Appropriate use criteria in dermatopathology: Initial recommendations from the American Society of Dermatopathology

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Background: Appropriate use criteria (AUC) provide physicians guidance in test selection, and can affect health care delivery, reimbursement policy, and physician decision-making.

Objectives: The American Society of Dermatopathology, with input from the American Academy of Dermatology and the College of American Pathologists, sought to develop AUC in dermatopathology.

Methods: The RAND/UCLA appropriateness methodology, which combines evidence-based medicine, clinical experience, and expert judgment, was used to develop AUC in dermatopathology.

Results: With the number of ratings predetermined at 3, AUC were developed for 211 clinical scenarios involving 12 ancillary studies. Consensus was reached for 188 (89%) clinical scenarios, with 93 (44%) considered "usually appropriate" and 52 (25%) "rarely appropriate" and 43 (20%) having "uncertain appropriateness."

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Limitations: The methodology requires a focus on appropriateness without comparison between tests and irrespective of cost.

Conclusions: The ultimate decision to order specific tests rests with the physician and is one where the expected benefit exceeds the negative consequences. This publication outlines the recommendations of appropriateness—the AUC for 12 tests used in dermatopathology. Importantly, these recommendations may change considering new evidence. Results deemed "uncertain appropriateness" and where consensus was not reached may benefit from further research. (J Am Acad Dermatol 2019;80:189-207.)

Key words: ancillary studies; appropriate use criteria; dermatopathology; evidence-based medicine; expert rating.

Medical leaders and consumers are calling for a safer, more efficient and effective health care system. In recent years, there has been an exponential increase in the number of diagnostic tests. Given the increase in cost from new technologies, physicians need tools to help them make decisions about health care, especially in appropriateness of care, that achieve value, increase quality, and control costs.[1]

CAPSULE SUMMARY

- Appropriate use criteria combine the best scientific evidence available with expert judgment yielding a statement of the appropriateness for performing a test in specific clinical scenarios.
- Initial recommendations for the use of selected ancillary studies in dermatopathology are outlined.
- Appropriate use criteria can affect health care delivery, inform reimbursement policy, and guide physician decision making.

Appropriate use criteria (AUC) combine the best scientific evidence available with the collective judgment of experts to yield a statement of the appropriateness for performing a test in specific clinical scenarios encountered in everyday practice. Qualifying appropriateness is the beginning of addressing cost-effectiveness, as studies have shown good correlation between the two.[2]

In 2015, the American Society of Dermatopathology (ASDP) created the AUC Task Force to help guide dermatopathologists in their use of ancillary studies. Four subgroups were established and each group chose 2-3 ancillary studies for which to develop AUC. The subgroups were divided into 4 broad categories: lymphoproliferative, melanocytic, soft tissue, and other.

This report provides a synopsis of the AUC for the ancillary studies chosen and developed using the

Drs Vidal, Armbrect, Andea, Bohlke, Comfere, Hughes, Kim, Kozel, Lee, Linos, Litzner, Missall, Novoa, Sundram, Swick, and Hurley were members of the Appropriate Use Criteria (AUC) Task Force.

Drs Alam, Argenyi, Duncan, Elston, Emanuel, Ferringer, Fung, Hosler, Lazar, Lowe, Plaza, Prieto, Robinson, Schaffer, Subtil, and Wang were members of the rating panel.

Dr Hurley, as designated, was the Chair of the AUC Task Force / Committee and is the senior author.

Drs Kim, Kozel, Litzner, and Sundram were AUC subgroup leaders.

Drs Argenyi, Duncan, Ferringer, Fung, Holser, Lowe, Plaza, Prieto, Subtil, and Wang and Emanuel were American Society of Dermatopathology representatives.

Dr Elston was the American Society of Dermatopathology President during the time of AUC development.

Drs Alam and Robinson were the American Academy of Dermatology representative.

Drs Lazar and Schaffer were College of American Pathologist representatives.

