COLLEGE of AMERICAN PATHOLOGISTS

March 3, 2023

Meredith Loveless, MD
Attn: Medical Review
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Re: Proposed LCD - Special Histochemical Stains and Immunohistochemical Stains (DL35986)

Dear Dr. Loveless,

The College of American Pathologists (CAP) appreciates the opportunity to comment on CGS' 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 CGS for their proposed updates to the LCD, including recognizing that Lynch Syndrome tumor screening for microsatellite instability is medically necessary for individuals with newly diagnosed colorectal cancer or endometrial cancer, per the current NCCN Clinical Practice Guideline in Oncology. We also want to express appreciation to CGS for acknowledging that the nuclear protein Ki67 is an established prognostic and predictive indicator for the management and grading of neuroendocrine tumors. We encourage CGS to make these proposed changes to the final LCD.

The CAP has identified additional areas of the LCD on Special Stains and/or IHC for the Prostate Pathology section that we believe require further revision. Specifically, we ask that (1) the LCD language be amended to allow for coverage for IHC staining of any suspicious core biopsy, irrespective of carcinoma in other cores; (2) CGS allow for further IHC workup, as needed, to assist with risk stratification; (3) language be amended to support coverage for AMACR; and (4) that CGS remove specified language from the final LCD related to utilization of stains for GI pathology. Additional details and explanation are below, and we respectfully ask that you consider these suggestions.

1. Special Stains and/or IHC for Prostate Pathology – Discordant Statements

The two LCD statements below appear to be contradictory. The CAP agrees with the first LCD statement that the number of positive biopsy sites and percentage of core involvement of the sites can affect therapeutic choices. However, the second LCD statement contradicts the first by stating it is not reasonable and necessary to perform IHC testing on cases with morphologically negative cores when prostate cancer is

present in other cores because it provides no additional actionable information to the treating physician.

LCD statement #1:
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.*

LCD statement #2:
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.

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] 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 any suspicious core biopsy, irrespective of carcinoma in other cores.

2. Special Stains and/or IHC for Prostate Pathology – Risk Stratification

While the CAP agrees with CGS 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.*

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 CGS 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 Prostate Pathology – AMACR Coverage

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 reiterate our previous request that the language (above) be amended to support coverage for AMACR in all specimens in which suspected cancer cannot be confirmed or excluded by morphology alone. Alternatively, we request CGS make the proposed edits, below:

> 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 alpha-methyl-CoA-Racemase (AMACR), a~~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,~~ due to heterogeneous staining, protocol used and interpretation criteria~~ and heterogeneous staining pattern~~, there is wide variation in the sensitivity and specificity of AMACR in diagnosing prostate cancer.~~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 used together with basal cell markers in work up ~~restricted to the evaluation~~ of morphologically highly suspicious foci[ii,iii,iv]. ~~in which negative immunoreactivity of basal cell markers alone is insufficient to establish a diagnosis of cancer.~~

4. Utilization of Stains for GI Pathology

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.

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****.*

The threat of unspecified "additional action" against providers utilizing special stains in excess of the threshold was first used in an “educational” posting by another MAC on its

website in 2014. The CAP expressed strong concerns regarding the language in a June 25, 2014, letter to CMS and respectfully requested that the posting be either removed from the MAC website or significantly modified. CMS deemed the language inappropriate in the article and the language was rescinded. The CAP is concerned that this same language has resurfaced in an LCD and believes that the language is equally inappropriate in this Medicare coverage policy.

CAP Request: We ask that CGS remove this language from the final LCD. Alternatively, CGS may choose to amend the LCD with more appropriate language 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.*

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.

[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

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