Fung Maxwell (Orcid ID: 0000-0003-1771-8257)
Vidal Claudia (Orcid ID: 0000-0003-2672-4974)
Cassarino David (Orcid ID: 0000-0001-8875-0858)
Comfere Nneka (Orcid ID: 0000-0002-8001-2639)
Emanuel Patrick (Orcid ID: 0000-0003-1068-6969)
Kim Jinah (Orcid ID: 0000-0002-5065-5916)
Linos Konstantinos (Orcid ID: 0000-0001-9462-652X)
Missall Tricia (Orcid ID: 0000-0001-9062-0606)
Motaparthi Kiran (Orcid ID: 0000-0003-0562-0826)
PATEL Rajiv (Orcid ID: 0000-0002-1521-4947)
Sundram Uma (Orcid ID: 0000-0002-0695-0045)
Hosler Gregory (Orcid ID: 0000-0002-6281-0565)
Hurley Maria (Orcid ID: 0000-0002-1162-7250)
Messina Jane (Orcid ID: 0000-0002-0332-0224)
Plaza Jose (Orcid ID: 0000-0003-1123-5078)
Prieto Victor (Orcid ID: 0000-0001-9204-7161)
Subtil Antonio (Orcid ID: 0000-0002-6401-1900)

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Title:

Appropriate Use Criteria (AUC) for Ancillary Diagnostic Testing in Dermatopathology: New Recommendations for 11 tests and 220 clinical scenarios from the American Society of Dermatopathology AUC Committee

Authors:

Committee Members:

Maxwell A. Fung (Vice Chair),[1] Claudia I. Vidal (Chair),[2] Eric A. Armbrecht,[3] Aleodor A. Andea,[4] David S. Cassarino,[5] Nneka I. Comfere,[6] Patrick O. Emanuel,[7] Tammie Ferringer,[8] Alexandra C. Hristov,[4] Jinah Kim,[9] Scott R. Lauer,[10] Konstantinos Linos,[11] Tricia A. Missall,[12] Kiran Motaparthi,[12] Roberto A. Novoa,[13] Rajiv Patel,[4] Sara C. Shalin,[14] Uma Sundram[15]

Rating Panel:

Antoanella Calame,[16] Daniel D. Bennett,[17] Lyn M. Duncan,[18] Dirk M. Elston,[19] Gregory A. Hosler,[20] Yadira M. Hurley,[21] Alexander J. Lazar,[22] Lori Lowe,[4] Jane Messina,[23] Jonathan Myles,[24] Jose A. Plaza,[25] Victor G. Prieto,[26] Vijaya Reddy,[27] András Schaffer,[28] Antonio Subtil[29]

1. Departments of Dermatology and Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, California
2. Dermatology Center of Southern Indiana, Bloomington, Indiana
3. Center for Health Outcomes Research, Saint Louis University, Saint Louis, Missouri
4. Departments of Pathology and Dermatology, Michigan Medicine, University of Michigan, Ann Arbor, Michigan
5. Department of Pathology, Kaiser Permanente Southern California, Los Angeles, California

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6. Departments of Dermatology and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota
7. Clinica Ricardo Palma, Lima, Peru
8. Departments of Dermatology and Laboratory Medicine, Geisinger Medical Center, Danville, Pennsylvania
9. Palo Alto Medical Foundation, Palo Alto, California
10. Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, Nebraska
11. Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, and Geisel School of Medicine at Dartmouth, Hanover, New Hampshire
12. Department of Dermatology, University of Florida College of Medicine, Gainesville, Florida
13. Departments of Dermatology and Pathology, Stanford University School of Medicine, Stanford, California
14. Departments of Dermatology and Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas
15. Department of Anatomic Pathology, Oakland University William Beaumont School of Medicine and Beaumont Health Systems, Royal Oak, Michigan
16. Compass Dermatopathology, San Diego, California
17. Department of Dermatology, University of Wisconsin, Madison, Wisconsin
18. Pathology Service and Dermatopathology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts
19. Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina, Charleston, South Carolina
20. ProPath; Departments of Dermatology and Pathology, University of Texas Southwestern Medical Center, Dallas, Texas
21. Departments of Dermatology and Pathology, Saint Louis University School of Medicine, Saint Louis, Missouri
22. Departments of Pathology, Dermatology, and Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
23. Department of Dermatology and Cutaneous Surgery, University of South Florida, Moffitt Cancer Center, Tampa, Florida
24. Department of Pathology, Cleveland Clinic, Cleveland, Ohio
25. Departments of Pathology and Dermatology, The Ohio State University Wexner Medical Center, Columbus, Ohio
26. Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas
27. Departments of Pathology and Dermatology, Rush Medical College, Chicago, Illinois
28. Division of Dermatology, Florida State University College of Medicine, Tallahassee, Florida
29. Royal Jubilee Hospital, Victoria, British Columbia, Canada; Department of Pathology, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence**:** Claudia I. Vidal MD PhD**,** Dermatology Center of Southern Indiana**,** 1200 South Rogers Street**,** Bloomington, IN 47403 Email: vidalcmd@gmail.com

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ABSTRAC

Background: Appropriate use criteria (AUC) provide patient-centered physician guidance in test selection. An initial set of AUC were reported by the American Society of Dermatopathology (ASDP) in 2018. AUC reflect evidence collected at single timepoints and may be affected by evolving evidence and experience.

Objective: Update and expand AUC for selected tests.

Methods: RAND/UCLA methodology used includes: 1) Literature review; 2) Review of previously-rated tests and previously-employed clinical scenarios; 3) Selection of previously-rated tests for new ratings; 4) Development of new clinical scenarios; 5) Selection of additional tests; 6) Three rating rounds with feedback and group discussion after rounds 1 and 2.

Results: For 220 clinical scenarios comprising lymphoproliferative (light chain clonality), melanocytic (CGH, FISH, RT-PCR, TERT promoter), vascular disorders (MYC), and inflammatory dermatoses (PAS, GMS) consensus by panel raters was reached in 172/220 (78%) scenarios, with 103/148 (70%) rated "usually appropriate" or "rarely appropriate" and 45/148 (30%), "appropriateness uncertain."

Limitations: The study design only measures appropriateness. Cost, availability, test comparison, and additional clinical considerations are not measured. The possibility that the findings of this study may be influenced by the inherent biases of the dermatopathologists involved in the study cannot be excluded.

Conclusions: AUC are reported for selected diagnostic tests in clinical scenarios that occur in dermatopathology practice. Adhering to AUC may reduce inappropriate test utilization and improve health care delivery.

DISCLAIMER

The recommendations presented in this study were developed using the RAND Corporation (Santa Monica, CA)/University of California Los Angeles (RAND/UCLA) Appropriateness Method. Appropriateness ratings reflect an assessment by expert panel raters based on their best interpretation of the current literature combined with their clinical experience and judgement at the time of their development. Responsibility for decisions to test and test selection ultimately lie with the ordering physician who may assess multiple factors associated with an individual patient and clinical setting. The clinical scenarios used are not inclusive of all situations in which a test/study should or can be performed. Changes to these recommendations may be justified by future evidence and clinical experience.

1. INTRODUCTION

Amidst efforts to improve quality and efficiency and reduce waste in healthcare, a substantial portion of provided health care services remains inappropriate or equivocally appropriate (independent of payer or other factors).[1] While most studies of appropriateness in health care have focused on treatments,[2] the selection of ancillary diagnostic tests by pathologists remains an area conducive to appropriateness assessment.

Since 2015, the American Society of Dermatopathology (ASDP) has supported development of appropriate use criteria (AUC). AUC reflect the judgment of experts in the context of published evidence, yielding patient-centered conclusions about the degree of consensus regarding the appropriateness of an intervention (test).

Since AUC may be affected by new data and experience, we herein update and expand initial recommendations reported by the AUC Task Force in 2018.[3-6]

2. METHODS

Study design was based on the RAND Corporation (Santa Monica, CA)/University of California Los Angeles (RAND/UCLA) Appropriateness Method,[7] as previously reported.[4]

2.1 Ancillary diagnostic tests, clinical scenarios, definitions, literature review (Figure 1)

The ASDP AUC Committee designated four Committee subgroups, each composed of volunteer ASDP members with subject expertise: lymphoproliferative (NC, AH, US), melanocytic (AA, JK, KM, TM, RN, PO), soft tissue (KL, SL, RP), other (DC, TF, SS). Each subgroup: 1) proposed additional tests for AUC review, which were subsequently approved by the ASDP Executive Committee, and performed a literature review; 2) reviewed existing AUC data and recommended updates, if any; 3) reviewed definitions (Supplemental Table 1) and clinical scenarios and recommended any updates and/or new clinical scenarios.

