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Appropriate use criteria for ancillary diagnostic testing in dermatopathology: New recommendations for 11 tests and 220 clinical scenarios from the American Society of Dermatopathology Appropriate Use Criteria Committee

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Abstract

Background: Appropriate use criteria (AUC) provide patient-centered physician guidance in test selection. An initial set of AUC was 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. The objective of this study was to update and expand AUC for selected tests.

Methods: RAND/UCLA (RAND Corporation [Santa Monica, CA]/University of California Los Angeles) methodology used includes the following: (a) literature review; (b) review of previously rated tests and previously employed clinical scenarios; (c) selection of previously rated tests for new ratings; (d) development of new clinical scenarios; (e) selection of additional tests; (f) three rating rounds with feedback and group discussion after rounds 1 and 2.

Results: For 220 clinical scenarios comprising lymphoproliferative (light chain clonality), melanocytic (comparative genomic hybridization, fluorescence in situ hybridization, reverse transcription polymerase chain reaction, telomerase reverse transcriptase promoter), vascular disorders (MYC), and inflammatory dermatoses (periodic acid-Schiff, Gömöri methenamine silver), consensus by panel raters was reached in 172 of 220 (78%) scenarios, with 103 of 148 (70%) rated "usually appropriate" or "rarely appropriate" and 45 of 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 healthcare delivery.

KEYWORDS

ancillary studies, angiosarcoma, appropriate use criteria, choosing wisely, cMYC, dermatitis, dermatology, dermatopathology, dermatophytosis, diagnosis, evidence-based medicine, expert rating, Gömöri methenamine silver, Grocott-Gömöri, immunohistochemistry, in situ hybridization, kappa, lambda, lymphoma, onychomycosis, pathology, periodic acid-Schiff, RAND/UCLA appropriateness method, TERT promoter, tinea

1 | INTRODUCTION

Amidst efforts to improve quality and efficiency and reduce waste in health care, a substantial portion of provided healthcare services remains inappropriate or equivocally appropriate (independent of payer or other factors).[1] Although 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 the 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/UCLA (RAND Corporation [Santa Monica, CA]/University of California Los Angeles) Appropriateness Method,[7] as previously reported.[4]

2.1 | Ancillary diagnostic tests, clinical scenarios, definitions, literature review

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), and other (DC, TF, SS). Each subgroup (a) proposed additional tests for AUC review, which were subsequently approved by the ASDP Executive Committee and performed a literature review; (b) reviewed existing AUC data and recommended updates, if any; (c) reviewed definitions (Table S1) and clinical scenarios and recommended any updates and/or new clinical scenarios (Figure 1).

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

Fifteen volunteer panel raters with collective balance and expertise were recruited (Figure 1). 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 judgment 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 (19 October 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 ≥7.0 was classified as "usually appropriate"; mean′ of ≤3.0 was classified as "rarely appropriate." Clinical scenarios with mean′ between 3.1 and 6.9 with an SD ≥ 2.0 were designated as not having reached consensus ("no consensus"). Clinical

