AMERICAN CLINICAL LABORATORY ASSOCIATION

July 20, 2023

Shane R. Mull, M.D., MHA, FAAFP, CPC
Palmetto GBA, LLC
17 Technology Circle
Columbia, South Carolina 29203

RE: Lab: Special Histochemical Stains and Immunohistochemical Stains (DL35922)

Dear Dr. Mull,

The American Clinical Laboratory Association (ACLA) is pleased to submit our written comments on the Draft Local Coverage Determination entitled "Special Histochemical Stains and Immunohistochemical Stains (DL35922)", hereafter referred to as the dLCD. ACLA is the national trade association representing leading laboratories that deliver essential diagnostic health information to patients and providers by advocating for policies that expand access to the highest quality clinical laboratory services, improve patient outcomes, and advance the next generation of personalized care.

ACLA would like to thank Palmetto for developing a new dLCD following reconsideration requests on the current policy of the same name. Following our review of the new draft policy, we offer the following comments and recommendations:

IHC for Breast Pathology

We appreciate that Palmetto acknowledges that in at least one instance, testing for Ki-67 has prognostic value for breast cancer testing. However, we are concerned that the restriction of coverage for only the PharmDx Ki-67 (MIB-1) for the use of Cyclin-dependent 4 and 6 (CDK 4/6) inhibitor abermaciclib in addition to endocrine therapy will prevent patient access to clinically relevant testing for other approved treatments.

Reflecting the current use of Ki-67 testing in breast cancer, the College for American Pathologists' (CAP) *Template for Reporting Results of Biomarker Testing of Specimens From Patients With Carcinoma of the Breast (2020)*[1] includes reporting for Ki-67 while noting that routine testing of Ki-67 is not currently recommended for all carcinomas. Testing for particular biomarkers such as Ki-67 is medically necessary in particular cases, however, and it is the pathologist's responsibility to make that determination and to document such medical necessity in the pathology report and/or medical record.

[1] https://documents.cap.org/protocols/cp-breast-biomarker-20-1400.pdf

In light of our concerns, we recommend the following red-line edits to the language in the "Coverage Indications, Limitations, and/or Medical Necessity" section for "IHC for Breast Pathology":

> *PharmDx Ki-67 (MIB-1) by Agilent Technologies 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. ~~Outside of~~ Beyond this exception, Ki-67 is ~~not~~ considered reasonable and necessary for breast cancer and consequently will ~~not~~ be covered by Medicare only when ordered to directly inform treatment of the patient.*

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

Requirement for H&E Stain Prior to Ordering of Special Stains

While ACLA agrees that the review of routine H&E stain is generally performed prior to the ordering of special stains or IHC stains, there are many instances where it is unreasonable to wait for the result of an H&E stain to be performed and reviewed. We are concerned that not only will this requirement impose unnecessary lengthy delays for diagnosis and treatment decision for patients, but that this requirement also will restrict the ability of the ordering provider to practice medicine. We do not believe that an ordering provider should be barred from ordering a special stain or IHC for a patient if they have significant clinical suspicion and need the results of these tests to manage the patients care in a timely manner.

To remedy both of these concerns, we recommend the following red-line edits to the language in the "Coverage Indications, Limitations, and/or Medical Necessity" section for "Special Stains and/or IHC for Gastrointestinal (GI) Pathology":

> ~~*Only the pathologist may determine the medical necessity of a special stain.*~~ *Ordering special stains or IHC stains on every specimen prior to review of the routine H&E stain is not reasonable and necessary.*

Threshold for "Reasonable" Stains Ordered

Similar to our comments in 2014[2], ACLA remains concerned about the following language in the "Summary of Evidence":

> *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*

[2] Can be accessed here: https://aclacom-my.sharepoint.com/:b:/g/personal/sthibaultsennett_acla_com/EYz8T1JOm0RDso6ZPowebYkB-kHSrtLuDkv9_uNv6S2Ngg?e=40s3cS

> *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.*

Section 1869(f)(2)(B) of the Social Security Act defines a local coverage determination as a determination by a fiscal intermediary or a Medicare Administrative Contractor "respecting whether or not a particular item or service is covered on an intermediary- or carrier-wide basis" under Medicare Part A or Part B.[3] The Social Security Act does not authorize Medicare contractors to establish in an LCD the expected frequency of an item or service across a population of Medicare beneficiaries. Medicare coverage of an item or service is not determined based on the frequency with which a health care provider or practitioner furnishes an item or service. Palmetto expects a qualified pathologist to determine the reasonableness and medical necessity of each special stain and IHC on a case-by-case basis, and the suggestion that there is a set threshold that a pathology practice should not exceed is the antithesis of the concept of a case-by-case determination.

Further, this threshold has the potential to limit the ability of the pathologist to practice medicine – by potentially restricting them from ordering a medically necessary test for a patient to be in compliance with the 20% threshold – with downstream access issues for Medicare beneficiaries. The 20% threshold is applied across all laboratories and does not take into account the existence of laboratories that specialize in IHC testing for GI and can be expected to routinely go over that threshold due to ordering providers seeking them out for this service. Finally, medical centers that specialize in treating GI cancers will have a skewed patient population that will have implications for this threshold when tests are performed at affiliated laboratories.