New clinical scenarios were reviewed by clinical indication reviewers. Clinical scenarios were intended to represent > 85% of those encountered in routine practice.

Literature reviews included primary studies published in English from as early as 1940 through early 2019. Case series of n > 3 could be included if better evidence was lacking.[8-11] Prior AUC literature review served as the basis for an updated literature review.[12-16]

2.2 AUC rating process (Figure 1)

Fifteen volunteer panel raters with collective balance and expertise were recruited. Twelve ASDP members were selected for expertise in at least one subgroup. Others were nominated by American Academy of Dermatology (DB, AC) and College American Pathologists (JM, VR) to represent the views of dermatologists and pathologists. Panel raters received background information, rating instructions, subgroup literature reviews, and a booklet of definitions and clinical scenarios. All ratings were required to be performed individually. Panel raters were instructed to rate the level of appropriateness of each test/scenario using their own best judgement in the context of their assessment of the literature, *without* comparison between tests, consideration of test costs, or other factors.

Three rounds of rating were predetermined and conducted as previously described,[4] including a summary of the literature review presented by each subgroup prior to discussion at ASDP 56th Annual Meeting (October 19, 2019). Panel raters explored wording and definitional

understandings of clinical scenarios. Brief discussion was also conducted after round 2 via teleconference.

The adjusted mean of ratings for each clinical scenario was created by removing the highest and lowest scores (mean' or adj *M*). Previously utilized parameters were used. (3) A mean' of $\geq$ 7.0 was classified as "usually appropriate"; mean' of $\leq$ 3.0 was classified as "rarely appropriate". Clinical scenarios with mean' between 3.1 and 6.9 with a standard deviation $\geq$ 2.0 were designated as not having reached consensus ("no consensus"). Clinical scenarios with mean' of $\geq$ 4.0 and $\leq$ 6.0 with a standard deviation < 2.0 were classified as having reached a consensus of "uncertain appropriateness." Clinical scenarios with a standard deviation <2.0 with a mean' between 6.1 and 6.9 were classified as majority usually appropriate ("usually appropriate to uncertain") while those with a standard deviation <2.0 and a mean' between 3.1 and 3.9 were classified as majority rarely appropriate ("usually rarely appropriate").

RESULTS

Eleven ancillary diagnostic tests and 220 clinical scenarios were studied. Consensus by panel raters was reached in 172/220 (78%) scenarios, with 103/148 (70%) rated "usually appropriate" or "rarely appropriate" and 45/148 (30%), "uncertain appropriateness."

Lymphoproliferative Subgroup (Table 1)

Review of the literature indicated continued relevance of the previously developed AUC for T and B cell clonality by PCR. The Lymphoproliferative subgroup selected light chain monotypia (kappa/lambda immunohistochemistry (IHC) and *in situ* hybridization (ISH)) for AUC development. Summary and analysis of the literature was reported by Hristov and colleagues.[11]

Thirty-three clinical scenarios were rated for each test for a total of 66 ratings. Terminology followed the World Health Organization (WHO)(Supplemental Table 1)[17]. Consensus was reached in 38/66 clinical scenarios (58%). In general, AUC for kappa/lambda IHC and ISH in identical scenarios were largely the same with the exception of clinical scenarios 9 and 27.

For marginal zone lymphoma (MZL), there was panel rater consensus supporting the appropriate use of kappa/lambda IHC/ISH to evaluate any histologically suspicious tumor, whether or not the infiltrate was rich in plasma cells, as well as other scenarios wherein plasma cells were prominent, including suspected plasma-cell rich follicular lymphoma (FL) and clinically and histologically ambiguous infiltrates in which plasma cells were prominent. In contrast, for scenarios concerning diffuse large B cell lymphoma (leg type), chronic lymphocytic leukemia (CLL), IgG4-related disease, cases in which another cancer, such as Merkel cell carcinoma, was diagnosed with CLL, or cases in which a reactive process ("dermatitis") was favored, kappa/lambda IHC/ISH was rated "no consensus" or "rarely appropriate."

Melanocytic Subgroup (Table 2)

The Melanocytic subgroup added 3 new clinical scenarios to be rated for all tests and recommended AUC update for qRT-PCR. AUC updates for FISH and CGH were not recommended based on a current review of the literature. The subgroup selected *TERT* promoter (*TERT*-p) point mutation analysis for AUC review. Analysis of the literature for *TERT*-p was reported by Motaparthi and colleagues.[8] Updated and previously published literature reviews for

CGH, FISH, and qRT-PCR were provided to panel raters.[8,12] A total of 80 clinical scenarios were rated.

For CGH and FISH, the new clinical scenarios addressed the differential diagnosis of recurrent/persistent nevus versus melanoma and histologically ambiguous BAP-1 deficient tumors. Consensus was reached for FISH and CGH in 5/6 clinical scenarios (80%). Except for "no consensus" for FISH in BAP-1 deficient tumors, both CGH and FISH were rated in the context of recent data as "usually appropriate" or "majority usually appropriate" in these new clinical scenarios. To facilitate comparison, prior results for CGH and FISH are represented alongside new AUC in Table 2.

For qRT-PCR (23 genes, including: PRAME, S100A7, S100A8, S100A9, S100A12, PI3, CCL5, CD38, CXCL10, CXCL9 IRF1, LCP2, PTPRC, SELL, nine housekeeping genes) most clinical scenarios remained "uncertain" (23/37; 62%). Some clinical scenarios originally rated by the 2018 AUC Task Force panel raters as "uncertain appropriateness" were rated "majority usually appropriate," (6/37; 19%) including the differential diagnosis of nevus versus melanoma in fully sampled histologically ambiguous tumors in children and adults, partially sampled nevus versus melanoma in adults, nevus versus nevoid melanoma in children or adults, and nevus versus melanoma in cosmetically sensitive sites and special sites in pediatric population. Clinical scenarios for children and adults in which pathology is definitive for melanoma or definitive for nevus were rated "rarely appropriate." Similarly, distinction of incompletely sampled sclerosing (desmoplastic) nevus versus desmoplastic melanoma was also rated "rarely appropriate" in adults.

Clinical scenarios where pathology is definitive for melanoma or definitive for nevus were rated "rarely appropriate" for *TERT*-p, which is typically performed on paraffin tissue using PCR and direct sequencing. Several scenarios were rated "usually appropriate" or "majority usually appropriate." The strongest ratings were for *TERT*-p in pediatric spitzoid tumors, specifically, fully or partially sampled atypical Spitz tumor versus spitzoid melanoma. In adults, *TERT*-p was rated "majority usually appropriate" for fully or partially sampled atypical Spitz tumor versus spitzoid melanoma and for the distinction of nevus from metastatic melanoma. In the pediatric population, *TERT*-p was "majority usually appropriate" in clinical scenarios for the differential diagnosis of nevus versus nevoid melanoma or nevoid metastasis.

Soft Tissue Subgroup (Table 3)

The Soft Tissue subgroup did not find significant evidence warranting update of the t(17;22) in Dermatofibrosarcoma Protuberans (DFSP) AUC despite new data showing that a subset of DFSPs harbor an alternative rearrangement involving *PDGFD* gene fused to the *COL6A3* or *EMILIN2* gene.[18,19] Rather, FISH for this translocation may represent a candidate for AUC development in the future. The AUC for *EWSR1* FISH in clear cell sarcoma were also felt to remain relevant, ~~and~~ not necessitating update.

The Soft Tissue subgroup selected myc overexpression by immunohistochemistry (IHC) and *MYC* amplification by fluorescence *in situ* hybridization (FISH) in the diagnosis of angiosarcoma for AUC development. Review and analysis of the literature (1967-2018) covering 16 articles was reported by Motaparthi and colleagues.[9]

Fifteen clinical scenarios were rated for each test. The AUC for myc IHC and *MYC* FISH in identical scenarios were the same. The strongest consensus ("usually appropriate") supporting appropriate use of myc IHC or *MYC* FISH was for adults with radiotherapy-associated atypical vascular lesions (AVL) and for adults with chronic lymphedema of the extremities with pathology suspicious for angiosarcoma. In contrast, clinical scenarios involving sun damaged skin, or pathology definitive for angiosarcoma, or for AVLs without a history of radiation or lymphedema were either rated as "rarely appropriate" or "no consensus".