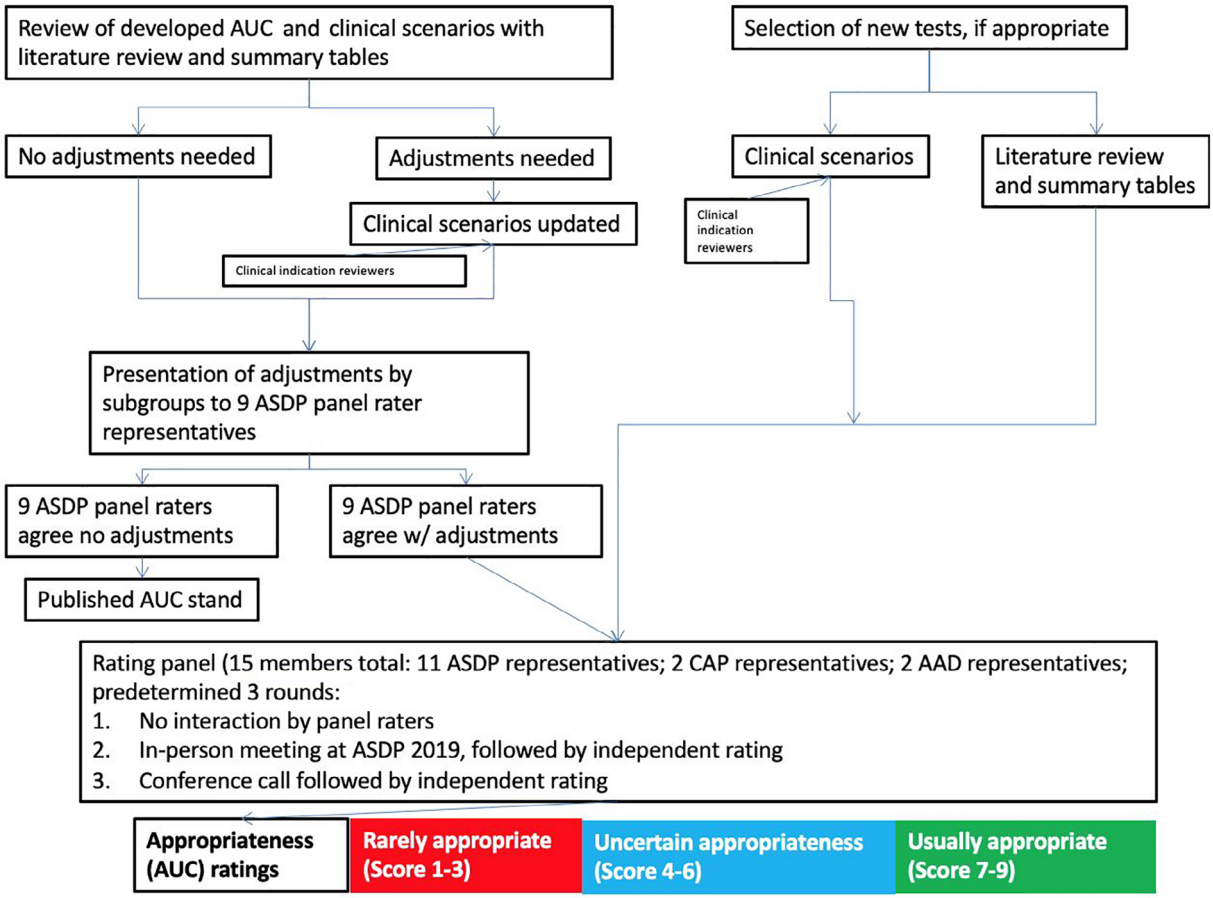

FIGURE 1 Process overview for update and development of appropriate use criteria (AUC)

scenarios with mean′ of ≥4.0 and ≤6.0 with an SD < 2.0 were classified as having reached a consensus of "uncertain appropriateness." Clinical scenarios with an SD < 2.0 with a mean′ between 6.1 and 6.9 were classified as majority usually appropriate ("usually appropriate to uncertain") while those with an SD < 2.0 and a mean′ between 3.1 and 3.9 were classified as majority rarely appropriate ("usually rarely appropriate").

3 | RESULTS

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

3.1 | Lymphoproliferative subgroup

Review of the literature indicated continued relevance of the previously developed AUC for T-cell and B-cell clonality by polymerase chain reaction (PCR) (Table 1). The lymphoproliferative subgroup selected light-chain monotypia (kappa/lambda immunohistochemistry [IHC] and in situ hybridization [ISH]) for AUC development. The summary and analysis of the literature was reported by Hristov et al.[11]

Thirty-three clinical scenarios were rated for each test for a total of 66 ratings. Terminology followed the World Health Organization (WHO) (Table S1).[17] Consensus was reached in 38 of 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 histopathologically 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 histopathologically 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."

3.2 | Melanocytic subgroup

The melanocytic subgroup added three new clinical scenarios to be rated for all tests and recommended AUC update for quantitative

TABLE 1 Clinical scenarios and appropriate use criteria (AUC) results: lymphoproliferative

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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" marginal zone lymphoma (MZL)	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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" MZL (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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" follicular lymphoma (FL)	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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" FL (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 histopathologically and immunophenotypically "concerning for," "suspicious for," or "suggestive of" MZL (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 histopathologically and immunophenotypically "concerning for," "suspicious for," or "suggestive of" MZL (plasma cells are plentiful)	8.8 (1.1)	8.8 (1.1)
Clinical presentation of solitary or multiple non-neoplastic papules and/or plaques with clinical impression of cutaneous lymphoid hyperplasia/"lymphocytoma cutis" and that are histopathologically and immunophenotypically "concerning for," "suspicious for," or "suggestive of" FL (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 histopathologically and immunophenotypically "concerning for," "suspicious for," or "suggestive of" FL (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 FL) 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, which 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, which has a predominant infiltrate of plasma cells histopathologically 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, which 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)

(Continues)

TABLE 1 (Continued)