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Conflicts of interest: None disclosed.

Disclaimer: The recommendations presented in this study were developed using the RAND Corporation (Santa Monica, CA) and University of California, Los Angeles, appropriateness method. Appropriateness ratings represent the best interpretation of the literature combined with expert judgment at the time of their development. The selection of a test ultimately lies with the physician and the assessment of multiple factors associated with the individual patient. The clinical scenarios used should not be considered inclusive of all situations in which a test or study should or can be performed. In the future, with the availability of additional information, changes to these recommendations may be required.

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Abbreviations used:

ASDP: American Society of Dermatopathology
AUC: appropriate use criteria
UQ: unqualified

RAND/UCLA appropriateness method.[3] The goal in a health system is for inappropriate care to be reduced while necessary and for appropriate care to be increased or maintained. It is imperative to

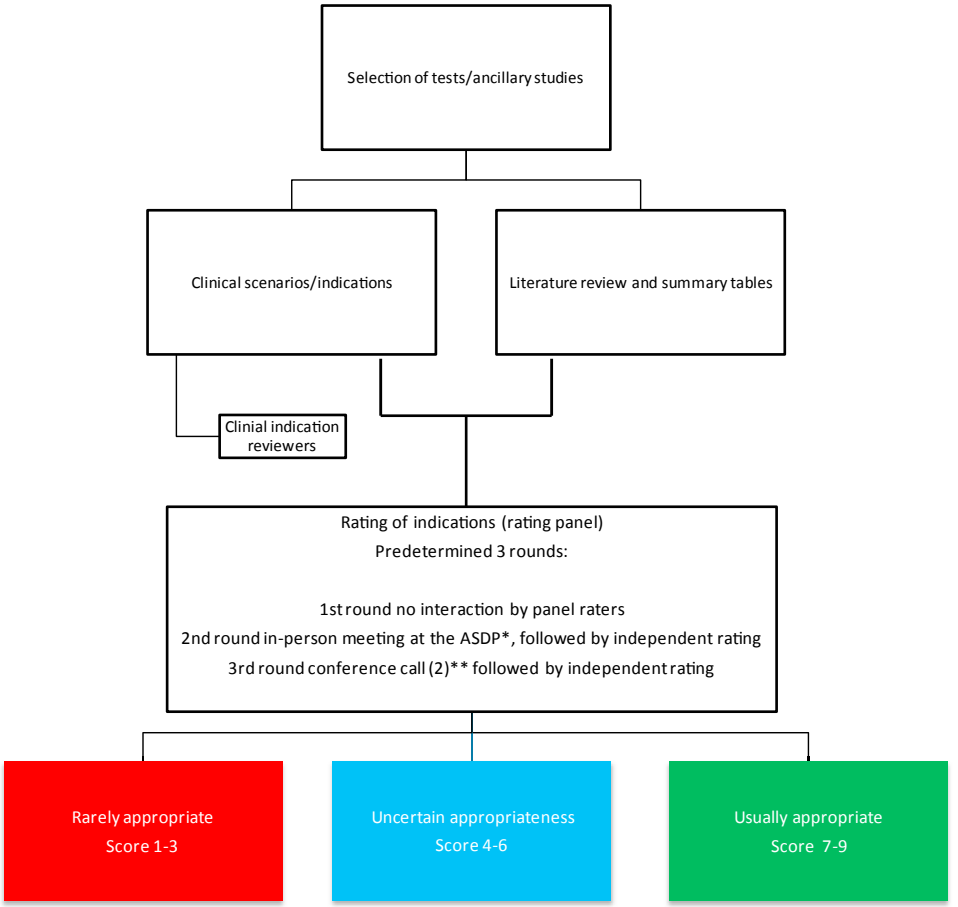

Fig 1. Overview of the AUC process followed by the ASDP. Following selection of ancillary tests and a comprehensive literature review, the rating panel ranked all ancillary studies. Appropriateness ratings were grouped into 3 categories. *An in-person moderated meeting of the panel raters occurred during the 51st annual ASDP meeting (Chicago, IL, 2016). During this meeting there was a discussion of clinical scenarios where consensus had not been achieved. The discussion was preceded by a summary of the literature review by an AUC Task Force member for each ancillary study for which AUC were being developed. The goal was to discuss the literature and draw from other experts in the field, while also being mindful of not requesting ratings or influencing the panel to seek consensus. During the in-person meeting, panel raters requested 2 additional options be allowed during the rating process: unqualified (UQ), which was to be used if "as a dermatopathologist I do not have expertise to decide if this is appropriate" and OUT, which was not an acronym but rather an indication that assessment of appropriateness of a test cannot be made without direct communication with the clinician and furthermore the appropriateness will change on a case by case basis depending on the clinical information provided. Panel raters were instructed that these 2 options should be used sparingly. **Prior to the third-round rating, there were two moderated teleconference sessions, which focused on clinical scenarios that were close to consensus. Panel raters explored wording of clinical scenarios or definitional understandings that needed clarification. Panel raters were also provided the statistical analysis based on results from the first and second rounds. *AUC*, Appropriate use criteria; *ASDP*, American Society of Dermatopathology.