GMS and PAS stains (Other Subgroup) (Table 4)

The AUC for mismatch repair proteins in Muir-Torre Syndrome and the AUC for human papilloma virus immunohistochemistry and in situ hybridization were determined to not require update at this time. The Other subgroup selected Gömöri methenamine silver (GMS; Grocott-Gömöri) and periodic acid-Schiff (PAS) stains for AUC development. Review and analysis of the literature (from 1957 to May 2019) was reported by Shalin and colleagues.[10] Twenty-eight clinical scenarios were rated with 16 of these rated for PAS and GMS (44 total ratings). Consensus by panel raters was reached in 31/44 clinical scenarios (70%) scenarios, with over 50% rated "usually appropriate" or "majority usually appropriate". The ratings for GMS and PAS stains in identical scenarios were largely the same.

For nail clippings, panel rater consensus supported the appropriateness of obtaining either stain as part of the diagnostic evaluation, including pre-ordering a fungal stain.

For cutaneous dermatophyte infections, obtaining either fungal stain for clinical-pathologic scenarios in which clinical or histopathologic features were suspicious for tinea was rated "usually appropriate". However, there was "no consensus" supporting pre-ordering fungal stains for dermatophytosis or granulomatous dermatitis prior to evaluation of the H&E, even when infection was clinically suspected.

For biopsy-confirmed granulomatous dermatitis, obtaining a fungal stain, irrespective of whether infection was a clinical concern, was rated "usually appropriate".

An additional 12 scenarios addressed the appropriateness of PAS stains in lupus erythematosus (LE), dermatomyositis (DM), vasculitis, and vasculopathy. There was limited panel rater consensus ("majority usually appropriate") for the use of PAS to evaluate LE, DM, or vasculopathy if histopathologic features were compatible, but not based on clinical suspicion alone as a pre-ordered stain, or if diagnostic features of vasculopathy were already present on H&E. Pre-ordering a PAS stain for a clinical suspicion of vasculitis or vasculopathy was "rarely appropriate."

Previously employed panel rater response options of "unqualified" and "OUT" (i.e., assessment of appropriateness of test cannot be made without communication with clinician) were not used or requested during rating rounds.

DISCUSSION

In reporting new and updated AUC, we concomitantly recognize their time-limited nature. Considering evolving experience and evidence, the estimated average lifetime of AUC is approximately 5 years but can be shorter or longer depending on the pace at which new literature is generated. The goal of the ASDP AUC Committee has been to establish, develop, and re-assess AUC in a manner that is accurate and current, using methods that are supported by and representative of practicing dermatopathologists.

Lymphoproliferative

Our results support paired kappa/lambda IHC or ISH as appropriate in multiple clinical scenarios, including histologically suspected MZL and a variety of clinical settings in which evidence of light chain restriction in a plasma cell rich infiltrate may be decisive for diagnosis. Kappa/lambda IHC or ISH was rated "no consensus" or "rarely appropriate" if another diagnosis could be independently established, or if there was no *a priori* clinical index of suspicion for B cell lymphoma or lymphoid hyperplasia and plasma cells were scarce.

There were two clinical scenarios where discordant ratings were found for kappa/lambda IHC and ISH (Table 1, clinical scenarios – "Clinical presentation of solitary or multiple nodules, papules and/or plaques with clinical impression of B cell lymphoma (favored diagnosis of marginal zone or follicular lymphoma) and that is 'not diagnostic' for cutaneous B lymphoma." and "Clinical presentation of solitary or multiple erythematous annular patches/plaques that are suggestive of a dermatitis clinically, with histological and immunophenotypical features that are 'diagnostic of' chronic lymphocytic leukemia (plasma cells are plentiful)"). For both scenarios, the variance was slight and may simply reflect statistical noise. Other potential explanations for these discordant ratings include insufficient available evidence reflecting these scenarios and high background staining which may limit the utility of kappa and lambda IHC.[11]

Melanocytic

Diagnostic testing for melanoma remains a dynamic, evolving field with many tests available and under development.[8,12,20] Thus, melanocytic AUC represent an area where more frequent AUC updates may be most critical, especially for newer tests. In general, the AUC ratings indicate that in most scenarios, there are multiple options for an appropriate ancillary test.

The original AUC data supported CGH and FISH as "usually appropriate" in most scenarios, with the exception of uncertainty in the realm of blue nevus-type tumors, particularly for FISH.[4]

The new AUC ratings for qRT-PCR represent the first time dermatopathology AUC have been updated with a few shifting to "majority usually appropriate" for some key scenarios. This likely reflects increased clinical experience combined with new literature supporting test validity and clinical utility.[21] With greater experience and supporting literature, the strength and nature of consensus for qRT-PCR AUC in the studied clinical scenarios may continue evolving.

Similarly, for *TERT*-p analysis, the most frequent AUC result was a consensus of "uncertain appropriateness" (24/37, 65%), with the strongest degree of consensus supporting the appropriate use of *TERT*-p for the differential diagnosis of atypical Spitz tumor versus spitzoid melanoma. Some committee members noted that the existing literature would also seem to support the use of *TERT*-p in other clinical scenarios. Although clinical scenarios reflecting differentiation of fully or partially sampled nevus from melanoma in adult and pediatric patients were of "uncertain appropriateness," mean scores were on the upper end of the range, near "majority usually appropriate". In morphologically unambiguous nevi and melanomas, the identification of *TERT*-p hotspot mutations demonstrates a specificity near 100 percent and sensitivity near 80 percent.[22] As an important caveat, *TERT-p* mutations occur early in tumorigenesis and may be identified in dysplastic nevi and melanoma in situ, thereby potentially reducing the real world specificity of this test.[22-25]

Compared to CGH and FISH, qRT-PCR and *TERT*-p are newer tests. While panel raters are not asked to explain individual ratings, our results suggest that newer tests tend to have lower and less definitive ratings. We suspect this may be at least partially attributable to the fact that clinical experience lags the release of newly published data (for practitioners not involved in the published studies). As newer studies for qRT-PCR[26] and *TERT*-p[22] have been published, it may be anticipated that these will likely be candidates for AUC update.

MYC (myc IHC, *MYC* FISH)

Our AUC attest to the valuable role of myc IHC and *MYC* FISH for the diagnosis of angiosarcoma in post-radiation vascular lesions and also for any suspicious vascular lesion in chronic lymphedema involving upper/lower extremity. Although AUC do not support MYC as a

routinely employed diagnostic marker in the evaluation of primary angiosarcoma of the face or scalp in adults, or in any clinical setting in which pathology is definitive, the utility of a positive result in selected cases has potential for future study in other clinical scenarios such as HHV8-negative atypical vascular proliferations. There was "majority rarely appropriate" consensus for the use of myc IHC and *MYC* FISH for margin evaluation in skin excisions for angiosarcoma. While studies have not been reported in this scenario for *MYC* ISH, Mentzel et al suggested that myc IHC can highlight subtle AVL-like areas at the periphery of post-radiation angiosarcoma, suggesting a utility.[27] Perhaps a lack of clarity in the clinical scenarios or limited literature played into this rating, and additional clinical scenarios specifying the clinical setting (radiated, sun-damaged, chronic lymphedema) or specifying that the tumor was confirmed to be myc positive may show discrimination in the future.

PAS and GMS stains

PAS and GMS stains are among the most commonly ordered tests in dermatopathology, consistent with the high prevalence of dermatophytosis and their superior sensitivity and specificity over H&E, especially when few organisms are present. We did not specifically study PAS-diastase (PASD), a variation of PAS. Literature review did not often make this distinction. Since the presence of glycogen was irrelevant in the tested clinical scenarios in this study, identical AUC results for PASD may be presumed.

