COLLEGE of AMERICAN PATHOLOGISTS

July 14, 2015

Medical Policy
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RE: Draft Local Coverage Determination: Special Histochemical Stains and Immunohistochemical Stains (DL36234)

Dear Dr. Corcoran and Dr. Polsky:

The College of American Pathologists ("CAP") appreciates the opportunity to comment on the First Coast Draft Local Coverage Determination ("dLCD") for Special Histochemical Stains and Immunohistochemical Stains (DL36234). The CAP is a medical society serving more than 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and the worldwide leader in quality assurance. The CAP advocates for accountable, high-quality and cost-effective patient care. The CAP's Laboratory Accreditation Program is responsible for accrediting more than 7,000 clinical laboratories worldwide.

The CAP has several significant concerns about this dLCD and its negative impact on the practice of pathology and patient care. They include the following:

- The dLCD's purported evidence base lacks credibility. The dLCD uses highly selective and partial literature citation, takes references out of context, overlooks fine points, misrepresents the opinions of national organizations, and is contrary to generally accepted guidelines. In several instances, key premises are unsubstantiated.

- The dLCD encroaches on matters of pathologist medical judgment, failing to take into account patient characteristics that vary from practice to practice and the full range of diagnostic considerations confronting a pathologist that are evaluated in establishing the patient's diagnosis.

- As a result of its lack of clarity and reliance on retrospective claims evaluation, neither providers nor patients are able to prospectively determine if a particular service is covered for a particular patient.

- Most concerning, the dLCD seems to approach the patient's diagnostic evaluation in an arbitrary fashion, potentially adversely affecting not only the efficiency with which care is delivered, but also diagnosis, clinical decisions, and treatment options. In some instances, services deemed not necessary under the dLCD are performed to improve diagnostic turnaround time which may be lifesaving. In other instances, the dLCD's provisions could direct pathologists to practices that predispose misdiagnosis, denying patients services from which they may benefit or subjecting them to harmful and unnecessary interventions, particularly in regard to some difficult-to-diagnose malignancies.

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Even more concerning is the adoption of this flawed policy by FCSO, whose regional coverage policies affect physicians and patients in Florida, Puerto Rico and the Virgin Islands. Due to these concerns, **CAP urges FCSO to withdraw this dLCD**.

In the sections that follow, CAP details its specific concerns regarding the dLCD's 1) inadequacy of evidentiary support, 2) conflict with established Medicare requirements, and 3) simultaneous breadth and ambiguity that preclude practical application.

1. Evidentiary Requirements Not Met – The dLCD proposes to establish rules regarding when special stains and IHC will be considered medically necessary. In several instances, CAP's experts have identified areas where the provisions of the dLCD are directly contradicted by the published medical literature. In other cases, the dLCD attempts to set coverage criteria in areas of pathology where experts in the field are actively engaged in developing the evidence base, but where no consensus has yet emerged. In the Attachment to this comment letter, CAP provides its feedback on a section-by-section basis on the merits of the dLCD. Some highlights of that feedback follow:

a. Contradictory Evidence

Under the Medicare Program Integrity Manual ("Program Integrity Manual"), Medicare Administrative Contractor ("MAC") LCDs shall be based on the strongest evidence available, beginning with a search of the published scientific literature. In contrast, the dLCD draws its evidence base from a retrospective analysis of Medicare claims data.

Further, the Program Integrity Manual states that contractors should place the highest priority on "published authoritative evidence . . . or other definitive studies. . ." followed by general acceptance by the medical community. (Program Integrity Manual, ch. 13, §§ 13.7.1). As detailed below and further in the Attachment to this letter, the dLCD directly contradicts the published medical literature in many places.

The Program Integrity Manual states that acceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community. (*Id.*). The LCD, though, cites "personal communication" with a single individual as the sole evidence supporting certain provisions of the dLCD.

CAP's review by experts in the various subspecialties within pathology covered by the dLCD were able to identify many examples of published literature and practices that are, in the view of those experts, generally accepted by the medical community and that directly contradict the content and requirements of the LCD including the following:

- The dLCD's standards on Lynch Syndrome tumor screening for DNA mismatch repair are incorrect and inconsistent with current National Comprehensive Cancer Network ("NCCN") guidelines, the recent American Society of Clinical Oncology ("ASCO") clinical practice guideline endorsement[42] and the Evaluation of Genomic Application in Practice and Prevention ("EGAPP"), a project sponsored by the Office of Public Health Genomics at the Center for Disease Control and Prevention. EGAPP determined sufficient evidence exists to offer genetic testing for Lynch Syndrome to all individuals with newly diagnosed CRC. Other published studies have also reported the cost effectiveness of universal CRC testing.[35]

- NCCN guidelines also contradict the dLCD's rules on IHC testing on cases with morphologically negative cores.

The examples above, together with those detailed in the Attachment to this letter, are illustrative of our contention that the dLCD is not based on published authoritative evidence or general acceptance by the medical community.

Citations for all studies are included in the Appendix to this letter.

b. Lack of Consensus

In addition to contradictory evidence, consensus is lacking for many of the dLCD's rules. While the Attachment identifies numerous examples, we call attention to the dLCD's assertion that "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." This utilization 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 are not generalizable and do not suggest nor support an across-the-board application to every provider regardless of the circumstances associated with individual patients and procedures. 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.

c. Practice Guideline

Program Integrity Manual provisions defining the LCD process clarify that LCDs are to "consist only of 'reasonable and necessary' information… [T]he LCDs specify under what clinical circumstances an item or service is considered to be reasonable and necessary. They are administrative and educational tools to assist providers in submitting correct claims for payment." (Program Integrity Manual, ch. 13, § 13.1.3).

The unusual format of the dLCD makes it difficult for pathologists to interpret and apply in practice. The dLCD does not clearly explain the criteria for Medicare coverage of the services. Indeed, at various points, it declares IHC and special stains in various situations to be "medically necessary and covered," "not usually reasonable and necessary," "reasonable and necessary in limited circumstances," "rare to need," and "unusual to require," without defining the differences, if any, among these terms and their application. Moreover, the seemingly random order of the dLCD's declarations make it even more difficult to ascertain in any particular case what is and is not covered by Medicare.

Further, the LCD process does not provide license to a MAC to define what constitutes appropriate medical practice. The dLCD, as written, addresses topics more typical of a clinical practice guideline than a coverage determination. Importantly, CMS does not develop clinical guidelines nor does a MAC, as a CMS contractor.

Even if considered as a clinical practice guideline, however, the dLCD falls woefully short both procedurally and substantively, providing a confusing, inconsistent and at times incorrect portrayal of appropriate standards of care for the diseases and conditions covered by the dLCD. In addition, the dLCD lacks the level of clinical evidence and expert input needed for guideline development.

Based on the evidentiary issues alone, FCSO should withdraw this dLCD.

