COLLEGE of AMERICAN PATHOLOGISTS

July 17, 2023

Part B Policy
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Re: Proposed LCD - Special Histochemical Stains and Immunohistochemical Stains (DL35922)

Dear Dr. Brito,

The College of American Pathologists (CAP) appreciates the opportunity to comment on Palmetto's proposed LCD - Special Histochemical Stains and Immunohistochemical Stains L35922 (hereinafter referred to as "Special Stains"). 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.

We want to thank Palmetto for their proposed updates to the LCD, including removing the age limit for Lynch Syndrome tumor screening for microsatellite instability (MSI)/DNA mismatch repair by qualitative IHC for individuals with newly diagnosed colorectal and endometrial cancer, per current NCCN Guidelines. We also want to express appreciation to Palmetto for their efforts to clarify the Coverage Guidance areas of the LCD. The proposed changes to the language have generally clarified coverage for special histochemical and immunohistochemical stains .

The CAP continues to have concerns regarding the 'Coverage Guidance' and the 'Summary of Evidence' areas of the LCD that we believe require further revision. Additional details and explanations are below, and we respectfully ask that you consider our recommendations.

I. Coverage Guidance

1. IHC for Breast Pathology

LCD Statement
PharmDx Ki-67 (MIB-1) by Agilent Technologies has prognostic value in the population of lymph node positive high risk breast cancer for use of the Cyclin-dependent 4 and 6 (CDK 4/6) inhibitor abermaciclib (Eli Lilly and Company) as adjuvant therapy in addition to endocrine therapy. Outside of this exception, Ki-67 is not considered reasonable and necessary for breast cancer and consequently will not be covered by Medicare.

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More recent evidence identifies the use of the PharmDx Ki-67 (MIB-1) by Agilent Technologies as a companion diagnostic test shown to define a high-risk population along with high risk clinicopathologic features (i.e., nodal status, tumor size, and grade). This is used to identify patients with an even greater risk of recurrence and thus has prognostic value in the population of patients with ER+, HER2- lymph node positive high risk breast cancer for use of the Cyclin-dependent 4 and 6 (CDK 4/6) inhibitor abermaciclib (Eli Lilly and Company) as adjuvant therapy in addition to endocrine therapy.

CAP Comment: The CAP agrees with Palmetto that Ki-67 has prognostic value in the population of patients with ER+, HER2-lymph node positive high risk breast cancer. We also agree that Ki-67 testing is reasonable and necessary for both prognosis and therapy. We note that the FDA has removed the requirement for the PharmDx Ki-67 clone.[v,vi]

There is no evidence that the specific clone (Dako) used in the PharmDx test is superior to other Ki67 clones. Further, there is no evidence that the methodology of interpretation of the results is superior with this clone. Limiting coverage of Ki-67 testing to this single test would likely limit access to care for patients as many institutions may not carry this particular clone and use other equally efficient Ki-67 clones.

CAP Request: Ki-67 has clinical utility in helping to determine the prognosis of Stage I and II breast cancer and we request Palmetto not preclude its coverage. In particular, the Dako PharmDX clone is no longer specified by the FDA in the algorithm for treatment with abemaciclib and therefore we request the removal of any reference to the specific clone in the LCD.

2. Special Stains and/or IHC for Prostate Pathology

The CAP is concerned that Palmetto's understanding of special stains and IHC for prostate is incomplete. Following are examples of discordant LCD statements and how the number of core biopsies inform risk stratification.

A. Discordant Statements

The two LCD statements below appear to be contradictory. The CAP agrees with the second LCD statement that the number of positive biopsy sites and percentage of core involvement of the sites CAN affect therapeutic choices. However, the first LCD statement contradicts the second by stating it is not reasonable and necessary to perform IHC testing on cases with morphologically suspicious cores when prostate cancer is present in other cores because it provides no additional actionable information to the treating physician.

LCD statement #1:

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 perform 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.