Our results support pre-ordering PAS or GMS for onychomycosis in nail clippings, which is not surprising given the superior sensitivity of the stains over H&E in nail clippings submitted to rule out onychomycosis. One difference between these stains is that GMS highlights living and dead organisms, whereas only viable organisms are highlighted by PAS;[10,28] our results did not indicate an attributable difference between these stains, likely because of limitations in the methodology employed to develop the AUC where tests are considered independently. Although one might favor the superior absolute sensitivity of GMS, detecting only viable organisms (i.e., by using PAS) might be more clinically relevant. Nail clippings represent a unique scenario in which the differential diagnosis is highly focused and the sensitivity of the stains when applied to nail specimens for the detection of onychomycosis is greater than that reported for cultures.[10] The rigid, brittle nature of the nail plate also creates

unique technical challenges. These considerations, along with considerations of relative cost, technical complexity, and test performance represent potential areas for future study.

For dermatophytosis and granulomatous dermatitis, compatible histology (not merely clinical suspicion) was required in order for a fungal stain to be rated "usually appropriate." It should be noted that clinical scenarios did not differentiate on specific types of granulomatous inflammation (i.e., necrobiotic, suppurative, etc). As some may approach these differently, it may be worth separating these out in future updates. Since PAS stains additionally highlight basement membranes and fibrin, we also tested clinical scenarios related to LE, DM, vasculitis, and vasculopathies. Our AUC support the appropriate use of PAS stain in these settings, judged on a per case basis after review of the H&E slide(s).

It should be recognized that the panel raters, while selected for broad representation and expertise, are only an approximation of the true population of test users. The possibility that the findings of this study may be influenced by the inherent biases of the dermatopathologists involved in the study cannot be excluded.In our study, the number of panel raters (15) was in the upper range in comparison to other studies using the RAND/UCLA methodology.[7] Nine of fifteen (60%) panel raters served previously.[4] While we did not pre-screen panel raters for conflict of interest (COI), none of the raters held any directly relevant COI that would preclude participation.

In practice, more than one ancillary test may be ordered for diagnostically challenging cases. This represents only the "tip of the iceberg" in translating AUC to clinical practice, where other factors may prevail that are not accounted for by RAND/UCLA. These may include real or perceived differences in test availability, test performance, turnaround time, specimen integrity, provider/patient preference, cost, and payer(s). Another unknown is the appropriateness of a test if pre-existing ancillary test data exists, including tests that have established clinical utility (MAF, personal observation) but lack extensive validation and not subjected to AUC review (e.g., p16, PRAME, which are viable tests for future AUC development).[29-33] The value of 2nd opinions should also be recognized as an ancillary "test" that also has not been appraised. Taken together, these considerations represent limitations and topics for future studies, and underscore

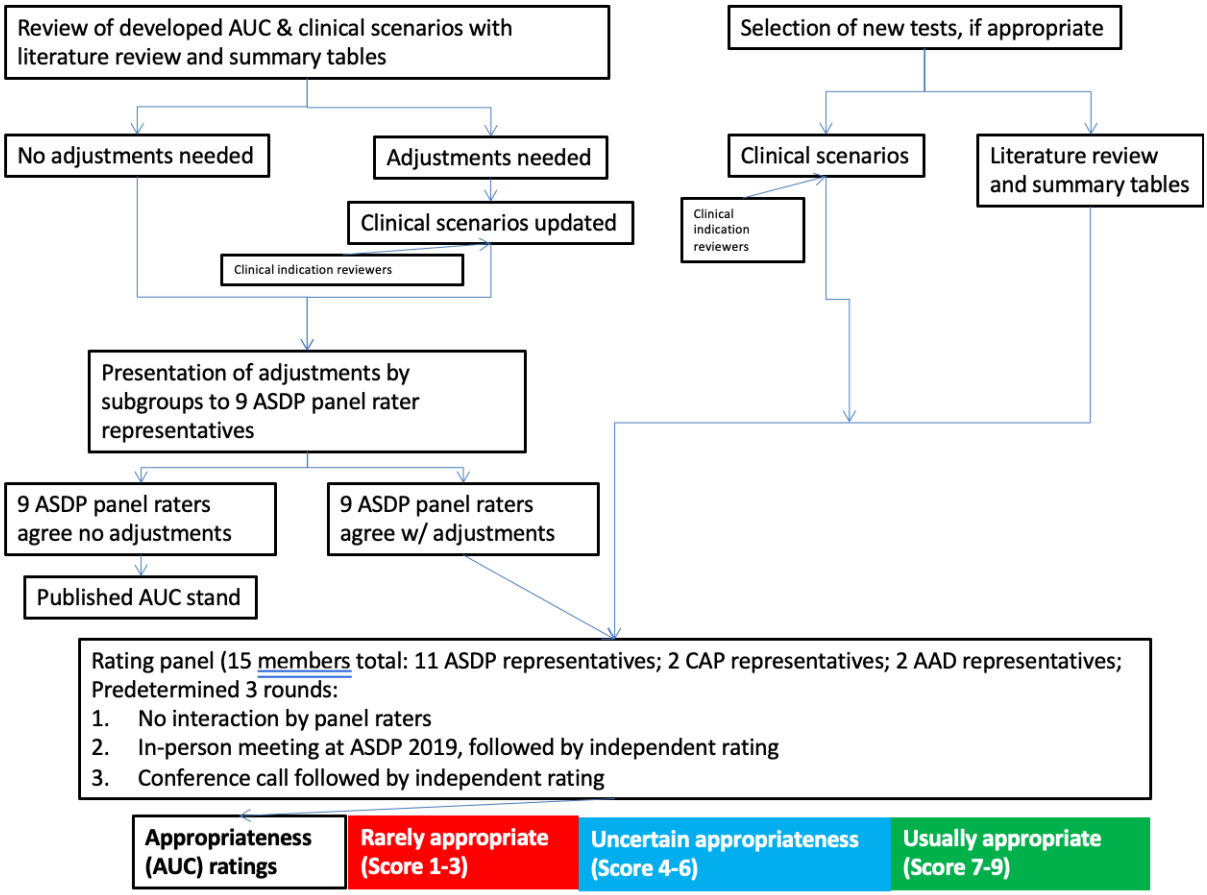
the critical point that the ultimate decision lies with physicians who are privy to and responsible for assessing all factors relevant to an individual patient.

Conclusions

We report new and updated AUC for ancillary tests in diagnostic dermatopathology based on the degree of consensus of experts, incorporating clinical experience and published literature regarding the appropriateness of kappa/lambda IHC and ISH; CGH, FISH, qRT-PCR and *TERT*-p for melanocytic proliferations; myc IHC and *MYC* ISH for angiosarcoma; and PAS and GMS stains. In an era of continuously evolving knowledge, the ASDP is committed to establishing and maintaining, via updates and review of additional tests, dermatopathology AUC for the betterment of the subspecialty and the patients it serves.

Figure legend

Figure 1. Process overview for update and development of AUC.



Tables

Table 1. Clinical scenarios and AUC results: Lymphoproliferative. Standard deviations are in parentheses.

Clinical scenario	kappa/lambda IHC AUC	kappa/lambda ISH AUC
Solitary or multiple erythematous nodules, plaques and/or papules that are clinically concerning for B cell lymphoma (clinical impression –rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma	8.7 (0.6)	8.8 (0.6)
Solitary or multiple erythematous nodules, plaques and/or papules that are clinically concerning for B cell lymphoma (clinical impression –rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (plasma cell rich)	8.9 (0.4)	8.8 (0.4)
Solitary or multiple erythematous nodules, papules and/or plaques that are clinically concerning for B cell lymphoma (clinical impression –rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' follicular lymphoma	6.2 (2.4)	6.3 (2.5)
Solitary or multiple erythematous nodules, papules and/or plaques that are clinically concerning for B cell lymphoma (clinical impression –rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' follicular lymphoma (plasma cell rich)	8.4 (1.9)	8.1 (1.9)
Clinical presentation of solitary or multiple non neoplastic papules and/or plaques with clinical impression of cutaneous lymphoid hyperplasia/ "lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' marginal zone lymphoma (plasma cells are few)	8.1 (1.7)	8.1 (1.7)
Clinical presentation of solitary or multiple non neoplastic papules and/or plaques with clinical impression of cutaneous lymphoid hyperplasia/"lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning	8.8 (1.1)	8.8 (1.1)