Clinical scenario	Kappa/lambda, IHC AUC	Kappa/lambda, ISH AUC
Unknown history, but histopathological and immunophenotypical features are "consistent with" MZL	8.3 (1.2)	8.2 (1.3)
Unknown history, but histopathological and immunophenotypical features are "consistent with" MZL (plasma cell rich)	8.5 (0.8)	8.4 (0.8)
Unknown history, but histopathological and immunophenotypical features are "consistent with" FL	5.4 (2.6)	5.4 (2.6)
Unknown history, but histopathological and immunophenotypical features are "consistent with" FL (plasma cell rich)	8.0 (2.0)	8.0 (2.0)
Pre-existing diagnosis of B-cell lymphoma (marginal zone or FL) and new or evolving lesions (nodules, papules, and/or plaques) similar to original lesions with clinical impression of rule out B-cell lymphoma and histopathological *and* immunophenotypical features "consistent with" marginal zone or FL	4.2 (2.6)	4.5 (2.6)
Pre-existing diagnosis of B-cell lymphoma (marginal zone or FL) and new or evolving lesions (nodules, papules, and/or plaques) similar to original lesions with clinical impression of rule out B-cell lymphoma and histopathological *and* immunophenotypical features "consistent with" marginal zone or FL (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 histopathologically 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 histopathologically 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 histopathologically 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 histopathologically 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, which has a diffuse infiltrate of lymphocytes and has a prominent plasma cell component histopathologically and immunophenotypically (B-cells are few)	5.4 (2.8)	5.5 (2.8)
Unknown clinical history, but histopathological and immunophenotypical features are those of a dermatitis with a diffuse lymphocytic infiltrate (plasma cells are plentiful)	4.8 (2.5)	4.9 (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 histopathological *and* immunophenotypical features that are "diagnostic of" chronic lymphocytic leukemia (CLL) (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 histopathological *and* immunophenotypical features that are "*diagnostic of*" CLL (plasma cells are few)	1.8 (1.5)	1.9 (1.9)

TABLE 1 (Continued)

Clinical scenario	Kappa/lambda, IHC AUC	Kappa/lambda, ISH AUC
Clinical presentation of solitary or multiple erythematous annular patches/plaques that are suggestive of a dermatitis clinically, with histopathological and immunophenotypical features that are "diagnostic of" CLL (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 histopathological and immunophenotypical features that are "diagnostic of" CLL (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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" MZL (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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" MZL (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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" MZL (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 histopathologically and immunophenotypically "concerning for," "suspicious of," or "suggestive of" MZL (*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)

Notes: SD values are 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.

reverse transcription PCR (qRT-PCR) (Table 2). AUC updates for fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH) were not recommended based on a current review of the literature. The subgroup selected telomerase reverse transcriptase promoter (*TERT*-p) point mutation analysis for AUC review. Analysis of the literature for *TERT*-p was reported by Motaparthi et al.[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 vs melanoma and histopathologically ambiguous BAP-1-deficient tumors. Consensus was reached for FISH and CGH in five of the six 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 vs melanoma in fully sampled histopathologically ambiguous tumors in children and adults, partially sampled nevus vs melanoma in adults, nevus vs nevoid melanoma in children or adults, and nevus vs 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 vs 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 vs spitzoid melanoma. In adults, *TERT*-p was rated "majority usually appropriate" for fully or partially sampled atypical Spitz tumor vs 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 vs nevoid melanoma or nevoid metastasis.

3.3 | Soft tissue subgroup

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 harbors an alternative rearrangement involving *PDGFD* gene fused to the *COL6A3* or *EMILIN2* gene (Table 3).[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, not necessitating update.

The soft tissue subgroup selected myc overexpression by IHC and *MYC* amplification by FISH in the diagnosis of angiosarcoma for AUC development. Review and analysis of the literature (1967-2018) covering 16 articles was reported by Motaparthi et al.[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 the 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".

3.4 | Gömöri methenamine silver and periodic acid-Schiff stains (other subgroup)

The AUC for mismatch repair proteins in Muir-Torre syndrome and the AUC for human papilloma virus IHC and ISH were determined to not require update at this time (Table 4). 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 et al.[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 of 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 of the fungal stains for clinicopathologic scenarios in which clinical or histopathological 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 histopathological 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" (ie, assessment of appropriateness of test cannot be made without communication with clinician) were not used or requested during rating rounds.

4 | 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.

4.1 | Lymphoproliferative

Our results support paired kappa/lambda IHC or ISH as appropriate in multiple clinical scenarios, including histopathologically suspected

TABLE 2 Clinical scenarios and AUC results: melanocytic

Clinical scenario	CGH AUC[a]	FISH AUC[a]	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, and 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)

(Continues)

TABLE 2 (Continued)

Clinical scenario	CGH AUC[a]	FISH AUC[a]	qRT-PCR AUC	TERT-p AUC
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, and 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 histopathologically ambiguous beyond what would be expected)	6.5 (1.6)	5.6 (2.0)	5.5 (1.5)	5.0 (1.7)

Notes: Previously reported AUC with no update are included without SDs.[4] SD values are 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.