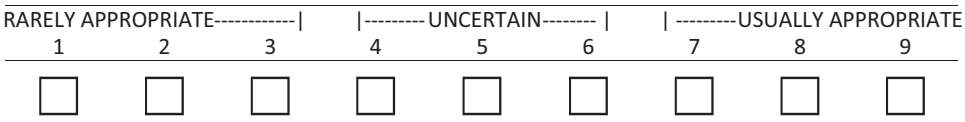

Fig 2. Nine-point rating scale used for each clinical scenario. A score of 9 to 7 indicated the test or procedure belonged to the "usually appropriate" category where higher scores indicate greater agreement within the category. A score of 1 to 3 indicated that the test or procedure is "rarely appropriate" in that specific clinical scenario while acknowledging clinician discretion might be suitable for ordering the test under selected circumstances. A lower score within the range would indicate strength in conviction of the test being less appropriate. The category nomenclature was chosen to reflect that the ultimate decision in selecting to do a test lies with the physician taking into account the individual patient. Scores in the range of 4 to 6 were used to indicate "uncertain appropriateness" for ordering the test/procedure in that clinical scenario. Scores in this midrange generally indicated that the panel raters' assessment was there was a lack of scientific evidence for the need for that test or procedure in general or for that individual clinical scenario. Insufficient scientific evidence could be due to the data being considered as emergent or underdeveloped.

understand that the ancillary studies and clinical scenarios chosen are not exhaustive and that this publication is not a comparison of the different tests, as each ancillary study was reviewed independently for each clinical scenario. In addition, as literature emerges updates to the AUC will need to be made and are already planned by the ASDP.

MATERIALS AND METHODS

The AUC process combines evidence-based medicine with clinical scenarios and expert judgment by engaging a rating panel in a modified Delphi exercise by using the validated appropriateness method of RAND/UCLA to yield a statement regarding the appropriateness of performing a test or procedure in a specific patient scenario (Fig 1). The process begins by the selection of tests and procedures for which AUC will be created. In general, AUC focus on tests that are widely and frequently used, consume significant resources, or have wide variations in their use. The process overview taken by the ASDP is outlined in Fig 1. In total, 12 dermatopathology ancillary studies underwent the AUC process (Supplemental Table I; available at https://www.jaad.og).