for', 'suspicious for' or 'suggestive of' marginal zone lymphoma (plasma cells are plentiful)		
Clinical presentation of solitary or multiple non neoplastic papules and/or plaques with clinical impression of cutaneous lymphoid hyperplasia/"lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' follicular lymphoma (plasma cells are scarce)	5.5 (2.6)	5.8 (2.7)
Clinical presentation of solitary or multiple non neoplastic papules and/or plaques with clinical impression of cutaneous lymphoid hyperplasia//"lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' follicular lymphoma (plasma cells are plentiful)	8.2 (2.0)	8.2 (2.0)
Clinical presentation of solitary or multiple nodules, papules and/or plaques with clinical impression of B cell lymphoma (favored diagnosis of marginal zone or follicular lymphoma) and that is 'not diagnostic' for cutaneous B lymphoma	6.9 (2.2)	7.0 (2.3)
Clinical presentation of a solitary lesion (nodule, papule and/or plaque), suggestive of a non neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B cells immunophenotypically; (plasma cells are few)	6.0 (2.1)	6.3 (2.2)
Clinical presentation of a solitary lesion (nodule, papule and/or plaque), suggestive of a non neoplastic process clinically, that has a predominant infiltrate of plasma cells histologically and immunophenotypically (B cells are few)	7.3 (2.0)	7.3 (2.0)
Clinical presentation of a dermatitis, suggestive of a non neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B cells immunophenotypically (plasma cells are few)	4.2 (2.7)	4.2 (2.7)
Unknown history, but histopathologic and immunophenotypic features are 'consistent with' marginal zone lymphoma	8.3 (1.2)	8.2 (1.3)
Unknown history, but histopathologic and immunophenotypic features are 'consistent with' marginal zone lymphoma (plasma cell rich)	8.5 (0.8)	8.4 (0.8)
Unknown history, but histopathologic and immunophenotypic features are 'consistent with' follicular lymphoma	5.4 (2.6)	5.4 (2.6)

Unknown history, but histopathologic and immunophenotypic features are 'consistent with' follicular lymphoma (plasma cell rich)	8.0 (2.0)	8.0 (2.0)
Pre-existing diagnosis of B cell lymphoma (marginal zone or follicular lymphoma) and new or evolving lesions (nodules, papules, and/or plaques) similar to original lesions with clinical impression of rule out B cell lymphoma and histopathologic and immunophenotypic features 'consistent with' marginal zone or follicular lymphoma	4.2 (2.6)	4.5 (2.6)
Pre-existing diagnosis of B cell lymphoma (marginal zone or follicular lymphoma) and new or evolving lesions (nodules, papules, and/or plaques) similar to original lesions with clinical impression of rule out B cell lymphoma and histopathologic and immunophenotypic features 'consistent with' marginal zone or follicular lymphoma (plasma cell rich)	4.8 (2.8)	4.8 (2.9)
Solitary or multiple erythematous nodules and/or plaques that are clinically concerning for aggressive B cell lymphoma (clinical impression –rule out B cell lymphoma-leg type) and that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' large B cell lymphoma-leg type (B cells predominate over plasma cells)	3.8 (2.4)	3.8 (2.5)
Solitary or multiple erythematous nodules and/or plaques that are clinically concerning for aggressive B cell lymphoma (clinical impression –rule out B cell lymphoma-leg type) and that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' large B cell lymphoma-leg type (plasma cells predominate)	6.5 (2.8)	6.5 (2.4)
Clinical presentation of a papule, nodule, plaque or mass with clinical impression of IgG4-related disease and features that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' IgG4-related disease	5.3 (2.1)	5.4 (2.1)
Clinical presentation of a papule, nodule, plaque or mass with a non-neoplastic clinical impression and features that are histologically and immunophenotypically 'concerning for', 'suspicious for' or 'suggestive of' IgG4-related disease	5.5 (2.4)	5.4 (2.4)
Clinical presentation of a dermatitis, suggestive of a non neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a prominent plasma cell component histologically and immunophenotypically (B cells are few)	5.4 (2.8)	5.5 (2.8)
Unknown clinical history, but histopathologic and immunophenotypic features are those of a dermatitis with	4.8 (2.5)	4.9 (2.6)

a diffuse lymphocytic infiltrate (plasma cells are plentiful)		
Clinical presentation of a solitary lesion diagnostic of a non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma) clinically and histologically and immunophenotypical features that are 'diagnostic of' chronic lymphocytic leukemia (plasma cells are plentiful)	2.8 (2.8)	2.5 (2.6)
Clinical presentation of a solitary lesion diagnostic of a non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma) clinically and with histological and immunophenotypical features that are 'diagnostic of' chronic lymphocytic leukemia (plasma cells are few)	1.8 (1.5)	1.9 (1.9)
Clinical presentation of solitary or multiple erythematous annular patches/plaques that are suggestive of a dermatitis clinically, with histological and immunophenotypical features that are 'diagnostic of' chronic lymphocytic leukemia (plasma cells are plentiful)	3.1 (2.7)	2.8 (2.5)
Clinical presentation of solitary or multiple erythematous annular patches/plaques that are suggestive of a dermatitis clinically, with histological and immunophenotypical features that are 'diagnostic of' chronic lymphocytic leukemia (plasma cells are scarce)	1.8 (1.4)	1.8 (1.8)
Solitary or multiple erythematous nodules, plaques and/or papules on the eyelid skin and/or conjunctiva, oral mucosa, and/or genital skin/mucosa that are clinically concerning for B cell lymphoma (clinical impression – rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (B cells predominate over plasma cells)	7.9 (2.0)	8.0 (2.0)
Solitary or multiple erythematous nodules, papules and/or plaques on the eyelid skin and/or conjunctiva, oral mucosa, and/or genital skin/mucosa that are clinically concerning for B cell lymphoma (clinical impression – rule out B cell lymphoma) and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (plasma cell rich)	8.8 (1.1)	8.7 (1.1)
Clinical presentation of solitary or multiple non neoplastic nodules, papules and/or plaques on the eyelid and/or conjunctiva, oral mucosa, and/or genital skin/mucosa with clinical impression of cutaneous lymphoid hyperplasia/"lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (B cells predominate over plasma cells)	8.5 (1.1)	8.5 (1.1)

Clinical presentation of solitary or multiple non neoplastic nodules, papules and/or plaques on the eyelid and/or conjunctiva, oral mucosa, and/or genital skin/mucosa with clinical impression of cutaneous lymphoid hyperplasia/"lymphocytoma cutis" and that are histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (plasma cells predominate over B cells)	8.8 (1.1)	8.6 (1.1)
New skin lesion in a patient with a known history of systemic B cell lymphoma, multiple myeloma, or lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia)	7.3 (2.1)	7.4 (2.1)

Standard deviation (SD) is indicated in parentheses.
Usually appropriate (UA)indications (Mean' ≥7.0) are dark green.
Usually appropriate to uncertain ("Majority usually appropriate"; UAU) indications (Mean' between 6.1 and 6.9, and SD<2.0) are light green.
Consensus around Uncertain ("Uncertain appropriateness"; U; Mean' ≥4.0 and ≤6.0, and SD <2.0) are blue.
Rarely appropriate (RA) indications (Mean' ≤3) are red.
Usually rarely appropriate ("Majority rarely appropriate"; URA) indications (Mean' between 3.1 and 3.9, and SD<2.0) are light red.
Scenarios where there is no consensus (NC; Mean' between 3.1 and 6.9, and SD≥2.0) are white.