2. Interference with Pathologist's Medical Necessity Determinations – Current Medicare requirements identify the pathologist's clinical assessment of individual medical need as the critical element in determining whether the use of special stains and/or IHC is medically necessary. These rules clearly bestow responsibility upon the pathologist for determining that the "services are medically necessary so that a complete and accurate diagnosis can be reported to the treating physician/practitioner." (Medicare Benefit Policy Manual, ch. 15, § 80.6.5.) As shown below, the dLCD departs from this and from other current Medicare requirements in a way that is not in the best interest of timely diagnosis and patient care.

a. Medicare Benefit Policy Manual ("Policy Manual")

Specifically, Section 80.6.5 of the Policy Manual provides:

When a surgical or cytology specimen is sent to the pathology laboratory, it typically comes in a labeled container with a requisition form that reveals the patient demographics, the name of the physician/practitioner, and a clinical impression and/or brief history. There is no specific order from the surgeon or the treating physician/practitioner for a certain type of pathology service. While the pathologist will generally perform some type of examination or interpretation on the cells or tissue, there may be additional tests, **such as special stains**, **that the pathologist may need to perform**, even though they have not been specifically requested by

the treating physician/practitioner. The pathologist may perform such additional test under the following circumstances:

- These **services are medically necessary** so that a complete and accurate diagnosis can be reported to the treating physician/practitioner;
- The results of the test are communicated to and are used by the treating physician/practitioner in the treatment of the beneficiary; and
- The pathologist documents in his/her report why additional testing was done.

EXAMPLE: A lung biopsy is sent by the surgeon to the pathology department, and the pathologist finds a granuloma which is suspicious for tuberculosis. The pathologist cultures the granuloma, sends it to bacteriology, and requests smears for acid fast bacilli (tuberculosis). **The pathologist is expected to determine the need for these studies** so that the surgical pathology examination and interpretation can be completed and the definitive diagnosis reported to the treating physician for use in treating the beneficiary.

(*Id.* [emphasis added]).

In stark contrast, the dLCD imposes a new requirement that a pathologist may not order special stains prior to review of hematoxylin and eosin ("H&E") stains. The dLCD states "A Pathologist must first review the H&E stain prior to ordering special stains or IHC." (dLCD, page 3). Nowhere, however, does the Policy Manual provision state that review of an initial H&E stain is a prerequisite to ordering additional testing services.

Portions of the Policy Manual provision preceding the language cited by FCSO in the dLCD indicate that "While a pathologist will generally perform some type of examination or interpretation on the cells or tissue . . ." (*Id.*). FCSO does not cite this language in its dLCD, yet seems to make the huge leap from this broad statement to the specific mandate that pathologists *must* review the H&E stain first in order for other ordered services to be "reasonable and necessary". This is inconsistent with both the letter and the spirit of the Policy Manual. The Policy Manual gives the pathologist the right to determine if and when use of a special stain or other service is reasonable and necessary.

b. Program Integrity Manual

First Coast's establishment of such a prerequisite is also in conflict with the Program Integrity Manual. The Program Integrity Manual defines a "prerequisite" as the "concept that use of an alternative item or service precedes the use of another item or service." The Program Integrity Manual specifically states that "[w]henever national policy bases coverage on an assessment of need by the beneficiary's provider, prerequisites should not be included in LCDs." Program Integrity Manual, ch. 13, § 13.5.4.

Elsewhere in the Program Integrity Manual, LCDs are required to be "consistent with all statutes, rulings, regulations, and national coverage, payment, and coding policies." Program Integrity Manual, ch. 13, § 13.1.3. The dLCD's attempt to automatically deny coverage of IHC and special stains in a wide array of instances involving various medical conditions contradicts Policy Manual requirements that squarely place in the hands of pathologists the medical necessity determination related to all surgical pathology and cytopathology services, including IHC and special stains. **The dLCD is inconsistent with various existing Medicare requirements and should therefore be withdrawn.**

c. Physicians' Role in Determining Medical Necessity of Specific Services

Also with respect to physician judgment in medical necessity determinations, we point out that MACs have in recent years rescinded and refrained from finalizing dLCDs that were inconsistent with Medicare requirements regarding the physician's role in determining the medical necessity of specific services. *See* Cahaba Government Benefit Administrators, LLC, "IRF Admission after Single Joint Replacement with CMGs A0801-A0806 (DL32816)," rescinded Sept. 13, 2012 *available at* http://www.cahabagba.com/news/lcd-surgery-irf-admission-after-single-joint-replacement-with-cmgs-a0801-a0806-dl32816-update/. **Given precedent as well as inconsistency and inappropriate interpretation of medical necessity requirements under existing Medicare requirements, FCSO should withdraw the dLCD**.

3. Documentation Requirements - While Title XVIII of the Social Security Act, § 1833(e) prohibits Medicare payment for any claims lacking the necessary documentation to process the claim, the documentation requirements set forth in the dLCD are inappropriate for reasons including the following: 1) LCDs per Medicare requirements should include only "reasonable and necessary" provisions and 2) The documentation requirements suggested here conflict with existing national guidance regarding documentation of pathology services.

In addition to its overreaching scope on coverage, the dLCD sets forth similarly broad documentation requirements. Some examples include:

- IHC for cervical/gyn/bladder/kidney tumors – The dLCD indicates "…it is rare to need stains to prove that an endometrial or ovarian cancer is a serous cancer… The use of IHC stains in these circumstances requires adequate documentation in the pathology report… (dLCD, page 8)

- Special stains and/or IHC for prostate pathology – The dLCD indicates "[t]he surgical pathology report is expected to designate the specific block(s) upon which IHC testing is performed, the reason for IHC testing, the specific markers, and whether single antibody(ies) or a cocktail of antibodies is utilized. A statement alone in the pathology report that states "IHC confirms the diagnosis" will not be covered as reasonable and necessary." (dLCD, page 5)

In these examples it seems FCSO is attempting to use documentation requirements as a proxy for defining when care is "reasonable and necessary", likely because it is unable to clearly define actual coverage criteria. Coverage criteria cannot be easily defined by FCSO here because utilization of particular IHC and special stain services is based on the pathologist's assessment of the patient's individual medical need that cannot be generalized across-the-board to all patients at all times.

Similarly, while providing documentation of how and why services were performed may help demonstrate that a service is medically necessary, simply meeting a documentation requirement does not make an item or service "reasonable and necessary." At the same time, failure to meet such a requirement does not mean such an item or service is not "reasonable and necessary." These documentation requirements are therefore not only onerous, but also inappropriate.

In addition, documentation requirements for physician services and pathology services are already set forth in regulations and Policy Manual provisions, which are either less specific or silent. They simply do not require any specific documentation in order for surgical pathology or cytopathology services to be covered and reimbursed.[1] The Program Integrity Manual requires that LCDs be "consistent with all statutes, rulings, regulations, and national coverage, payment, and coding policies." (Program Integrity Manual, ch. 13, § 13.1.3.) These additional documentation requirements are inconsistent with existing national policy and should be withdrawn.