Development of definitions and clinical indications

Each of the 4 subgroups developed a set of definitions to clearly explain the meaning of assigned terms and histologic diagnoses as well as clinical scenarios ("indications") to simulate situations most likely to be encountered in practice. A total of 211 clinical scenarios were produced and then reviewed independently by 12 clinical indication reviewers composed of dermatopathologists from across the country with expertise in various areas for conciseness and completeness. They were then modified so that they comprised the most often encountered situations in dermatopathology practice. The clinical scenarios were not intended to be exhaustive, but to represent at least 85% of anticipated scenarios. They were based on information that is readily available to dermatopathologists during routine practice. Further specific information regarding definitions and clinical scenarios for each subgroup is summarized in Supplemental Tables II-VIII (available at http://www.jaad.org).[4-9]

Evidence

The development of UAC is founded on combining evidence review and analysis with expert judgment that is provided by the panel raters. A detailed literature review was performed by the AUC Task Force to provide the best available evidence on each ancillary study. The 4 subgroups received general guidelines for evidence review including: journal articles written in English, search years beginning in 1940 to 2016, overlapping studies removed and case series ($n > 3$) included only if no other evidence was available.

In total, 239 articles were identified and summarized for the development of the literature review tables that were provided to the panel raters for use during rating. Each subgroup added additional parameters if deemed necessary. Synopses of the best scientific evidence for each of the ancillary studies chosen are separately published in the *Journal of Cutaneous Pathology*.[10-14]

Rating process

Seventeen panel raters were carefully selected for balance, expertise in a field, and breadth of

Table I. Appropriate use scores: clinical scenarios ranked usually appropriate and usually appropriate to uncertain (majority usually appropriate)

Lymphoproliferative group: TCR beta and gamma appropriate use scores			
Clinical scenario	**Beta ratings**	**Gamma ratings**	**Commentary**
≥1 scaly patch/plaque concerning for MF; histology and IHC concerning for or suggestive of MF	UA (8.0)	UA (7.9)	Evidence supports the use of both beta and gamma clonality assays and is reflected in the results with panel raters ranking the appropriateness of beta and gamma clonality similarly for each scenario. T-cell clonality is recommended as a confirmatory test in cases in which the histology and immunophenotype are concerning for or suggestive of MF, if a folliculotropic infiltrate is encountered, and for clone comparison
Histology of a T-cell infiltrate not diagnostic for MF in a patient with a history of MF and known clone (comparison of past and present clones)	UA (7.1)	UA (7.1)	
Histology of a folliculotropic T- cell infiltrate	UA (7.1)	UA (7.2)	
T-cell infiltrate in a patient with a history of systemic T-cell lymphoma	UAU (6.8)	UAU (6.9)	Interestingly, despite the lack of robust literature, experts still ranked the scenario dealing with a T-cell infiltrate in a patient with a history of T-cell lymphoma as "majority usually appropriate." This may be reflective of the knowledge that in some cases of systemic T-cell lymphomas (ie, angioimmunoblastic T-cell lymphoma), secondary cutaneous infiltrates are often not histologically atypical in appearance. In addition, some specialized immunohistochemical stains (ie, programmed cell death 1) are not uniformly available in all laboratories. In these cases, TCR clonality assays may be a rapid and inexpensive way to confirm the diagnosis of secondary cutaneous involvement by systemic T-cell lymphoma. Testing would also be a good approach to cases in which the systemic T-cell lymphoma has the TCR in the germline configuration or if the patient has synchronous primary lymphomas