Table 2. Clinical scenarios and AUC results: Melanocytic. Standard deviations for new AUC are in parentheses. Previously reported AUC with no update are included without standard deviations.[4]

Clinical scenario	CGH AUC*	FISH AUC*	qRT-PCR AUC	TERT-p AUC
Adult patient with pathology definitive for melanoma	1.2	1.1	1.1 (1.0)	1.4 (1.6)
Adult patient with pathology suggestive or suspicious for melanoma: Nevoid melanoma vs. benign melanocytic nevus	7.7	7.4	6.7 (1.2)	5.3 (1.8)
Adult patient with pathology suggestive or suspicious for melanoma: Nevoid cutaneous metastatic melanoma vs. benign melanocytic nevus	7.8	7.3	4.5 (1.8)	5.8 (1.7)
Adult patient with pathology suggestive or suspicious for melanoma: Melanoma arising within a nevus/dysplastic nevus	7.7	7.0	5.6 (1.5)	4.8 (2.0)
Adult patient with pathology suggestive or suspicious for melanoma: Atypical blue nevus vs. benign blue nevus	7.0	4.4	5.1 (1.7)	3.8 (2.1)
Adult patient pathology suggestive or suspicious for melanoma: Blue nevus-like cutaneous metastatic melanoma vs. benign blue nevus	7.6	4.9	5.4 (1.8)	5.2 (1.8)
Adult patient with pathology suggestive or suspicious for melanoma: Blue nevus-like melanoma (malignant blue nevus) vs. benign blue nevus	7.4	4.6	5.6 (1.8)	5.2 (1.9)
Adult with pathology suggestive or suspicious for melanoma: Congenital nevus with proliferative nodule (clarification: with atypia in the nodule) vs. melanoma	7.9	7.6	5.6 (1.6)	5.0 (1.4)
Adult patient with pathology suggestive or suspicious for melanoma: Atypical Spitz tumor vs. Spitzoid melanoma	7.7	7.6	5.5 (1.4)	6.8 (1.1)
Adult patient with pathology suggestive or suspicious for melanoma: Incompletely sampled unclassified Spitz tumor vs. Spitzoid melanoma	7.2	7.6	5.8 (2.0)	6.5 (1.5)
Adult patient with pathology suggestive or suspicious for melanoma: Sclerosing (desmoplastic) nevus incompletely sampled vs. desmoplastic melanoma	7.0	6.4	2.5 (1.7)	4.7 (1.8)
Adult patient with pathology suggestive or suspicious for melanoma: Severely atypical compound melanocytic proliferation vs. melanoma on cosmetically sensitive areas and special sites, including digits, acral, genital, ears, scalp	7.6	7.5	5.8 (1.7)	5.2 (1.8)

Adult patient with pathology definitive for nevus	1.1	1.1	1.1 (1.0)	1.1 (0.4)
Distinction of nevus from primary melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters	7.9	7.8	6.8 (1.2)	5.8 (1.9)
Distinction of nevus from primary melanoma in an adult patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters	7.2	7.5	6.5 (1.7)	5.0 (1.7)
Distinction of nevus from metastatic melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters	7.9	7.5	5.2 (1.8)	6.5 (1.5)
Distinction of nevus from metastatic melanoma in an adult patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters	7.3	7.5	4.4 (1.6)	5.8 (1.4)
Pediatric patient with pathology definitive for melanoma	1.4	1.5	1.9 (1.7)	2.2 (2.4)
Pediatric patient with pathology suggestive or suspicious for melanoma: Nevoid melanoma vs. benign melanocytic nevus	7.9	7.8	6.8 (1.1)	6.2 (1.6)
Pediatric patient with pathology suggestive or suspicious for melanoma: Nevoid cutaneous metastatic melanoma vs. benign melanocytic nevus	7.9	7.7	5.2 (1.8)	6.4 (1.6)
Pediatric patient with pathology suggestive or suspicious for melanoma: Melanoma arising within a nevus/dysplastic nevus	7.6	7.5	5.6 (1.6)	5.4 (1.8)
Pediatric patient with pathology suggestive or suspicious for melanoma: Atypical blue nevus vs. benign blue nevus	6.8	4.3	5.2 (1.8)	4.6 (1.8)
Pediatric patient with pathology suggestive or suspicious for melanoma: Blue nevus-like cutaneous metastatic melanoma vs. benign blue nevus	7.6	5.1	4.8 (1.6)	5.2 (1.8)
Pediatric patient with pathology suggestive or suspicious for melanoma: Blue nevus-like melanoma (malignant blue nevus) vs. benign blue nevus	7.6	4.8	5.5 (1.8)	5.1 (1.8)
Pediatric patient with pathology suggestive or suspicious for melanoma: Congenital nevus with proliferative nodule (clarification: with atypia in the nodule) vs. melanoma	7.9	7.7	5.7 (1.5)	5.3 (1.7)
Pediatric patient with pathology suggestive or suspicious for melanoma: Atypical Spitz tumor vs. Spitzoid melanoma	7.9	7.1	5.5 (1.3)	7.3 (0.5)
Pediatric with pathology suggestive or suspicious for melanoma: Incompletely sampled unclassified Spitz tumor vs. Spitzoid melanoma	7.6	7.1	5.4 (2.1)	7.2 (1.2)

Pediatric with pathology suggestive or suspicious for melanoma: Sclerosing (desmoplastic) nevus incompletely sampled vs. desmoplastic melanoma	7.3	6.2	3.5 (2.4)	4.8 (2.0)
Pediatric patient with pathology suggestive or suspicious for melanoma: Severely atypical compound melanocytic proliferation vs. melanoma on cosmetically sensitive areas and special sites, including digits, acral, genital, ears, scalp	7.8	7.8	6.4 (1.5)	5.3 (1.6)
Pediatric patient with pathology definitive for nevus	1.1	1.1	1.2 (1.1)	1.1 (0.4)
Distinction of nevus from primary melanoma in a pediatric patient when the morphologic findings are ambiguous by light microscopic parameters	8.0	7.9	6.5 (1.1)	5.8 (1.4)
Distinction of nevus from primary melanoma in a pediatric patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters	7.5	7.3	5.9 (1.9)	5.2 (1.6)
Distinction of nevus from metastatic melanoma in a pediatric patient when the morphologic findings are ambiguous by light microscopic parameters	7.9	7.6	5.0 (1.4)	5.9 (1.5)
Distinction of nevus from metastatic melanoma in a pediatric patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters	7.5	7.4	4.8 (1.5)	5.3 (1.5)
Adult patient with pathology features of recurrent or persistent melanocytic nevus but some features suspicious for melanoma (original biopsy not available for review and / or review did not resolve question)	7.1 (1.6)	6.6 (1.4)	4.7 (1.4)	5.7 (1.7)
Pediatric patient with pathology features of recurrent or persistent melanocytic nevus but some features suspicious for melanoma (original biopsy not available for review and / or review did not resolve question)	6.8 (1.7)	6.2 (1.4)	4.7 (1.4)	5.6 (1.8)
Ambiguous melanocytic lesion by light microscopy with an epithelioid morphology and loss of BAP-1 expression with immunohistochemistry. (clarification: Lesion with a BAP-1 deficiency but histologically ambiguous beyond what would be expected)	6.5 (1.6)	5.6 (2.0)	5.5 (1.5)	5.0 (1.7)

*Previously developed AUC; values are taken from the published AUC paper, with the exception of the last 3 clinical scenarios.
Standard deviation (SD) is indicated in parentheses for newly developed AUC.
Usually appropriate (UA)indications (Mean' ≥7.0) are dark green.
Usually appropriate to uncertain ("Majority usually appropriate"; UAU) indications (Mean' between 6.1 and 6.9, and SD<2.0) are light green.
Consensus around Uncertain ("Uncertain appropriateness"; U; Mean' ≥4.0 and ≤6.0, and SD <2.0) are blue.
Rarely appropriate (RA) indications (Mean' ≤3) are red.
Usually rarely appropriate ("Majority rarely appropriate"; URA) indications (Mean' between 3.1 and 3.9, and SD<2.0) are light red.
Scenarios where there is no consensus (NC; Mean' between 3.1 and 6.9, and SD≥2.0) are white.

Table 3. Clinical scenarios and AUC results: MYC Standard deviations are in parentheses.