Finally, the dLCD creates practical conflicts with Advance Beneficiary Notice ("ABN") requirements[2]. CAP, therefore, finds the dLCD's statements on documentation requirements related to advanced beneficiary notices (ABNs) particularly troubling. The confusing nature of the dLCD and the huge number of topics covered in this single LCD make it virtually impossible for pathologists to determine if a particular IHC or special stain is not covered. Under these circumstances, requiring an ABN be issued let alone obtaining the information needed to issue a valid ABN (e.g., a description of the non-covered service) and apply the applicable claim modifier is not a viable option. We note that among the examples of valid reasons why Medicare may not pay include the broad statement: "Medicare does not pay for this test for your condition."

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[1]The Policy Manual provision defining coverage for surgical pathology and cytopathology services requires only that the pathologist document in the report why additional testing was done for surgical/cytopathology services. Policy Manual, ch. 15, § 80.6.5; *see also* 42 CFR § 415.130 (conditions of payment for physician pathology services do not include documentation requirements for surgical/cytopathology services); CMS pub. 100-04, ch. 16, § 60 (conditions of payment for the professional component of physician laboratory or pathology services in provider settings do not include documentation requirements for surgical/cytopathology services).

[2]CMS Pub. 100-04, ch. 16, § 40.7; id. Ch. 30, §§ 50.3, 50.3.1., 50.4.1; Medicare Benefit Policy Manual, CMS Pub 100-02, ch. 15, § 40.24.

The dLCD is so confusing that a pathologist cannot determine for which condition IHC and special stain tests are not paid, and thus cannot reasonably use even a general explanation as set forth in this broad statement. In addition to creating a compliance problem for pathologists, most importantly, this situation leaves the patient confused and ill-informed with respect to individual Medicare coverage, potentially resulting in decreased access to needed care.

4. Scope - The dLCD is incredibly broad in its scope, which complicated the task of providing comments on it within the allotted time period. It covers nine different clinical areas where IHC is used in diagnosis, including breast, gastrointestinal, lung, urogenital and skin disorders. This breadth gives rise to a heightened need for response; hence, the CAP has engaged a broad team of pathologist experts in each of those fields to respond within the 45-day comment period. Notably, the CAP has a consensus-based process for formulating clinical practice guidelines through its Pathology and Laboratory Center ("Center"), and typically requires 18 - 24 months to create an evidence-based guideline that meets Institute of Medicine criteria for clinical guidelines.

The Policy Manual provision defining coverage for surgical pathology and cytopathology services requires only that the pathologist document in the report why additional testing was done for surgical/cytopathology services. Policy Manual, ch. 15, § 80.6.5; see also 42 CFR § 415.130 (conditions of payment for physician pathology services do not include documentation requirements for surgical/cytopathology services); CMS pub. 100-04, ch. 16, § 60 (conditions of payment for the professional component of physician laboratory or pathology services in provider settings do not include documentation requirements for surgical/cytopathology services).

In addition to its breadth, the deviation of the dLCD from the standard dLCD format presents unique challenges in interpreting and commenting on it as well as in applying it to the practice of pathology. Typically a dLCD includes indications (i.e. covered items and services) and limitations (i.e. non-covered or restricted coverage items and services) in a relatively standardized format that gives physicians clear guidelines for whether or not tests are medically necessary at the time that the tests are performed. The dLCD, on the other hand, comprises assertions about the expected utilization of special stains over the course of time as might be seen on a retrospective analysis of aggregated claims. This is of no practical use to a pathologist at the point of making any particular diagnosis or determining the billable service(s) for an individual patient. It is also of no practical use to a MAC in adjudicating individual claims. Moreover, LCDs are intended to define when a service is reasonable and necessary whereas the dLCD describes "scenarios that might be driving medically unnecessary over utilization".

In closing, for those evidentiary, compliance, and process issues stated above, **we urge FCSO to rescind the dLCD**.

Once again, we would like to thank you for opportunity to comment and appreciate your consideration of our comments. Please do not hesitate to contact me should you have questions or need additional information.

Sincerely,

Gene N, Herbek, MD, FCAP
President

ATTACHMENT

Coverage Indications and Limitations

dLCD Statement: This policy identifies the medically necessary criteria for the use of special stains and/or IHC stains and addresses, based on claims review, the scenarios that may be driving medically unnecessary over utilization or incorrect billing of these services including

CAP Comment: The evidence for the medical overutilization is not cited so the premise of this document has not been substantiated. The similar concern applies to the assertion of incorrect billing.

dLCD Statement: This policy identifies the following scenario as driving medically unnecessary overutilization of special stains and/or IHC stains:

a) Reflex templates or pre-orders for special stains and/or IHC stains prior to review of the routine hematoxylin and eosin (H&E) stain by the pathologist.

CAP Comment: In the case of small specimens it is essential that any slides for special stains be cut serially with the H&E sections, to assure that morphological features can be correlated with staining characteristics, and to avoid loss of tissue in refacing the block. It is a matter for medical judgment by the pathologist whether the likelihood of need for the special studies and/or the need for expeditious management of the patient merits special staining prior to review of the H&E sections. In some instances this pre-ordering of special stains and/or immunohistochemical studies is performed to avoid an unnecessary delay in patient care. IHC stains may also be proactively ordered after the review of core biopsy touch imprint cytology preparations that may be used to assess adequacy of a specimen at the time of invasive radiologically enhanced biopsies and after the review of frozen section samples. This is performed to provide improved diagnostic turnaround time. This may actually be lifesaving, in the clinical example of superior vena cava syndrome, as an example. The ASCO/CAP HER2 guidelines dictate the HER2 be performed on all recurrent breast cancers.[50] Medical liver biopsies and medical renal biopsies require special stains to fully evaluate the tissue and patient diagnosis is not delayed by providing the stains available at the same time as the hematoxylin and eosin stained section. The extent of the use of these techniques must be left up to the medical judgment of the pathologist responsible for rendering a diagnosis on a patient beneficiary as they are the sole responsible party to provide the most complete evaluation possible on what may be a very limited tumor sample. Additional examples are provided in the various comments on the specific subsections of this document.

b) **dLCD Statement:** The words “usually”, “rarely”, “often”, etc. are used throughout the LCD.

CAP Comment: The meaning of the words in the context of an LCD is unclear. The contents of the proposal do not fit into the context of the definition of an LCD. The proposal also discusses what stains and immunohistochemical studies should not usually be billed, but there is minimal discussion as to what is covered.

dLCD Statement: The policy also states that, “A major use of IHC to identify the type and origin of poorly differentiated malignant neoplasms (tumors) as carcinoma, lymphoma, melanoma and sarcoma.”

CAP Comment: This statement suggests that the rather crude diagnostic subclassification is the only medically necessary level of specificity required or desirable by Medicare recipients. This is an error of oversimplification of the diagnostic process.

IHC for Breast Pathology

dLCD Statement: While there are a number of promising additional biomarkers, such as Ki-67, PI3K and gene expression assays, the College of American Pathologists (CAP), American Society of Clinical Oncologists

(ASCO), and that National Comprehensive Cancer Networks (NCCN) have not recognized these markers in patient treatment pathways.