Lymphoproliferative group: B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores		
Clinical scenario	**IgH ratings**	**Commentary**
≥1 erythematous nodule creating concern; clinical findings rule out B-cell lymphoma; histology and IHC concerning for or suggestive of PCMZL	UA (7.8)	There were 6 clinical scenarios in which testing for rearrangement of the B-cell receptor (IgH) by PCR was usually appropriate. It is not surprising that testing was found to be usually appropriate for scenarios when the histology and immunophenotype of the infiltrate was concerning for or suggestive of either PCMZL or FCL. These entities tend to be difficult to diagnose primarily on the basis of histology or immunohistochemistry. In PCMZL, definitive diagnosis often relies on detection of light chain restriction, which can be difficult unless plasma cells are abundant. In FCL, the typical histologic features relied on by hematopathologists, such as back-to-back follicle formation or bcl-2 expression, are often absent even in grade 2 FCL. Although in FCL with a diffuse pattern, the presence of sheets of B-cells is concerning for lymphoma, again, the lack of typical follicular lymphoma markers such as expression of CD10 and bcl-2 can lead to confusion even among experienced dermatopathologists. In these scenarios, testing with clonality assays can confirm the diagnosis.[9] As expected, testing was usually appropriate in cases in which the clonality assay was being used for clone comparison
≥1 erythematous nodule creating concern; clinical findings rule out B-cell lymphoma; histology and IHC concerning for or suggestive of FCL	UA (8.1)	
≥1 nodule(s); clinical CLH; histology and IHC concerning for or suggestive of PCMZL	UA (8.2)	
≥1 nodule(s); clinical CLH; histology and IHC concerning for or suggestive of FCL	UA (8.2)	
≥1 nodule(s); clinical findings concerning for aggressive B-cell lymphoma rule out B-cell lymphoma, leg type; histology and IHC concerning for or suggestive of PCLBCL, primary cutaneous large B-cell lymphoma, leg type	UA (7.7)	
Cutaneous B-cell infiltrate not diagnostic for B-cell lymphoma but in a	UA (7.9)	

Continued

Table I. Cont'd

Lymphoproliferative group: B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores		
Clinical scenario	**IgH ratings**	**Commentary**
patient with history of B-cell lymphoma known clone (comparison of past and present clones)		
1 lesion; clinical findings suggestive of non-neoplastic process; B-cell predominant infiltrate	UAU (6.6)	Testing was recommended by the majority of panel raters in cases in which the clinical impression was of a single lesion suggestive of a non-neoplastic process or dermatitis but the histology showed a B-cell—predominant infiltrate
Dermatitis; clinical findings suggestive of non-neoplastic process; B-cell predominant infiltrate	UAU (6.9)	
Cutaneous B-cell infiltrate in a patient with a history of any systemic B-cell lymphoma	UAU (6.8)	

Melanocytic group: FISH and CGH appropriate use scores					
Clinical scenario	**Patient type**	**FISH ratings**	**CGH ratings**	**qRT-PCR ratings**	**Commentary**
Pathology suggestive of MM (DDx nevoid MM vs benign melanocytic nevus)	Adult/pediatric	UA (7.4/7.8)	UA (7.7/7.9)	Please refer to Table III	Ratings indicate that in most scenarios in which the diagnosis of melanoma is in question it is reasonable to use FISH or CGH as an ancillary test. In general, the results of expert panel ratings for FISH and CGH were similar. Results were also similar across age groups (adult vs pediatric) In most scenarios, except for those in which the pathology was definitive for melanoma or melanocytic nevus, expert rating found that it was usually appropriate to perform FISH or CGH on melanocytic lesions when the diagnosis was in question
Pathology suggestive of MM (DDx nevoid cutaneous metastasis vs benign melanocytic nevus)	Adult/pediatric	UA (7.3/7.7)	UA (7.8/7.9)		
Pathology suggestive of MM (DDx MM arising within nevus/dysplastic nevus)	Adult/pediatric	UA (7.0/7.5)	UA (7.7/7.6)		
Pathology suggestive of MM (DDx congenital nevus with proliferative nodule vs MM)	Adult/pediatric	UA (7.6/7.7)	UA (7.9/7.9)		
Pathology suggestive of MM (DDx atypical Spitz vs spitzoid MM)	Adult/pediatric	UA (7.6/7.1)	UA (7.7/7.9)		
Pathology suggestive of MM; incompletely sampled (DDx unclassified Spitz vs spitzoid MM)	Adult/pediatric	UA (7.6/7.1)	UA (7.2/7.6)		
Pathology suggestive of MM (DDx severely atypical melanocytic proliferation vs MM on cosmetically sensitive areas and special sites)	Adult/pediatric	UA (7.5/7.8)	UA (7.6/7.8)		
Light microscopy not definitive	Adult/pediatric	UA (7.8/7.9)	UA (7.9/8.0)		
Partial biopsy; light microscopy not definitive	Adult/pediatric	UA (7.5/7.3) 1/16 OUT (adult patient); 1/16 OUT (pediatric patient)	UA (7.2/7.5) 1/16 OUT (adult patient); 1/16 OUT (pediatric patient)		
DDx nevus vs metastasis; light microscopy not definitive	Adult/pediatric	UA (7.5/7.6)	UA (7.9/7.9)		
DDx nevus vs metastasis; partial biopsy; light microscopy not definitive	Adult/pediatric	UA (7.5/7.4) 1/16 OUT (adult patien); 1/16 OUT (pediatric patient)	UA (7.3/7.5) 1/16 OUT (adult patient); 1/16 OUT (pediatric patient)		