Clinical Scenario	myc IHC AUC	*MYC* FISH AUC
Adult patient sun damaged scalp or face skin, pathology definitive for angiosarcoma	1.3 (1.3)	1.2 (1.3)
Adult patient sun damaged scalp or face skin, pathology suggestive of angiosarcoma	2.7 (1.9)	2.7 (1.9)
Adult patient sun damaged scalp or face skin, pathology consistent with benign vascular lesion	1.6 (1.0)	1.3 (0.9)
Adult patient, radiated breast skin, pathology definitive for angiosarcoma	1.8 (1.8)	1.9 (1.7)
Adult patient, radiated breast skin, atypical vascular proliferation, suspicious for angiosarcoma	8.6 (0.5)	8.6 (0.6)
Adult patient, radiated breast skin, atypical vascular proliferation, favor benign	7.8 (1.3)	7.8 (1.3)
Adult patient, non-radiated breast skin, pathology definitive for angiosarcoma	1.3 (0.8)	1.2 (0.8)
Adult patient, non-radiated breast skin, atypical vascular proliferation, suspicious for angiosarcoma (Clarification: patient has no lymphedema)	3.5 (2.0)	3.9 (2.6)
Adult patient, non-radiated breast skin, atypical vascular proliferation, favor benign (Clarification: patient has no lymphedema)	2.6 (1.9)	2.8 (2.0)
Adult patient, upper extremity chronic lymphedema, pathology definitive for angiosarcoma	1.6 (1.6)	1.6 (1.6)
Adult patient, upper extremity chronic lymphedema, pathology suspicious for angiosarcoma	7.9 (1.4)	7.7 (1.4)
Adult patient, lower extremity chronic lymphedema, pathology definitive for angiosarcoma	1.5 (1.4)	1.5 (1.4)
Adult patient, lower extremity chronic lymphedema, pathology suspicious for angiosarcoma	7.5 (1.4)	7.7 (1.4)
Adult patient, cutaneous angiosarcoma any location, without history of radiation, chronic lymphedema, or evidence of chronic sun damage	2.2 (1.3)	2.2 (1.3)
Adult patient, skin excision for angiosarcoma, distinguish angiosarcoma from benign non-neoplastic vessels at margin	3.5 (1.9)	3.8 (1.9)

Standard deviation (SD) is indicated in parentheses.
Usually appropriate (UA)indications (Mean' ≥7.0) are dark green.
Usually appropriate to uncertain ("Majority usually appropriate"; UAU) indications (Mean' between 6.1 and 6.9, and SD<2.0) are light green.
Consensus around Uncertain ("Uncertain appropriateness"; U; Mean' ≥4.0 and ≤6.0, and SD <2.0) are blue.
Rarely appropriate (RA) indications (Mean' ≤3) are red.
Usually rarely appropriate ("Majority rarely appropriate"; URA) indications (Mean' between 3.1 and 3.9, and SD<2.0) are light red.
Scenarios where there is no consensus (NC; Mean' between 3.1 and 6.9, and SD≥2.0) are white.

Table 4. Clinical scenarios and AUC results: GMS and PAS stains Standard deviations are in parentheses.

Clinical scenario	PAS AUC	GMS AUC
*Patient with a rash clinically suspected to be a dermatophyte infection**	3.4 (3.3)	3.2 (3.3)
*Patient with a rash for which the clinical differential diagnosis includes a dermatophyte infection**	3.8 (3.4)	3.0 (3.2)
Patient with non-specific clinical findings and pathologic findings (e.g. parakeratosis, compact hyperkeratosis, intracorneal neutrophils) consistent with a dermatophyte infection	8.8 (0.6)	8.8 (0.6)
Patient with non-specific clinical findings and pathologic findings which could be suggestive of a dermatophyte infection	8.7 (0.8)	8.8 (0.8)
Patient with a clinical history of prior fungal treatment and skin histologic findings of parakeratosis and neutrophils	8.7 (1.1)	8.6 (0.6)
Patient with nonspecific "rash" and non-specific pathologic findings (clarification: non-diagnostic pathology for a dermatophyte infection).	6.1 (2.0)	6.2 (1.9)
*Patient with nail changes clinically consistent with onychomycosis**	8.3 (2.1)	7.5 (2.8)
*Patient with nail changes for which the clinical differential diagnosis includes onychomycosis**	8.4 (2.1)	7.8 (2.7)
Patient with non-specific nail changes and pathologic findings (parakeratosis, degenerative debris, neutrophils) consistent with onychomycosis (Clarification: nail clipping submitted)	8.9 (0.4)	8.8 (2.1)
Patient with nonspecific nail changes and pathologic findings which could be suggestive of onychomycosis (Clarification: nail clipping submitted)	8.8 (0.4)	8.8 (2.1)
Patient with a clinical history of prior fungal treatment and nail biopsy histologic findings of parakeratosis and neutrophils (Clarification: nail clipping submitted)	8.8 (0.5)	8.7 (2.0)
Patient with nonspecific nail changes and nonspecific pathologic findings. (Clarification: nondiagnostic pathologic findings for onychomycosis Clarification: nail clipping submitted)	7.3 (1.4)	7.4 (2.1)

*Patient with a rash clinically suspected to be a granulomatous or dermal infectious process**	4.5 (3.3)	3.8 (3.4)
*Patient with a rash for which the clinical differential diagnosis includes a granulomatous process or infection**	4.0 (3.1)	3.4 (3.3)
Patient with nonspecific clinical findings and pathologic findings showing a granulomatous dermatitis	7.8 (1.4)	8.2 (1.2)
Patient with nonspecific clinical findings and pathologic findings showing features suggestive of a dermal infection (necrotizing granulomas, neutrophils)	8.2 (1.4)	8.6 (1.1)
*Patient with clinical findings suggestive of lupus or dermatomyositis**	3.3 (2.7)	
*Patient with clinical findings for which the clinical differential diagnosis includes lupus or dermatomyositis**	3.1 (2.7)	
Patient with nonspecific clinical findings and pathologic findings consistent with lupus of dermatomyositis (interface changes, basement membrane thickening, increased mucin)	4.7 (2.4)	
Patient with nonspecific clinical findings and pathologic findings which could be compatible with lupus or dermatomyositis	6.6 (1.6)	
*Patient with a purpuric rash clinically suspected to be a vasculitis**	2.6 (1.9)	
*Patient with a purpuric rash for which the clinical differential diagnosis includes a vasculitis**	2.1 (1.7)	
Patient with nonspecific clinical findings and pathologic findings showing a vasculitis (vascular inflammation, endothelial swelling or necrosis, fibrinoid thrombi)	5.1 (2.0)	
Patient with nonspecific clinical findings and pathologic findings showing changes suspicious for vasculitis.	5.5 (2.1)	
*Patient with a purpuric rash clinically suspected to be vasculopathy**	2.4 (2.1)	
*Patient with a purpuric rash for which the clinical differential diagnosis includes a vasculopathy**	2.2 (2.0)	

Patient with nonspecific clinical findings and pathologic findings showing a vasculopathy (minimal inflammation, fibrinoid thrombi, extravasated red blood cells)	5.5 (2.1)	
Patient with nonspecific clinical findings and pathologic findings showing changes suspicious for a vasculopathy	6.5 (1.5)	

*Clinical scenarios that indicate that the stain is being ordered based on information in the pathology requisition, prior to any histologic review, are ***italicized***.
Standard deviation (SD) is indicated in parentheses.
Usually appropriate (UA)indications (Mean' ≥7.0) are dark green.
Usually appropriate to uncertain ("Majority usually appropriate"; UAU) indications (Mean' between 6.1 and 6.9, and SD<2.0) are light green.
Consensus around Uncertain ("Uncertain appropriateness"; U; Mean' ≥4.0 and ≤6.0, and SD <2.0) are blue.
Rarely appropriate (RA) indications (Mean' ≤3) are red.
Usually rarely appropriate ("Majority rarely appropriate"; URA) indications (Mean' between 3.1 and 3.9, and SD<2.0) are light red.
Scenarios where there is no consensus (NC; Mean' between 3.1 and 6.9, and SD≥2.0) are white.

Supplemental Table 1. Definitions used in AUC clinical scenarios.

Lymphoproliferative	
Marginal zone lymphoma	
#1. Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma	• Presence of one or more typical histopathologic features of marginal zone lymphoma (Grenz zone, 'bottom heavy' infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and 'monocytoid' B cells, diffuse infiltrate of monotonous lymphocytes) • Normal immunophenotypic features (mixed B and T cell infiltrate) • B cells appear monocytoid with few plasma cells (B cells predominate over plasma cells)
#2. Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' marginal zone lymphoma (**plasma cell rich**)	• Presence of one or more typical histopathologic features of marginal zone lymphoma (Grenz zone, 'bottom heavy' infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and 'monocytoid' B cells, diffuse infiltrate of monotonous lymphocytes) • Normal immunophenotypic features (mixed B and T cell infiltrate) • Significant plasmacytic differentiation is observed (includes cases of pure plasma cell populations [plasmacytoma] and amyloid deposition [so-called amyloidoma]
'consistent with' marginal zone lymphoma	Histopathologic diagnostic criteria of marginal lymphoma are present (see definition #1) • Predominance of B cells; B cells cannot be explained by normal architecture (i.e., confined to lymphoid follicles) • Plasma cells are scarce (B cells predominate over plasma cells)
'consistent with' marginal zone lymphoma (**plasma cell rich**)	Histopathologic diagnostic criteria of marginal zone lymphoma are present (see definition #2) • Predominance of B cells; B cells cannot be explained by normal architecture (i.e., confined to lymphoid follicles) • Plasma cells are plentiful.
Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' **mucosa**l (eyelid skin, conjunctiva ,oral and genital skin/mucosa) marginal zone lymphoma	• Presence of one or more typical histopathologic features of marginal zone lymphoma (Grenz zone, 'bottom heavy' infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and 'monocytoid' B cells, diffuse infiltrative of monotonous lymphocytes, lymphoepithelial lesions) • Normal immunophenotypical features (mixed B and T cell infiltrate) • B cells appear monocytoid with few plasma cells (B cells predominate over plasma cells)
Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' **mucosa**l (eyelid skin, conjunctiva ,oral and genital skin/mucosa) marginal zone lymphoma (**plasma cell rich**)	• Presence of one or more typical histopathologic features of marginal zone lymphoma (Grenz zone, 'bottom heavy' infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and 'monocytoid' B cells, diffuse infiltrative of monotonous lymphocytes, lymphoepithelial lesions) • Normal immunophenotypical features (mixed B and T cell infiltrate) • A predominance of plasma cells is observed (plasma cells predominate over B cells)