CAP Comment: While it is true that CAP, ASCO and NCCN do not recommend routine performance of Ki-67 or gene assays in all patients, those organizations have not stated that these markers have no role in patient management. The statement in the LCD that these markers have no role in patient evaluation is thus a misrepresentation of the opinion of the above organizations.

dLCD Statement: The clinical utility of testing for hormone receptors in in-situ breast cancer differs from those of invasive disease. Guidelines and the peer reviewed literature support the use of ER testing for in-situ breast neoplasia and PR testing only when the ER status is negative (Lester, personal communication).

CAP Comment: The guidelines and references that are referred to are not specified so cannot be evaluated. A personal communication from a single practitioner does not constitute evidence of sufficient strength to warrant an LCD. Until that evaluation is enabled, the statement is overreaching.

dLCD Statement: In addition, basal phenotype markers (e.g., IHC for CK5) are not routinely necessary. Neither are IHC stains such as E-cadherin, p27, or high molecular weight cytokeratin to distinguish ductal from lobular differentiation necessary on every breast case, nor are myoepithelial cell markers such as p63 or smooth muscle myosin heavy chain necessary on every case.

CAP Comment: This statement fails to acknowledge that these markers are often necessary to determine ductal vs. lobular differentiation and invasive vs. in situ disease in morphologically ambiguous cases, and should be ordered at the discretion of the pathologist. This results in information that allows the clinician to manage patients appropriately. (To achieve its purpose, an LCD needs to define the circumstances under which a test or procedure is or is not payable. Statements like 'not routinely necessary' or 'not necessary in every case' do not serve to define conditions for coverage). This statement does not provide the eligible provider or beneficiary the kind of prospective coverage information that is necessary to know if a service is covered. The very nature of these comments requires a retrospective evaluation of numerous beneficiaries' records. In fact, the payment for the diagnostic medical evaluation of one beneficiary appears to be dependent on the complexity and extent of other beneficiaries' diagnostic evaluation in a nearly random fashion.

Special Stains and/or IHC for GI Pathology

dLCD Statement: Ordering special stains or IHC stains prior to review of the routine H&E stain is not reasonable and necessary. For most esophageal, gastric and duodenal specimens, it is not reasonable or necessary to perform special stains such as alcian blue – periodic acid Schiff (AB-PAS), or other mucin stains, such as diastase–PAS (D-PAS), or IHC stains such CDX-2 to determine if clinically meaningful intestinal metaplasia is present. In addition, it is not usually reasonable and necessary to perform special stains or IHC to determine the presence of H. pylori organisms.

CAP Comment: There is a lack of consensus in the medical community whether ordering of special stains or IHC stains prior to review of the H&E-stained slides for esophageal, gastric, and duodenal specimens is reasonable. Such discretion should be left to the individual physician. *H. pylori* is a treatable infectious disease that predicates severe chronic consequences (including carcinoma) and it is reasonable and necessary to assess for its presence on every gastric biopsy. As patient characteristics vary from practice to practice, the individual practitioner must determine what is appropriate for his or her particular patient population. In a recent survey of the membership of the Rodger C. Haggitt Gastrointestinal Pathology Society (GIPS), nearly 50% reported use of at least one ancillary stain to detect *Helicobacter* in all gastric biopsies.[4] The GIPS survey results were included in a white paper on the use of ancillary stains for identifying *H. pylori*. The group concluded that, performing "up front" staining on all gastric biopsies is "generally unnecessary," although they have outlined several instances in which staining upon review of the H&E is recommended.

In contrast, a 2009 UK-based study of 167 pathology departments concluded that "there is a strong argument for the routine deployment of special stains in the oesophagus, stomach, and duodenum."[17]

Special and/or immunohistochemical stains (e.g., AB-PAS, D-PAS, CDX2, etc.) may be used to detect intestinal metaplasia. Employment of these ancillary stains will generally assist in the detection of rare goblet cells, while more extensive intestinal metaplasia is generally detected on the H&E. For example, Harrison and colleagues, in a set of 92 cases with endoscopically apparent columnar-lined esophagus in which at least 6 biopsies had been taken, found that the addition of alcian blue/periodic-acid Schiff staining increased the rate of detection of intestinal metaplasia by 5.4%.[15]

Regarding the use of ancillary techniques for the detection of H. pylori, performance of these is often reasonable and necessary. There are clinical and pathologic associations with H. pylori infection. These may include but are not limited to the following: a) chronic active gastritis, b) chronic inactive gastritis (especially if concomitant ulcer disease, MALT lymphoma, or duodenal lymphocytosis are present; the patient has a history of treated H. pylori infection; or the patient is from an H.pylori-endemic geographic region), c) lymphocytic gastritis, d) chronic active carditis, e) chronic inactive carditis - the latter, if gastric biopsies are unavailable. It is generally accepted that either special stains or immunohistochemistry may be used to assist in the identification of H. pylori organisms.

dLCD Statement: Other examples of special stains or IHC that are not reasonable and necessary on every specimen include:

- Esophagus – fungal stains, trichrome, DPAS, CDX-2 or other mucin stains
- Gastric – AB-PAS, D-PAS, CDX-2 or other mucin stains, or special stains or IHC for H. pylori, or neuroendocrine markers such as synaptophysin or chromogranin
- Duodenum – AB-PAS, D-PAS, CD3, and trichrome, or other mucin stains
- Colon – CD3, p53 trichrome
- Hyperplastic polyps – Ki67, CK20, p53, CEA, BRAF
- Tubular or tubulovillous adenoma – Ki-67, CK20, CEA, p53, MMR

CAP Comment: These statements imply that these stains are not often indicated. Several examples follow:

Trichrome staining may be used to highlight a thickened subepithelial collagen table in suspected cases of collagenous gastritis. Gastrin and general neuroendocrine stains are very helpful to highlight pyloric metaplasia and neuroendocrine hyperplasia in suspected cases of atrophic gastritis.

In the duodenum, CD3 staining may be useful to highlight T-cells in cases with borderline intraepithelial lymphocytosis suspicious for celiac sprue. Trichrome staining is again useful in suspected cases of collagenous sprue. Special and immunohistochemical stains for mucin and infectious agents may be needed, e.g. to establish a diagnosis of Whipple's Disease or mycobacterial infection.

In the colon, CD3 staining may again be helpful in cases with borderline intraepithelial lymphocytosis, and Trichrome staining is again useful to diagnose collagenous colitis, especially in its distinction from lymphocytic colitis. p53 staining may be useful throughout the tubal gut (especially Barrett's esophagus, gastritis with intestinal metaplasia, and inflammatory bowel disease) to help distinguish reactive atypia from dysplasia.

Immunohistochemistry is useful in the evaluation of colon polyps in multiple situations. Sessile serrated polyps are often difficult to distinguish from hyperplastic polyps; the distinction is important, with bearing on the risk of neoplastic progression and on the colonoscopic surveillance interval. Immunohistochemistry may be useful in select cases to adjudicate this differential; potentially useful markers include Ki-67, CK20, MUC6, and annexin A10.[12,28,46] Absence of mismatch repair (MMR) protein expression is noted in 2/3^{rds} of adenomas from Lynch syndrome patients, and MMR testing may be indicated to support or refute that diagnostic consideration. The

NCCN Genetic/Familial High-Risk Assessment Colorectal Guideline specifically states that "**MSI and/or IHC testing of large polyps** when a tumor sample is not available **is justified in high-risk families**".[27]

dLCD Statement: Scientific data demonstrate that the combined number of gastric biopsies requiring special stains or IHC is roughly 20% of biopsies received and examined in a pathology practice.