LCD statement #2:
Prostate cases that may require reasonable and necessary IHC staining include but are not limited to the following:

- *In a multi-part biopsy with Gleason 3+3=6 cancer in 1 part, and atypical small acinar proliferation (ASAP) suspicious for Gleason 3+3=6 cancer in other part(s); the number of positive biopsy sites and % core involvement of these sites can affect therapeutic choices for active surveillance (AS), focal therapy or surgery;*
- *In a multi-part biopsy with 4+3=7 or 4+4=8 cancer in 1 part, and ASAP suspicious for the same grade cancer in other part(s); workup is justified since the extent of high-grade cancer affects treatments.*

The LCD's position that volume, multifocality, or additional findings in lower-grade tumor-positive biopsies do not influence treatment, prognosis, or have other clinical implications is inaccurate. 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 biopsy cores provides actionable information on risk stratification to the treating physician which, in turn, can have a significant impact on patient management, per the NCCN Guidelines Version 1.2023 Prostate Cancer.[i] Various treatment therapies can include:

- Active surveillance
- Brachytherapy
- External beam radiation therapy
- External beam radiation therapy + brachytherapy
- External beam radiation therapy + brachytherapy + androgen deprivation
- Pre-treatment bone imaging
- Radical prostatectomy
- Radical prostatectomy + lymph node dissection

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, so for pathologists and patients it is of great importance to determine the number and fraction of cores involved.

The following examples help demonstrate how the number of cores with tumor informs risk stratification and that each risk group carries designated therapies.[i]

Example #1 – how the number of cores demonstrate risk group:

- 3+3=6 cancer in 2 of 13 cores = very low risk group
- 3+3=6 cancer in 3 of 13 cores = low risk group
- 3+4=7 cancer in 6 of 13 cores = favorable intermediate risk group
- 3+4=7 cancer in 7 of 13 cores = unfavorable intermediate risk group

Example #2 – how laterality (right/left) of cores with tumor can change risk group:

- 3+3=6 cancer in 3 cores (3 right) **= low risk group**
- 3+3=6 cancer in 4 cores (3 right, 1 left) **= favorable intermediate risk group**

CAP Request: We request the LCD language be amended to allow coverage for IHC staining of SUSPICIOUS core biopsies.

B. Risk Stratification

While the CAP agrees with Palmetto that the use of stains should be conducted in a judicious manner, risk stratification is an important factor in determining prognosis and treatment therapies. Following are additional LCD statements that **inaccurately** assert when stains are not likely to change treatment. The accompanying examples further demonstrate how biopsy workup determine risk stratification, which CAN influence patient treatment.

LCD statement #3:

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*

Example #3 – how the number of IHC workups can influence treatment therapies."[i]

- 3+4=7 cancer in 6 of 13 cores **= favorable intermediate risk group**
- 3+4=7 cancer in 6 of 13 cores and 3+3=6 in 1 core **= unfavorable intermediate risk group**

LCD statement #4:

Prostate cases when IHC workup is Not Reasonable and Necessary include the following:

- *In a multi-part biopsy with =4+3=7 cancer in 1 part, and "atypical cribriform glands that include a differential of Intraductal Carcinoma of Prostate (ICD-P) "atypical cribriform lesson" (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 and the results will not change the overall highest Gleason grade/Grade group for the case and may not change treatment.*

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Example #4 – how a change in risk stratification changes patient management.[i]

- 4+3=7 cancer in 1 core and intraductal carcinoma in 1 core **= favorable intermediate risk group**
- 4+3=7 cancer in 1 core and 4+4=8 in 1 core **= high risk group**

CAP Request: We request Palmetto remove LCD statements #3 and #4 and related bullet points or amend them to allow additional workup to provide necessary risk stratification.