Abbreviations: AUC, appropriate use criteria; CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; qRT-PCR, quantitative reverse transcription polymerase chain reaction; TERT-p, telomerase reverse transcriptase promoter.

[a]Previously developed AUC; values are taken from the published AUC paper, with the exception of the last three clinical scenarios.

TABLE 3 Clinical scenarios and AUC results: MYC

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)

Notes: SD values are 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.

Abbreviations: AUC, appropriate use criteria; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

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 FL) and that is "not diagnostic" for cutaneous B-cell lymphoma" and "Clinical presentation of solitary or multiple erythematous annular patches/plaques that are suggestive of a dermatitis clinically, with histopathological and immunophenotypical features that are 'diagnostic of' CLL (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]

4.2 | 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 that for the first time dermatopathology AUC have been updated with a few shiftings 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 vs 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% and sensitivity near 80%.[22] As an important caveat, *TERT*-p mutations occur early in tumorigenesis and may be identified in dysplastic nevi

TABLE 4 Clinical scenarios and appropriate use criteria (AUC) results: Gömöri methenamine silver (GMS) and periodic acid-Schiff (PAS) stains

Clinical scenario	PAS AUC	GMS AUC
Patient with a rash clinically suspected to be a dermatophyte infection[a]	3.4 (3.3)	3.2 (3.3)
Patient with a rash for which the clinical differential diagnosis includes a dermatophyte infection[a]	3.8 (3.4)	3.0 (3.2)
Patient with non-specific clinical findings and pathologic findings (eg, 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 that 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 histopathological findings of parakeratosis and neutrophils	8.7 (1.1)	8.6 (0.6)
Patient with non-specific "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[a]	8.3 (2.1)	7.5 (2.8)
Patient with nail changes for which the clinical differential diagnosis includes onychomycosis[a]	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 non-specific 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 histopathological findings of parakeratosis and neutrophils (clarification: nail clipping submitted)	8.8 (0.5)	8.7 (2.0)
Patient with non-specific nail changes and non-specific 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[a]	4.5 (3.3)	3.8 (3.4)
Patient with a rash for which the clinical differential diagnosis includes a granulomatous process or infection[a]	4.0 (3.1)	3.4 (3.3)
Patient with non-specific clinical findings and pathologic findings showing a granulomatous dermatitis	7.8 (1.4)	8.2 (1.2)
Patient with non-specific 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[a]	3.3 (2.7)	
Patient with clinical findings for which the clinical differential diagnosis includes lupus or dermatomyositis[a]	3.1 (2.7)	
Patient with non-specific clinical findings and pathologic findings consistent with lupus of dermatomyositis (interface changes, basement membrane thickening, increased mucin)	4.7 (2.4)	
Patient with non-specific 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[a]	2.6 (1.9)	
Patient with a purpuric rash for which the clinical differential diagnosis includes a vasculitis[a]	2.1 (1.7)	
Patient with non-specific clinical findings and pathologic findings showing a vasculitis (vascular inflammation, endothelial swelling or necrosis, fibrinoid thrombi)	5.1 (2.0)	
Patient with non-specific clinical findings and pathologic findings showing changes suspicious for vasculitis.	5.5 (2.1)	
Patient with a purpuric rash clinically suspected to be vasculopathy[a]	2.4 (2.1)	
Patient with a purpuric rash for which the clinical differential diagnosis includes a vasculopathy[a]	2.2 (2.0)	
Patient with non-specific clinical findings and pathologic findings showing a vasculopathy (minimal inflammation, fibrinoid thrombi, extravasated red blood cells)	5.5 (2.1)	
Patient with non-specific clinical findings and pathologic findings showing changes suspicious for a vasculopathy	6.5 (1.5)	

Notes: SD values are 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.

[a]Clinical scenarios that indicate that the stain is being ordered based on information in the pathology requisition, prior to any histopathological review, are italicized.

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. Although 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.

4.3 | 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. Although 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.

4.4 | 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. The 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 (ie, 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 histopathology (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 (ie, necrobiotic, suppurative). 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 with other studies using the RAND/UCLA methodology.[7] Nine of 15 (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 (eg, p16, PRAME, which are viable tests for future AUC development).[29-33] The value of second 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.

5 | 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.

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CONFLICT OF INTEREST

Dr. Prieto served as consultant for Myriad Genetics, manufacturer of a proprietary test that was included in this study. All other authors reported no relevant conflict of interest.

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 judgment 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.

DATA AVAILABILITY STATEMENT

Data available on request from the authors - The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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