores.

C. LCD statement: "Prostate cases when IHC workup is Not Reasonable and Necessary include the following:

- In a multi-part biopsy with ≥3+4=7 cancer in 1 part, and ASAP suspicious for 3+3=6 cancer in other part(s), because stains are unlikely to change treatment; or
- In a multi-part biopsy with ≥4+3=7 cancer in 1 part, and "atypical cribriform lesson [(*sic*])" (ACL) suspicious for intra-ductal carcinoma versus invasive, Gleason pattern 4 cancer in other part(s), because intra-ductal carcinoma is almost always closely associated with invasive high-grade cancer. "

CAP position: The LCD's position that volume, multifocality, or additional findings in lower-grade tumor-positive biopsies (associated with high-grade lesions) do not influence treatment, prognosis, or have other clinical implications is inaccurate. According to the 2019 Genitourinary Pathology Society (GUPS) White Paper on Contemporary Grading of Prostate Cancer,[1] differentiation between atypical cribriforming lesions/intraductal carcinoma and invasive adenocarcinoma cannot be made on routine light microscopic evaluation alone and requires immunohistochemical staining for diagnosis and (if applicable) appropriate Gleason/grade grouping.[1] A tissue diagnosis is made by a pathologist while

treatment decisions are independently determined by the patient's treating physician. Accurate and complete pathologic diagnosis of each individual specimen is essential information for the treating physician's decision-making. Any implication that pathologic diagnosis should be limited based on the pathologist's presumption of the subsequent course of treatment is an unwarranted extension of the scope of pathology practice and impingement upon that of the treating physician.

CAP request: We request that Palmetto remove this LCD statement and related bullet points.

Summary

The CAP appreciates the opportunity to request a reconsideration of the Palmetto LCD for Special Histochemical Stains and Immunohistochemical Stains (L35922). We would also like to take this opportunity to observe that other areas of the LCD beyond those addressed in this letter are out of step with current standards of practice. Further, there are areas throughout the LCD where the use of non-standard, unconventional language obscures the policy's coverage intent, and is unhelpful to well-intentioned providers who seek to rely on the policy for clear guidance on whether IHC stains and special stains for a particular item or service are covered. We would welcome the opportunity to help Palmetto gain a broader understanding of the current standards of practice and to work with Palmetto to revise the policy language to provide greater clarity to the provider community. If you have any questions about our comments please contact Nonda Wilson, CAP's Manager, Economic and Regulatory Affairs, at nwilson@cap.org

Sincerely,

College of American Pathologists

References

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8. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 2.2022, November 30, 2021. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

9. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genetics in medicine: official journal of the American College of Medical Genetics. 2009;11(1):35-41.

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11. Zhou M, Aydin H, Kanane H, et al. How often does alpha-methylacyl-CoA-racemase contribute to resolving an atypical diagnosis on prostate needle biopsy beyond that provided by basal cell markers? Am J Surg Pathol. 2004;28:239-243.