3. Special Stains and /or IHC for Lung Cancer

LCD statement:
The diagnostic challenge of a lung biopsy can often prompt the need for additional stains to define the neoplasm. Two important considerations need to be considered in this regard:

- *The diagnosis of squamous cell cancer can often be made without the use of any special stains, and*
- *The diagnosis of non-small cell carcinoma often requires additional stains, but it is essential that tumor tissue be carefully triaged to allow the patient's sample to be tested for molecular markers (i.e., EGFR, ALK, and others) when clinically indicated.*

CAP Request: We recommend Palmetto delete the first bullet as this statement lacks any scientific validation and used in this context seems at odds with the statement that a lung biopsy often prompts the need for additional stains.

4. IHC for Cervical/Gyn/Bladder/Kidney Tumors

LCD statement:
A variety of IHC stains have found limited use in cervical, gynecologic, and urologic tumor settings. In unusual cases of cervical dysplasia, markers or surrogate markers for HPV may be useful where the diagnosis on conventional H&E stain cannot be made with certainty. These markers are clearly not reasonable and necessary on all biopsies.

Similarly, it is rare to need stains to prove that an endometrial or ovarian cancer is a serous cancer or that a kidney neoplasm is an oncocytoma, an eosinophilic or chromophobic renal cell cancer.

CAP Request: We recommend Palmetto delete both statements under this section as they are anecdotal and not based on scientific evidence as prescribed in the Medicare Program Integrity Manual Chapter 13 – Local Coverage Determinations. Section 13.5.3, describes the evidentiary content of proposed and final LCDs, which requires MACs to summarize the evidence that supports coverage, limited

coverage, maintenance of existing coverage or non-coverage and, at a minimum, the summary should include a narrative that describes the scientific evidence supporting the clinical indications for the item or service.

II. Summary of Evidence

1. Special Stains and/or IHC for Gastrointestinal (GI) Pathology

A. LCD statement:

Scientific data demonstrates that the combined number of gastric biopsies requiring special stains or IHC is roughly 20% of biopsies received and examined in a pathology practice. GI specialty practices with a large GI referral base or GI consultant pathologists may sometimes exceed this relative number of special stains/IHC, but one would not expect to see routine high utilization of special stains or IHC. To check utilization, we encourage providers to perform a self-audit on the number of separate gastric biopsies as compared to ancillary stains. The ancillary stain group should be less than 20% of the total gastric biopsies submitted. ***Providers that exceed the 20% criteria may be subject to additional action****.*

CAP Comment: The medical necessity and utilization of special stains for GI biopsy cases in the LCD imposes a predetermined numerical utilization threshold on providers utilizing special stains in gastric biopsies and threatens enforcement action against providers who use specials stains in excess of this threshold. The predetermined threshold is arbitrary and not supported by evidence or consensus of the pathology community. The dLCD appears to derive this standard from a single 2006 study whose results have never been demonstrated to be generalizable and do not suggest or support an across-the-board application to every provider regardless of the circumstances. The threshold does not capture the impact of the quantity and types of procedures and diagnostic tools used by the given practice, hospital or laboratory, or the variety of practice settings or populations served.

Further, the threat of unspecified "additional action" against providers utilizing special stains in excess of the threshold was first used in an "educational" posting by Palmetto on its website in 2014. The CAP expressed strong concerns regarding the language in a June 25, 2014, letter to CMS and CMS deemed the language inappropriate and consequently the language was rescinded. The CAP observes that this same language has now resurfaced, and believes it is still inappropriate in a Medicare local coverage policy.

CAP Request: We recommend that Palmetto strike this entire paragraph from the final LCD. Alternatively, a more general statement emphasizing compliance with the LCD coverage parameters may be expressed, such as:

"Compliance with the limitations provisions of this policy may be monitored and addressed through post payment data analysis and subsequent medical review audits."

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B. LCD statement:
LS tumor screening for microsatellite instability (MSI)/deoxyribonucleic acid (DNA) mismatch repair (MLH1, MSH2, MSH6 and PMS2) by qualitative IHC is considered medically necessary and covered by Medicare for individuals with newly diagnosed colorectal cancer or endometrial cancer.