CAP Comment: This statement appears to be derived specifically from a 2006 study by CL Wright and JK Kelly published in the *American Journal of Surgical Pathology* entitled "The use of routine special stains for upper gastrointestinal biopsies." This study represents the experience of two pathologists within a single anatomic pathology group (specifically at Royal Jubilee Hospital in Victoria, British Columbia), and, thus, the results are not necessarily generalizable.[51]

As mentioned above, this 20% figure is derived from a single pathology practice. It does not take into account at all the other instances in which special and/or immunohistochemical stains are helpful or necessary in gastric biopsies, including but not limited to gastrin and chromogranin immunohistochemistry for the diagnosis of atrophic gastritis, Ki-67 immunohistochemistry in neuroendocrine tumors, and HER2 immunohistochemistry in advanced gastric cancer. It also assumes a lack of utility for mucin histochemistry, though the reported incremental increase in detection of intestinal metaplasia with these special stains in other studies is 25-250x higher than in Wright and Kelly's.[15,25]

It assumes a constant rate of histologic chronic gastritis without demonstrable *Helicobacter* at 20%. The rate of *Helicobacter* gastritis has been shown to vary in the United States from state to state between 3 and 30%.[40] It is reasonable to assume that the frequency of chronic gastritis without demonstrable *Helicobacter* might vary similarly, based on geographic considerations as well as patient demographics. The GIPS *Helicobacter* white paper quotes a frequency of chronic active gastritis at 30%; chronic inactive gastritis is probably even more frequent, with a ratio of inactive to active cases in one national biopsy series of 4:1.[11] Non-Helicobacter chronic gastritis is especially prevalent in patients with inflammatory bowel disease (~20%), but this diagnosis can only be made after the exclusion of *Helicobacter* infection with ancillary stains.[11] The demographics of the patient beneficiary population will impact the prevalence of Helicobacter pylori –suspicious histologic features in a given population.[7,16,20] In addition, the "floor" for the distinction of mild chronic gastritis from normal is not well-defined and is thus subject to intra and inter-observer variability, influencing the rate of chronic inactive gastritis and thus the utilization of ancillary stains for *Helicobacter*.[6]

dLCD Statement: The policy states that, "over utilization of special stains has also been observed with duodenal biopsies where CD3 and AB/D-PAS are reportedly used to help exclude intraepithelial lymphocytosis and gastric metaplasia. Both of these conditions, if present, are easily recognizable on H&E morphology."

CAP Comment: It is unclear how the author(s) assessed the ease of recognition by a pathologist of these conditions in all clinical and histological milieus. This comment is out of place and inappropriate in an LCD. This would be the equivalent of stating that appendicitis is always clinically obvious and thereby never warrants a CT scan to evaluate a patient for whom appendicitis may be in the differential diagnosis.

In the duodenum, CD3 staining may be useful to highlight T-cells in select cases (e.g., borderline intraepithelial lymphocytosis suspicious for celiac sprue). Similarly, mucin stains to detect foveolar metaplasia are useful in certain circumstances. Specific references to substantiate the claim that "Overutilization of special stains has also been observed with duodenal biopsies" have not been cited.

dLCD Statement: Architectural and histologic features define colonic polyps including hyperplastic, inflammatory, and adenomatous lesions. Special stains and/or IHC stains are not reasonable and necessary for colon polyps despite text books noting, for example, thickened subepithelial collagen demonstrated by trichrome or collagen staining in hyperplastic polyps, or carcinoembryonic antigen (CEA) over expression in hyperplastic polyps. While the information is of academic interest, special stains are not reasonable and necessary to make the diagnosis of various colonic polyps.

CAP Comment: There are numerous instances where special stains and immunohistochemistry are useful in the evaluation of colon polyps. Specific examples in which ancillary techniques may be of value include, but are not limited to: a) distinction of sessile serrated polyp/adenoma from hyperplastic polyp, b) detection of deficient mismatch repair function which might suggest a diagnosis of Lynch syndrome and, c) situations where special stains may be helpful in identifying stromal invasion and therefore establishing a diagnosis of carcinoma.

dLCD Comment: 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 (CRC) diagnosed at age =50 years of age.
- CRC with high levels of microsatellite instability (MSI-H) histology diagnosed in an individual who is < age 60 regardless of age.
- Patients with synchronous, or metachronous CRC or other Lynch-associated tumor, regardless of age.
- Patients > 70 years of age who meet the revised Bethesda guidelines.
- Individuals with endometrial cancer diagnosed before age 50.

CAP Comment: This draft LCD appears to be referencing NCCN Guidelines, although in an incomplete manner; also, these NCCN Guidelines are internally inconsistent.

The Colon Cancer Guideline *does* recommend testing in colorectal cancer patients diagnosed at age ≤70 years old, as well as those >70 years old who meet Bethesda criteria[26]. The proposed less than 50 year old threshold deviates significantly from this and other guidelines discussed below. The guideline also suggests that "MMR testing should be considered for patients with stage II tumors," in which case the testing, in addition to screening for Lynch syndrome, provides the additional benefit of informing the decision as to whether to pursue adjuvant therapy. Thus, in the case of a stage II colon cancer in a patient over 70 failing to meet Bethesda criteria, MMR and/or MSI testing should not be denied.

The Genetics/Familial High-Risk Assessment: Colorectal Guideline similarly endorses testing in all patients <70 and in those ≥70 meeting Bethesda criteria.[27] It also recommends testing in two other scenarios not mentioned by the author of this draft LCD:

1. Patients with known Lynch syndrome in the family
2. Patients ≥5% risk of Lynch syndrome based on one of several clinical prediction models (e.g., MMRpro, PREMM, MMRpredict)

As an alternative to age-based or Bethesda-guideline-driven "selective testing," this **NCCN Guideline co-endorses universal testing of colon cancer patients** (i.e., screening of all colon cancers with MMR and/or MSI testing). . From this and other examples addressed above and below, it is apparent that the authors of the dLCD have selected references and sections of references to support preconceived notions of appropriate utilization which may be based on financial costs rather than the statutory and regulatory standard of reasonableness and necessity.