Pathology suggestive of MM (DDx atypical blue nevus vs benign blue nevus)	Adult/ Pediatric	Please refer to Table III	UA (7.0) Please refer to Table IV	Interestingly, the results also indicate that currently, CGH is the only test ranked usually appropriate when it comes to distinguishing benign blue nevi from more worrisome dermal melanocytoses
Pathology suggestive of MM (DDx blue nevus-like cutaneous metastasis vs benign blue nevus)	Adult/pediatric	Please refer to Tables III and IV	UA (7.6/7.6)	
Pathology suggestive of MM (DDx malignant blue nevus vs benign blue nevus)	Adult/pediatric	Please refer to Table IV	UA (7.4/7.6)	
Pathology suggestive of MM; incompletely sampled (DDx sclerosing desmoplastic nevus vs desmoplastic MM)	Adult/pediatric	Please refer to Table IV	UA (7.0/7.3)	In this scenario, CGH was rated usually appropriate. This may relate to the study by Gerami et al in 2011, which showed a low sensitivity but high specificity in this subset with FISH[17]

Other group: HPV appropriate use scores

Clinical scenario	ISH ratings	IHC ratings	Commentary
Pediatric; suggestive of condyloma Age <25 y; pathologic findings consistent with seborrheic keratosis of genital skin, perineum, lower abdomen, or inner thigh	UA (7.5) 4/16 OUT UAU (6.7) 4/16 OUT	Please refer to Table IV Please refer to Table III	Only in pediatric cases in which pathology was suggestive of condyloma did experts believe that testing by ISH was usually appropriate. Literature on this topic suggests that sensitivities for detection of HPV by ISH in the pediatric population ranges from 60% to 100%,[23-26] which may be the reason for the recommendation A significant number of panel raters utilized the OUT rating in scenarios dealing with the use of ISH and IHC for the detection of HPV. The scenarios with a significant number of OUT ratings were those in which the pathology was suggestive of a condyloma in the pediatric population and in cases in which the pathology was consistent with a seborrheic keratosis of the genital skin, perineum, lower abdomen, or inner thigh. This likely reflects the psychosocial implications surrounding a diagnosis of HPV, especially in the genital area and in children, emphasizing the importance of direct communication between dermatopathologist and clinician before these tests are performed

Other group: MTS appropriate use scores

Clinical scenario	4-AB panel ratings	2-AB panel ratings	Commentary
Age >60 y; multiple sebaceous tumors	UA (7.2)	UA (7.2)	MTS is a clinical variant of Lynch syndrome defined by the synchronous or metachronous occurrence of at least 1 sebaceous neoplasm or keratoacanthoma and at least 1 Lynch syndrome—related internal cancer in a patient irrespective of family history or age at onset.[6,28] A universal screening for Lynch syndrome has been recommended by major task forces and groups for all new colorectal cancers in patients age ≤70 y [29]; however, with respect to MTS-associated skin neoplasms, no formal screening guidelines have been established. Although a sensitivity as high as 81% has been reported in the literature for MMR analysis by IHC in sebaceous neoplasms, studies in which germline mutation analysis is also available point to a high false-positive rate, presumably from nonheritable molecular events within the lesion[30-32]
Age >60 y; KA with sebaceous differentiation	UA (7.1)	UAU (6.6)	
Age >60 y; cystic sebaceous neoplasm	UA (7.3)	UAU (6.9)	
Age >60 y; MTS-associated neoplasm and/or visceral malignancy	UA (7.3) 1/16 OUT	UAU (6.9)	
Age >60 y; 1 sebaceous tumor non—head and neck	Refer to Table IV	UAU (6.9) 1/16 OUT	