Follicular lymphoma	
#3. Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' follicular lymphoma	• Presence of one or more typical histopathologic features of follicular lymphoma (Grenz zone, predominance of cleaved cells (centrocytes) and/or large non-cleaved cells (centroblasts), nodular infiltrate composed of disorganized follicles, 'bottom heavy' infiltrate, follicle like structures without tingible body macrophages, diffuse infiltrate of monotonous small cleaved or large non-cleaved lymphocytes) • Normal immunophenotypical features (mixed B and T cell infiltrate, B cells confined to follicles, high Ki67 proliferative rate within follicles, lack of bcl-6 + CD10 + B cells outside of follicles) • A predominance of B cells is observed with few plasma cells (B cells predominate over plasma cells)
#4. Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' follicular lymphoma (**plasma cell rich**)	• Presence of one or more typical histopathologic features of follicular lymphoma (Grenz zone, predominance of cleaved cells (centrocytes) and/or large non-cleaved cells (centroblasts), nodular infiltrate composed of disorganized follicles, 'bottom heavy' infiltrate, follicle like structures without tingible body macrophages, diffuse infiltrate of monotonous small cleaved or large non-cleaved lymphocytes) • Normal immunophenotypical features (mixed B and T cell infiltrate, B cells confined to follicles, high Ki67 proliferative rate within follicles, lack of bcl-6 + CD10 + B cells outside of follicles) • Significant plasmacytic differentiation is observed
'consistent with' follicular lymphoma	Histopathologic diagnostic criteria of follicular lymphoma are present (see definition #3) • Predominance of B cells; B cells cannot be explained by normal architecture (i.e., confined to lymphoid follicles) • B cells predominate over plasma cells (plasma cells are scarce)
'consistent with' follicular lymphoma (**plasma cell rich**)	Histopathologic diagnostic criteria of follicular lymphoma are present (see definition #4) • Predominance of B cells; B cells cannot be explained by normal architecture (i.e., confined to lymphoid follicles) • Plasma cells are plentiful.
Large B cell lymphoma, leg type	
Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' large B cell lymphoma-leg type	• Presence of one or more typical histopathologic features of large B cell lymphoma-leg type (Grenz zone, predominance of large immunoblastic cells, diffuse infiltrate, necrosis, easily observable mitotic activity in neoplastic appearing cells) • Predominance of B cells via immunohistochemistry; the infiltrate is bcl-2+ and MUM1 +, and lacks expression of CD10 • Plasma cells are scarce (B cells predominate over plasma cells)
Histologically and immunophenotypically 'concerning for', 'suspicious of'	• Presence of one or more typical histopathologic features of large B cell lymphoma-leg type (Grenz zone, predominance of large

or 'suggestive of' large B cell lymphoma-leg type (**plasma cell rich**)	immunoblastic cells, diffuse infiltrate, necrosis, easily observable mitotic activity in neoplastic appearing cells) • Predominance of B cells via immunohistochemistry; the infiltrate is bcl-2+ and MUM1 +, and lacks expression of CD10 • Plasma cells are plentiful (plasma cells predominate over B cells)
IgG4-related disease	
Histologically and immunophenotypically 'concerning for', 'suspicious of' or 'suggestive of' IgG4-related disease	• Increased IgG4 plasma cells (ratio of IgG4/IgG-positive cells >40% and >200 IgG4-positive plasma cells/high-power field) • Storiform fibrosis • Obliterative venulitis • Eosinophilia
Chronic lymphocytic leukemia	
Histological and immunophenotypic features that are 'diagnostic of' chronic lymphocytic leukemia; **plasma cells are plentiful**	• Presence of one of three patterns of lymphoid infiltrate – 1) patchy perivascular and periadnexal, 2) nodular-diffuse or 3) band-like • Neoplastic cells express CD5, CD20 and CD43
Histological and immunophenotypic features that are 'diagnostic of' chronic lymphocytic leukemia; **plasma cells are scarce**	• Presence of one of three patterns of lymphoid infiltrate – 1) patchy perivascular and periadnexal, 2) nodular-diffuse or 3) lichenoid/band-like • Neoplastic cells express CD5, CD20 and CD43
Non-diagnostic specimen	
'not diagnostic' for cutaneous B lymphoma	• Grenz zone is absent and there is epidermal involvement by lymphocytes • Minimal number of B cells and plasma cells within a nodular or diffuse infiltrate
<u>Melanocytic</u>	
Adult patient	>/= 18 years of age
Atypical blue nevus	Lesion of spindled melanocytes with or without an admixed epithelioid component which have any of the following: pronounced cytologic atypia or hyperchromasia, necrosis, increased mitotic rate or dysmaturation
Atypical melanocytic proliferation	Pathology suggestive of /suspicious for melanoma
Atypical Spitz tumor	Lesion of Spitzoid melanocytes which have any of the following: marked architectural asymmetry, dysmaturation, ulceration, increased mitotic rate or increased and/or atypical mitoses in the deep portion of the lesion, marked cytologic atypia

Benign blue nevus	Lesion of benign spindled melanocytes occurring within a fibrotic stroma, subtypes include cellular, deep penetrating and epithelioid
Benign melanocytic nevus	Lesion of benign melanocytes with either a compound or intradermal configuration
Blue nevus-like cutaneous metastatic melanoma	Lesion of metastatic malignant melanoma composed of spindled and pigmented melanocytes which closely mimic architectural and cytologic features of a benign blue nevus or blue nevus subtype
Blue nevus-like melanoma (malignant blue nevus)	Lesion of malignant melanocytes which closely mimic architectural and cytologic features of benign blue nevus or arises within a histologically recognizable benign blue nevus remnant
Congenital nevus with proliferative nodule	Nodular lesion of atypical epithelioid or spindled melanocytes occurring within a pre-existing congenital nevus
Desmoplastic melanoma	Lesion of malignant melanocytes with a predominantly spindled shaped, prominent desmoplasia and frequent neurotropism
Fluorescence *in situ* hybridization panel	RREB1 (6p25), MYC (8q24), CDKN2A (9p21), CCND1 (11q13)
Incompletely sampled unclassified Spitz tumor	Lesion of Spitzoid melanocytes which is partially sampled to the degree it is not able to be subclassified and with atypical features
Nevoid cutaneous metastatic melanoma	Lesion of metastatic malignant melanoma with some histologic features which closely mimic architectural and cytologic features of a benign compound or intradermal nevus
Nevoid melanoma	Lesion of malignant melanocytes with some histologic features which closely mimic architectural and cytologic features of a benign compound or intradermal nevus
Pediatric patient	Less than 18 years of age
qRT-PCR	23 genes, including: PRAME, S100A7, S100A8, S100A9, S100A12, PI3, CCL5, CD38, CXCL10, CXCL9 IRF1, LCP2, PTPRC, SELL, nine housekeeping genes measured to normalize RNA expression analysis
Sclerosing (desmoplastic) nevus	Lesion of benign melanocytes which may be ovoid, dendritic or Spitzoid occurring within a distinctive eosinophilic stroma with overall architectural symmetry and without significant cytologic atypia or mitotic activity
Spitzoid melanoma	Lesion of malignant melanocytes with some histologic features which closely mimic architectural and cytologic features of a benign Spitz nevus

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