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[35] and the Association for Molecular Pathology (AMP) Mismatch Repair-Defective CRC Working group.[10] A subsequent cost-effectiveness analysis from the EGAPP demonstrated an incremental cost-effectiveness ratio for universal testing similar to that seen with screening colonoscopy.[24]

The Association for Molecular Pathology white paper specifically recommends concurrent mismatch repair protein immunohistochemistry, microsatellite instability testing, and *BRAF* V600E mutation analysis on all colon cancers.[10] The NCCN Guidelines do not recommend a specific algorithm because MMR IHC-based and MSI-

based algorithms have been shown to perform similarly.[26,27] These tests may be performed in series, rather than in parallel, to maximize the sensitivity for detecting Lynch syndrome (i.e., we concur that if IHC is done first and is normal, MSI testing may be warranted) without having to perform MSI testing in the ~15% of colon cancers with abnormal MMR IHC results (i.e., we concur that MSI testing is generally not warranted if IHC is done first and is abnormal). Occasionally the results of either MMR IHC or MSI testing is equivocal in which case interpretation may be aided by knowledge of the results of the complementary test (e.g., in neoadjuvant-treated cancers in which MMR IHC testing may be difficult to interpret).[3,34]

Special Stains and/or IHC for Prostate Pathology

dLCD Statement: 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 Comment: We believe that prostate IHC generally requires one or two basal markers and AMACR because of the tiny size of the atypical focus and the fact that it is often present on only one or two profiles, thus, AMACR cannot be restricted to cases with negative basal markers because the markers and the AMACR are typically performed together in order to conserve the limited amount of tissue obtained through the small gauge needle used for prostate biopsy.

dLCD Statement: 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 PIN-4 testing.

CAP Comment: There are indications to utilize ERG in high-grade prostatic intraepithelial neoplasia (HGPIN) diagnosed on H&E and/or immunohistochemical stains. In patients with HGPIN, those who express ERG have a higher risk of progression to developing adenocarcinoma than patients who have HGPIN and do not express ERG. Furthermore, basal cell markers are not always positive in benign acini (i.e., atrophy, inflammation, etc.) and are not always negative in cancer. The addition of AMACR adds significant information that is complementary to the basal cell markers and is required in combination in order to adjudicate between benign and malignant diagnosis. The suggestion that AMACR be used only after the use of basal cell markers is impractical as suspicious foci are typically small and may be lost on deeper levels of the paraffin tissue block. In fact, in a study by Green et al, in 52 cases of suspicious lesions, deeper sections did not contain the worrisome focus in 31cases.[13]

dLCD Statement: Neuroendocrine markers, such as IHC for synaptophysin, may be indicated in cases of recurrent/metastatic prostate carcinoma that have undergone small cell transformation after hormone therapy. The latter marker is only necessary for high grade, undifferentiated tumors and should not be used routinely.

CAP Comment: These markers are also necessary for accurately classifying low grade neuroendocrine tumors (carcinoid tumors) of the prostate.[23]

dLCD Statement: The use of PIN-4 is best restricted to evaluation of morphologically highly suspicious foci.

CAP Comment: PIN-4 can also be used to differentiate high-grade prostatic intraepithelial neoplasia (HGPIN) from a focus of cribriform pattern of Gleason pattern 4 adenocarcinoma. Furthermore, the published literature has been unable to stratify suspicious foci into suspicious and “highly suspicious” subsets, despite repeat attempts.[5]

dLCD Statement: It is not reasonable and necessary to bill for 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 Comment: We disagree with the conclusion that IHC would not provide additional information if adenocarcinoma is detected on another core biopsy. For example:

1) If cancer is reported in only one core, it may appear to be a low volume tumor for which active surveillance is recommended, but confirming cancer in other cores might indicate a more extensive tumor for which surgery or radiation is considered as staging may change.

2) If the patient has only a single focus of low grade (Gleason pattern 3) carcinoma, he would probably have only 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 this case, IHC testing of those foci could have a major impact on patient management.

NCCN Guidelines Version 1.2015 Prostate Cancer (10/24/2014) state:

For very low risk group patients, defined as T1c with Gleason score equal or less than 6, PSA less than 10 ng/m, fewer than 3 prostate biopsy cores positive, equal or less than 50% of cancer in any core, PSA density <0.15ng/mL/g, 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; observation if expected survival is less than 10 years.

For pathologists it is of the highest importance to determine the number of cores involved and the percentages of tumor in each core as this information provides actionable information to the treating physician.

dLCD Statement: Prostate cases that may require reasonable and necessary IHC staining include but are not limited to the following:

- Indeterminate/suspicious focus and no other cores are positive for cancer;
- Single worrisome core with minimal % tumor (roughly <5%);
- Single worrisome core contralateral to a positive core(s); unless the patient is to be treated with unilateral XRT, billing for IHC on the contralateral side to a positive prostate cancer diagnosis is not reasonable and necessary;
- Identify tumor invasion of adjacent structures;
- Determine origin of undifferentiated/poorly differentiated neoplasm, such as bladder vs. prostate;
- Other unexpected results when specific cell stains would be necessary

CAP Comment: There are lesions larger than 5% that can mimic prostatic adenocarcinoma on a prostate biopsy. These lesions would require immunohistochemical stains including HMWCK, p63, AMACR (racemase) or PIN-4.

It is necessary to perform immunohistochemical staining of small suspicious lesions on contralateral cores in a patient with definitive adenocarcinoma diagnosed on the opposite side of the prostate gland. These stains include HMWCK, p63, AMACR (racemase) or PIN-4. There are universally accepted guidelines (NCCN) in which the urologist and/or oncologist utilizes the presence of adenocarcinoma and percentage of the core length involved with adenocarcinoma at multiple sites including but not limited to the right and left sides of the prostate gland in determining treatment. The treatment decision may include surveillance of the patient, radiation, and/or surgical resection. Clinical decisions are made based on the percentage of tumor present and the number of sites or quadrants the tumor is present in prostate biopsies of a patient.

SEE FOLLOWING NCCN GUIDELINES.

AJJC Staging Manual

NCCN Guidelines Version 1.2015 Prostate Cancer (10/24/2014)

Low Risk Group Patients, defined as T1-T2a, Gleason score equal or less than 6 and PSA < 10 ng/mL, the

initial therapy can be active surveillance, EBRT or brachytherapy, or RP +/- PLND if expected survival is 10 or more years or, observation if expected survival is < 10 years.

T2a is defined by AJCC Staging as the cancer in one half or less of only one side (left or right) of the prostate gland.

Special Stains and/or IHC for Lung Cancer

dLCD Statement: Experts in pulmonary pathology recommend starting the evaluation of non-small cell carcinomas with a combination of TTF-1 and p40 or p63 IHCs. Often these two stains are all that are needed to come to a reasonable diagnosis and retain enough tumor sample to complete molecular studies. In rare patients, a few additional IHCs or mucin stains may be needed.

CAP Comment: It is not rare to need additional IHC stains. It is not uncommon to get equivocal results on the first stains and additional ones are needed. It is frequently necessary to exclude metastatic carcinoma as part of the diagnostic workup, requiring multiple additional markers. Napsin-A is also important to make the diagnosis of pulmonary adenocarcinoma, especially in TTF-1 negative cases. Mucin stains may be utilized in some cases. In the upcoming WHO histologic classification of lung tumors, there is a comment indicating that mucin stains may be used to exclude solid pattern ADC before performing 2 marker-panel IHC. Furthermore, the differential diagnosis of primary lung carcinoma commonly includes metastatic carcinoma. Not uncommonly, it is critical to subsequent treatment decisions to determine the origin of a carcinoma presenting as a lung mass.