While ACLA appreciates that Palmetto has added language specifying that this information is to be used by providers as a self-audit, we still anticipate that this arbitrary threshold in the LCD could be misunderstood by a Medicare auditor as a high water mark. Palmetto makes its position about the potential for overutilization of special stains and IHC staining procedures clear in other places in the Draft LCD. We believe the above language is not suitable for inclusion in an LCD and that it is not necessary. We recommend removing the paragraph entirely from the "Summary of Evidence."

<u>Special Stains and/or IHC for Prostate Pathology</u>

ACLA is concerned by the blanket non-coverage determination for IHC testing on cases with morphologically negative cores and/or IHC testing in a negative or suspicious core biopsy when obvious prostate cancer is present in other cores. IHC testing is medically necessary in particular negative or suspicious cases and it is the pathologist's responsibility to make that

[3] 42 U.S.C. § 1395ff(f)(2)(B).

determination and to document such medical necessity in the pathology report and/or medical record.

To address our concerns, we recommend the following red-line edits to the "Coverage Indications, Limitations, and/or Medical Necessity" section for the "Special Stains and/or IHC for Prostate Pathology":

> ~~*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 1 or more cores in a case where the diagnosis of cancer has already been made, it is* ~~*not*~~ *only a Medicare covered service* ~~*because*~~ *if it provides* ~~*no*~~ *additional actionable information to the treating physician.*

Additionally, the LCD includes the following sentence in the "Summary of Evidence" section:

> *ERG is another IHC that is more likely to be positive in cancer than in benign tissue, but it does not add information to conventional PIN4 testing.*

ACLA disagrees that ERG never provides a pathologist with additional actionable information. Both basal cell markers and the prostate-specific marker alpha-methyl-CoA-Racemace (AMACR) offer high sensitivity but low specificity for prostate cancer detection. In contrast, ERG has low sensitivity but high specificity for prostate cancer detection. Where a high-grade prostatic intraepithelial neoplasia is ruled out, ERG positivity in small atypical glands can be used to confirm a prostate cancer diagnosis.[4] We recommend that the sentence above be removed to allow patient access to medically necessary testing.

IHC for Skin & Cutaneous/Soft Tissue/Central Nervous System (CNS) & Peripheral Nervous System (PMS) Lesions

ACLA appreciates that Palmetto acknowledges there are some types of skin and skin appendage lesions that require immunohistochemical stains, including the three examples listed in the LCD, as well as others not specifically listed. We would like to highlight that lesions involving the nail unit, while often not requiring IHC evaluation, may need such differential diagnostic work-up due to the nature of the anatomic location and the relative difficulties in obtaining diagnostic material. Additionally, as with any other anatomic specimen, clinical samples obtained from the skin/skin appendages, soft tissue, and bone may not always show clearly diagnostic features on H&E alone necessitating the use of IHC staining to provide an accurate diagnosis to the ordering physician. Beyond H&E and IHC stains, histochemical stains have diagnostic utility in certain circumstances, including Fontana-Masson in cases of onychodystrophy where melanin deposition, potentially due to a subclinical melanocytic process, may be influencing the clinical appearance of the nail.

[4] Shah R.B., Clinical applications of novel EGR immunohistochemistry in prostate cancer diagnosis and management, *Adv. Anat. Pathol.* 2013; 20:117-124.

The use of IHC morphometric analyses for skin lesions is reasonable and necessary in certain clinical indications. Specifically, in the case of small fiber peripheral neuropathy (SFPN), intra-epidermal nerve fiber density (ENFD) testing, the diagnostic gold standard, requires morphometric evaluation of a skin biopsy to render an intra-epidermal nerve density and therefore a diagnosis.[5,6] In order to ensure that the standard of care is available for patients with lesions of these types, we recommend the following red-line edits to the language in the "Coverage Indications, Limitations, and/or Medical Necessity" section for "IHC for Skin & Cutaneous/Soft Tissue/Central Nervous System (CNS) & Peripheral Nervous System (PMS) Lesions":

> *Most skin lesions are diagnosed with routine H&E slides. A minority of skin lesions require immunostains (e.g., atypical fibroxanthomas, Merkel cell lesions, lymphomas, as well as others). Most common skin lesions (e.g., seborrheic keratosis) do not require IHC stains. Use of IHC morphometric codes for skin lesions, outside of the diagnosis of small fiber peripheral neuropathy, is not reasonable and necessary.*
>
> *Similarly, most routine soft tissue lesions do not require IHC stains or other "special" stains.*
>
> *Many CNS and PNS lesions are readily diagnosed with routine stains. It is unusual for a meningioma to require an IHC.*

Thank you for your consideration of ACLA's comments and recommendations. We appreciate that Palmetto is revisiting the Special Histochemical Stains and IHC Stains Local Coverage Determination and we welcome the opportunity to work collaboratively on this draft policy.

Please contact Sarah Thibault-Sennett at sthibaultsennett@acla.com with any questions or to discuss further.

Sincerely,

Adam Borden
Senior Vice President, Policy & Strategy, ACLA

[5] Lauria G, Cornblath DR, Johansson O, McArthur JC, Mellgren SI, Nolano M, Rosenberg N, Sommer C; European Federation of Neurological Societies. EFNS guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy. Eur J Neurol. 2005 Oct;12(10):747-58. doi: 10.1111/j.1468-1331.2005.01260.x. PMID: 16190912.
[6] Zhou L. Small Fiber Neuropathy. Semin Neurol. 2019 Oct;39(5):570-577. doi: 10.1055/s-0039-1688977. Epub 2019 Oct 22. PMID: 31639840.