If IHC is normal and there is clinical evidence to consider additional testing, MMR gene mutation testing may be warranted. IHC testing for LS is qualitative and does not require the use of tumor morphometry for evaluation.

CAP Comment:
MMR/MSI (mismatch repair/microsatellite instability) status in carcinoma is evaluated for multiple purposes including diagnosing patients for LS and for predicting response to therapies including PD-1 axis inhibition. MMR tumor screening is a rapidly changing field and can inform several cancer types other than colorectal and endometrial cancers.

As stated in the College of American Pathologists Guideline and endorsed by the American Society of Clinical Oncology (ASCO), results of this testing are used by providers to help select immune check point inhibitor therapy. The guideline addresses multiple issues around such testing across multiple cancer types. ASCO has published guidelines recommending testing for MMR for breast, ovarian, gastroesophageal and small bowel cancer. In general, MMR testing should be permitted for patients with gastroesophageal and small bowel cancer, being considered for immune check point inhibitor therapy.[vii]

CAP Request: We request Palmetto expand coverage for MMR/MSI testing beyond colorectal cancer and endometrial cancers to include patients with gastroesophageal junction cancer, small bowel cancer and other solid tumors that are being considered for immune checkpoint inhibitor therapy.

2. Special Stains and/or IHC for Prostate Pathology

The CAP continues to stress that 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.

LCD statement:
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 prostatic intraepithelial neoplasia (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 Request: We request that the language (above) be amended to support coverage for AMACR in all specimens suspicious for carcinoma which cannot be confirmed or excluded by morphology alone.

3. **IHC for Skin & Cutaneous/Soft Tissue/Central Nervous System (CNS) & Peripheral Nervous System (PNS) Lesions.**

LCD statement #1:
It is well recognized that most skin lesions are diagnosed with routine H&E slides. That is the case for most melanomas and other pigmented lesions as well. Soft tissue masses may require stains (e.g., smooth muscle differentiation in a malignant mass) but the most do not.

LCD statement #2:
The primary role of IHC for CNS and PNS lesions is to differentiate primary from metastatic lesions.

CAP Request: We request Palmetto remove the first statement from the final LCD as it is not based on any available scientific evidence. We also request that Palmetto amend the second statement to include other uses of IHC including classifying CNS tumors and for prognosis and therapy.[viii]

Thank you for the opportunity to comment on this proposed LCD and for your consideration of our requests. Please contact Nonda Wilson, Manager, Economic and Regulatory Affairs, at nwilson@cap.org if you have any questions or would like additional information.

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[i] NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer, Version 1.2023.

[ii] Epstein JI, Egevad L, Humphrey PA, Montironi R, Group IIiDUP. Best practices recommendations in the application of immunohistochemistry in the prostate: report from the International Society of Urologic Pathology consensus conference. The American journal of surgical pathology 2014;38(8):e6-e19.

[iii] Hameed O, Humphrey PA, Immunohistochemistry in diagnostic surgical pathology of the prostate. Semin Diagn Pathol 2005 Feb;22(1):88-104. PMID: 16512601

[iv] Wu C-L, et al. Analysis of alpha-methylacyl-CoA racemase (P504S) expression in high-grade prostatic intraepithelial neoplasia Hum Pathol 2004 Aug;35(8):1008-13.

PMID: 15297968.

[v] Denkert, Carsten, et al. "Strategies for developing Ki67 as a useful biomarker in breast cancer." *The Breast* 24 (2015): S67-S72.

[vi] Nielsen, Torsten O., et al. "Assessment of Ki67 in breast cancer: updated recommendations from the international Ki67 in breast cancer working group." *JNCI: Journal of the National Cancer Institute* 113.7 (2021): 808-819.

[vii] Vikas, P, Messersmith, H, Compton, C, et al. "Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline."Journal of Clinical Oncology, v.41, Issue 10 (2022). https://ascopubs.org/doi/full/10.1200/JCO.22.02462

[viii] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. doi: 10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013. https://doi.org/10.1093%2Fneuonc%2Fnoab106