Ki-67/MIB-1

dLCD Statement: Furthermore, Ki-67/MIB-1 antibodies have suffered from a lack of international standardization which has limited their clinical usefulness.

CAP Comment: Ki-67 immunohistochemistry has been well-vetted, perhaps with greatest experience in gastroenteropancreatic neuroendocrine tumors, in which determination of the Ki-67 "proliferation index" is an essential component of tumor grading in the 2010 WHO Classification of Tumors of the Digestive System.[36] This system specifies that grade requires "mitotic count in at least 50 HPFs and Ki67 index using the MIB antibody as a percentage of 500-2000 cells counted in areas of strongest nuclear labeling ("hot spots").

Ongoing scientific inquiry is centered not on whether Ki-67 immunohistochemistry is valid, but rather on finer points including, a) what represent the optimal proliferation index cut points (e.g., >2% vs. >5% to assign an intermediate grade) and, more importantly, b) how the Ki-67 proliferation index will be best incorporated along with traditional histologic features (e.g., mitotic activity, necrosis, architecture) in contemporary grading systems.

In well-differentiated neuroendocrine tumors of the GI tract, the grade assigned based on the Ki-67 proliferation index has been shown to be greater than that assigned based on mitotic counting in one-third of cases, and in these instances, survival is determined by that higher grade, proving the value of Ki-67 immunohistochemistry in this setting.[48] Determination of Ki-67 proliferation indices is more objective and reproducible than traditional mitotic counting, and interobserver agreement of proliferation index determination has been proven to exceed that of mitotic counting, including in pulmonary carcinoids.[49]

The reference to a lack of international standardization appears to have been taken out of context. The relevant reference cited acknowledges that "there is no uniform methodology for Ki-67 IHC and evaluation of results," but goes on to say, "most studies pinpointed monoclonal antibody MIB-1 on paraffin sections after antigen retrieval procedures and the assessment of the Ki-67 labeling index (LI) as the most widely agreed-upon methodologies, which have been optimized within each laboratory by longstanding experience with this marker." This is a conspicuous example of the use of highly selective and partial literature citation, which undercuts the credibility of the purported evidence base of this dLCD.

IHC for Chemosensitivity and Resistance Tumor Profiling

CAP Comment: It is difficult to comprehend what is being described in this section. The first two paragraphs discuss predictive factor testing and contrast that in the third and part of the fourth paragraphs with chemosensitivity/resistance assays. The last part of paragraph 4 is not clear due to incomprehensible sentence construction. The long bulleted list of "IHC panels" is not clearly described, does not follow what comes before,

and mostly does not represent IHC assays (most of these are molecular tests). It appears to be describing acceptable companion diagnostics, but the construction of this section is such that the intent of the carrier is unclear.

IHC for Cervical/Gyn/Bladder/Kidney Tumors

dLCD Statement: Claims data indicate combinations of gram stain, PAS, Ki-67, p16 and ProExC stains on all cervical biopsies from select pathology practices, and combinations of p53, Ki-67, CD20 and CD44 on bladder biopsies from select pathology practices.

Similarly, it is rare to need stains to prove that an endometrial or ovarian cancer is a serious (sic) cancer or that a kidney neoplasm is an oncocytoma or an eosinophilic or chromophobic renal cell cancer. The use of IHC stains in these circumstances requires adequate documentation in the pathology report, such as "Because the differential histologic diagnosis is between an endometrioid carcinoma and a serious carcinoma, I performed an xxx stain. The controls worked appropriately and the results were positive indicating the tumor is a yyy."

CAP Comment: In various circumstances IHC stains are useful in the evaluation of cervical lesions or ovarian neoplasms.[14,39,47] Distinction between serous carcinoma and other types of endometrial and ovarian carcinoma is clinically relevant as the results help determine the need for and type of adjuvant therapies. In morphologically ambiguous cases, immunohistochemistry performed at the discretion of the pathologist is helpful in making such a determination.[38]

Bladder*:* In certain situations IHC can be critical to achieving the correct diagnoses of a bladder specimen. Expert Genitourinary pathologists recently published a consensus statement regarding useful IHC stains in the context of bladder cancer and bladder biopsy IHC.[1] They highlight the utility of IHC in the following contexts:

a) Confirmation of a urothelial primary at a metastatic site, or addressing the possibility of metastases to the bladder;

b) Distinction of reactive urothelial atypia from carcinoma in situ. diagnosis;

c) Role of IHC in staging bladder cancer. Experts acknowledge the utility of cytokeratin immunohistochemical staining to identify invasive tumor cells when "there are few cells, there is significant cautery artifact or there is an intense inflammatory infiltrate obscuring invasion of the tumor cell." They mention that desmin staining could also be useful when the morphologic differential diagnosis requires separation of muscle from desmoplasia. Muscularis propria invasion is an important cut-point in clinical management and prognosis for invasive urothelial carcinoma, especially in terms of surgical decision-making for cystectomy/partial cystectomy (NCCN guidelines, version 2.2104);

d) Distinction between spindle cell lesions of the bladder. In terms of the rare but potentially malignant spindle cell lesions of the bladder (such as, but not limited to, pseudosarcomatous myofibroblastic proliferation/inflammatory myofibroblastic tumor (PMP/IMT), sarcomatoid urothelial carcinoma, leiomyosarcoma, and rhabdomyosarcoma), experts acknowledge that judicious IHC in the context of morphology has an important supportive role in this differential diagnosis setting, particularly among the tumors in the malignant category.

Kidney*:* Classification of renal tumors has changed with the characterization of important new morphologic and clinical variants of renal neoplasia, which differ in molecular genetics, prognosis and available therapies. In 2013, experts in genitourinary pathology, under auspices of the International Society of Urologic Pathology (ISUP), extensively reviewed the literature and proposed updates to the classification scheme for renal tumors.[41] Many of these new entities were characterized based on IHC and molecular features, and as described above, have clinical relevance. Another subgroup of ISUP recently reviewed literature and surveyed experts on IHC in renal tumors, resulting in a consensus publication.[45]

The expert authors acknowledge that while morphology plays the major role in classification of renal tumors, IHC and other ancillary studies may be helpful in the following scenarios, among others: verify histologic subtype, or to distinguish primary RCC from benign mimics and other tumor types that can occur in the kidney or from the rare metastasis to the kidney. Metastases of RCC to distant sites also usually need to be confirmed with the use of a panel of markers. The classification of the tumor type on limited material, such as core

biopsies, may warrant immunohistochemical assessment from their survey, 87% of expert GU pathologists use IHC "occasionally" or "sometimes" in histologic subtyping. These experts further state that Oncocytoma, angiomyolipoma, and metanephric adenoma are benign mimics of RCC. Morphologic distinction can be problematic on occasion, and immunohistochemistry may then be required to assist in confirming the diagnosis.