Continued

Table I. Cont'd

Other group: MTS appropriate use scores			
Clinical scenario	**4-AB panel ratings**	**2-AB panel ratings**	**Commentary**
	for the results with the 4-AB panel		The average age of presentation of sebaceous neoplasms in MTS is 53 y; however, the range is broad (range, 21-88 y). Of note, these neoplasms can present before (22%), concurrently with (6%), or after (56%) the internal malignancy.[33] An age >60 y was analyzed here, given the larger potential for misuse of MMR IHC. At a cellular level, MMR proteins bind as heterodimers, with MLH1 binding to its secondary partner PMS2 and MSH2 binding to MSH6. Mutations in MLH1 and MSH2 account for the vast majority of mutations in MTS, and isolated loss of secondary partners PMS2 and MSH6 is rare. With this in mind, and with the preponderance of literature using a panel of MLH1 and MSH2, this was chosen as the 2-AB panel to be rated. However, a panel using PMS2 and MSH6 may show greater promise but needs validation that includes germline mutation analysis and a larger cohort of sebaceous neoplasms[34] The results for the 4- and 2-AB panels rated were similar and mirror the weak-to-moderate support for the global use of MMR protein analysis by IHC in sebaceous neoplasms and neoplasms associated with MTS. Recent scientific evidence suggesting a tailored approach using clinical parameters is reflected by the ratings. Only those scenarios in which multiple sebaceous neoplasms were encountered and scenarios in which the patient had a history of an MTS-associated neoplasm and/or visceral malignancy was the test found to be usually appropriate. Not surprisingly, other strong indicators of MTS, such as the presence of sebaceous differentiation within a keratoacanthoma and the presence of a cystic sebaceous neoplasm, were also found to be usually appropriate following the rounds of expert rating Interestingly, the OUT option was not used frequently in the rating of these clinical scenarios

Soft-tissue group: t(17:22) in dermatofibrosarcoma protuberans appropriate use scores		
Clinical scenario	**t(17:22) ratings**	**Commentary**
Histology not typical for DFSP; $CD34^+$ Tyrosine kinase therapy is being considered	UA (7.2) UA (7.2) 1/16 OUT	Cytogenetically, DFSP is characterized by a balanced or unbalanced translocation, t(17;22)(q22;q13), or a supernumerary ring chromosome, resulting in the fusion of exon 2 of *PDGFB* gene encoding the platelet-derived growth factor beta with various exons (from 6 to 47) of *COL1A1* gene encoding the alpha chain type 1 collagen. Multiple modalities of FISH can be utilized to detect the translocation. These include dual-fusion *COL1A1/PDGFB* FISH, *PDGFB* break-apart FISH, and *COL1A1* break-apart FISH.[35-40] The overall sensitivity of the dual-fusion FISH test in the literature is 94.3% (range, 86%-100%). This was similar for *PDGFB* break-apart FISH, which has an overall sensitivity of 95% (range, 91%-100%). The sensitivity of the *COL1A1* break-apart probe is probably in the same range; however, there is only 1 study that explicitly mentioned this probe being identified.[41-44] Given the high sensitivity of FISH and the therapy potential if the translocation is detected, it is not surprising that the 2 scenarios in which the test was found to be usually appropriate were situations in which the histology of the tumor is not typical for DFSP and the tumor is CD34 reactive and situations in which tyrosine kinase therapy is being considered