Several recent reviews highlight the important role of IHC in subtyping RCCs in unique settings. Ross, Martignoni and Argani (Johns Hopkins) review the differential diagnosis of RCC with both clear cell and papillary features, and the important role of IHC and other ancillary studies in classifying tumors with this rare constellation of morphology and outcome differences.[37]

Kryvenko et al. from the same institution review the differential diagnosis of eosinophilic renal neoplasms, including judicious use of immunohistochemistry.[18] In contrast to the statement above that "it is rare to need stains to prove that….a kidney neoplasm is an oncocytoma or an eosinophilic or chromophobic renal cell cancer," these expert authors state, "Although in excision specimens with the classic morphology of oncocytoma the use of CK7 may be avoided, in core biopsy specimens CK7 immunostain is more widely accepted to avoid misclassification of low-grade RCC as oncocytoma".

IHC for Skin & Cutaneous/Soft Tissue/CNS & Peripheral Nervous System Lesions

dLCD Statement: Many CNS and peripheral nervous system lesions are readily diagnosed with routine stains. It is unusual for a meningioma to require an IHC. The primary role of IHC for CNS and peripheral nervous system lesions is to differentiate primary from metastatic lesions.

CAP Comment: These statements are not accurate. For meningiomas, a measure of proliferation index is of prognostic significance which requires Ki-67 staining. Neuro-oncologists often request information on progesterone receptor status to guide possible treatment decisions as well. It has been established in the literature that expression of progesterone receptor may relate to tumor grade and recurrence of these neoplasms.[30] Although some meningiomas do not require immunohistochemistry staining to identify them as meningioma, specific pathological subtypes may require immunostains to adjudicate the differential diagnosis. Similarly, for gliomas for grade II tumors, proliferation markers are prognostically important. For all gliomas, the classification and treatment decisions require knowledge of IDH1 mutation status (which can be more rapidly and more cheaply determined by immunohistochemistry stains if the canonical mutation is present). Similarly, the status for 1p/19q co-deletion is critical (and this can be approached in a surrogate manner through the use of p53 staining).

dLCD Statement: 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. A minority of skin lesions require immunostains (e.g., atypical fibroxanthomas, Merkel cell lesions, lymphomas). Most common skin lesions (e.g., seborrheic keratosis) do not require IHC stains. Use of IHC morphometric codes for skin lesions is incorrect coding.

CAP Comment: There are subsets of skin biopsies in which immunohistochemistry (IHC) and special stains are required for diagnosis. The dLCD statement about only a "minority of skin lesions" requiring immunostains is vague, incomplete (for example most vesiculo-bullous and infectious diseases require immuno-fluorescence or special stains for diagnosis) and incorrect (melanocytic lesions for example may require IHC). The proportion of these cases varies from practice to practice depending on the case mix, so a uniform policy that does not take into consideration individual variations is not applicable. By way of example, a referral center for melanocytic lesions will examine a higher percentage of ambiguous melanocytic lesions that require IHCs compared to a general dermatopathology practice. Moreover, the decision as to whether IHC is needed for diagnosis in a specific case is complex and may be dependent upon several factors including specific morphologic appearance, clinical presentation, clinical history patient demographics, anatomic location, and others. Establishing rigid exclusion criteria fails to take into consideration the complexity of this process and will likely prevent establishing the correct diagnosis in a significant number of cases. The decision to use a certain test should be left to the pathologist working on the case who is best positioned to determine the need for the test. The purpose of an LCD is to provide clear guidance on the circumstances in which it is appropriate to report services to Medicare for payment. Implementation of such sweeping guidelines in this vague and practice nonspecific form has the potential to negatively affect all pathologists in their provision of medically necessary services. The following are several more common examples in dermatopathology that routinely require the use of

IHC and special stains:

1. Melanocytic lesions. Histologic diagnosis of melanocytic proliferations is difficult even by experts in the field as it requires integration of multiple criteria. While most lesions can be diagnosed by histology alone, there is a category of melanocytic lesions that cannot be reliably classified as benign or malignant by conventional histologic examination.[52] These lesions include dysplastic nevi with severe atypia, atypical Spitz nevi and Spitz tumors, atypical blue nevi, atypical deep penetrating nevi, clonal nevi and proliferative nodules which cannot be reliably distinguished from melanoma as well and nevoid melanomas that are often misdiagnosed as nevi. Such lesions require ancillary IHC stains to refine the diagnosis in almost all instances. The most common IHC stains used in these instances include dual labeling for Ki-67/ Melan-A, HMB-45 and p16.[8,31] There are other indications for IHC in melanocytic proliferations. Desmoplastic melanomas are notoriously prone to be missed on histologic examination alone.[21] IHC helps in differentiating desmoplastic/ spindle cell melanoma from a desmoplastic or sclerosing nevus (S100, MART1, HMB-45), differentiating desmoplastic melanoma from a scar (S100, SOX10, p75) or delineating the extent and depth of a desmoplastic melanoma (S100, SOX10, p75).[8,31]

2. Sentinel lymph nodes. Sentinel lymph node (SLN) biopsy is routinely performed as part of the therapy and staging protocols in melanomas with a Breslow depth deeper than 1 mm, for Merkel cell carcinomas (MCC) or for other high grade cutaneous carcinomas.[32,33] Typical protocols for SLN include routine IHC staining.

3. Cutaneous lymphomas, myeloid and histiocytic derived tumors. These tumors require IHC stains most of the time for a correct classification.

4. Differential diagnosis of dermal spindle cell tumors. Several spindle cell tumors involving dermis including desmoplastic melanoma, atypical fibroxanthoma, spindle squamous cell carcinoma, leiomyosarcoma and spindle cell variants of angiosarcoma have overlapping histologic features. IHC including S100, various cytokeratins, p63, smooth muscle markers and endothelial markers are usually employed to establish a diagnosis.[9]

5. Infectious lesions. Histological identification of infectious organisms in skin biopsies most often requires the use of special stains. Common stains used are GMS and PAS for fungal elements, Ziel-Nielson and Fite for mycobacteria, Gram stain for bacteria and Giemsa stain for parasites.

6. Vesiculobullous lesions. All immunologically mediated vesiculobullous lesions require immunofluorescence for a correct diagnosis and classification.[22]

dLCD Statement: Similarly, most soft tissue lesions do not require IHC stains or other “special” stains. Soft tissue masses may require stains (e.g., smooth muscle differentiation in a malignant mass) but the most do not.

CAP Comment: Soft tissue tumors/skin tumors, like lymphomas, require immunophenotype for classification, prognosis and treatment. It is very important to separate tumors of different immunophenotype, even within the same diagnosis, based on syndromic associations and prognosis. In soft tissue and skin, benign and malignant tumors mimic each other and it is important to immunophenotype these tumors in order to correctly classify them and understand their behavior. Examples when a panel of immunohistochemical stains must be used include undifferentiated pleomorphic, round cell, and spindle cell soft tissue tumors. IHC helps to separate these mesenchymal tumors from spindle cell carcinoma and melanoma which have a different treatment protocol. The requirement for immunohistochemistry in soft tissue tumors is dependent upon the individual case, clinical and radiologic features, anatomic location, depth, patient demographics, and specific morphologic appearance. This decision must be made by the individual pathologist who is signing out the case and is ultimately responsible for the diagnosis.

APPENDIX

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