Histology not typical for DFSP; CD34^{+}; subcutis not visualized	UAU (6.5)
Fibrosarcoma-like (high-grade) histology; no histology typical for DFSP	UAU (6.9)
Tissue that has been decalcified or processed with fixative other than 10% formalin	UAU (6.6)
Histology typical for DFSP; CD34^{+}; treating physician requesting cytogenetics to confirm diagnosis	UAU (6.3) 3/16 OUT

These clinical scenarios were found to be "majority usually appropriate." It is interesting that the clinical scenario in which the tissue was not processed appropriately was not ranked differently or the use of the OUT option was not ranked higher, as one may argue that it may be more appropriate to discuss the case with the clinician and, depending on clinical circumstances, obtain an additional/larger sample of the tumor to visualize deeper structures. The OUT option was used by panel raters and considered significant for the clinical scenario where the histology is typical for DFSP, the lesion is CD34 positive, and the clinician is requesting cytogenetics to confirm the diagnosis. This may be the result of a bias of the panel raters that perhaps the clinician is planning targeted therapy and signifies the importance of a better dialogue between the pathologist and clinician.

Soft-tissue group: *EWSR1* FISH clear cell sarcoma appropriate use scores

Clinical scenario	*EWSR1* FISH ratings	Commentary
Age <50 y; typical location; tumor with histology typical for CCS, expressing melanocytic markers, involving reticular dermis, subcutis, or aponeurosis. No history of MM	UA (8.3)	CCS is a very rare aggressive soft-tissue sarcoma showing neuroectodermal and melanocytic differentiation.[45,46] It typically occurs in individuals age <50 y and preferentially arises in the deep soft-tissue of distal extremities. Although it shares some histologic overlap with melanoma, it is genetically and biologically distinct, resulting in prognostic differences.[47,48] As there are significant consequences for misdiagnosis of CCS, it follows that expert rating found it usually appropriate to perform the dual-color break-apart *EWSR1* FISH assay in cases in which a histology typical of CSS is encountered, especially given the test's high specificity of 97.91%.[49] This rating holds true regardless of age and whether an intraepidermal component is found histologically. Additionally, testing is usually appropriate when a metastatic lesion is encountered in a patient with a previously diagnosed CCS but the histology of the metastatic lesion appears distinct, and also for situations in which CCS is suspected but the specimen was not fixed in standard fixative or decalcified. The majority of the panel raters would also do testing despite a *BRAF* or *NRAS* mutation having already been detected in either a primary or metastatic lesion
Age ≥50 y; typical location; tumor with histology typical for CCS, expressing melanocytic markers, involving reticular dermis, subcutis, or aponeurosis. No history of MM	UA (8.1)	
Dermal tumor expressing melanocytic markers and demonstrating typical histology of CCS. Patient has a history of invasive MM at another site	UA (7.9)	
Typical location; tumor in dermis/subcutis; histology typical for CCS, expressing melanocytic markers, but also has an intraepidermal in situ component	UA (7.5)	
Nontypical location; tumor in dermis/subcutis; histology typical for CCS expressing melanocytic markers, but it also has an intraepidermal in situ component	UA (7.4)	
Metastatic tumor with histology different from previous that of CCS	UA (7.3)	
Tissue that has been decalcified or processed with fixative other than 10% formalin	UA (7.0)	
Primary or metastatic tumor expressing melanocytic markers; *BRAF* or *NRAS* mutation detected	UAU (6.3)	

UA indicates mean' scores higher than 7.0, and UAU (majority usually appropriate) indicates a mean' score between 6.1 and 6.9 with a standard deviation less than 2.0. Please refer to the Supplemental Tables for complete wording of the clinical scenarios and associated definitions.

AB, Antibody; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase gene; *CCS*, clear cell sarcoma; *CGH*, comparative genomic hybridization; *CLH*, cutaneous lymphoid hyperplasia; *COL1A1*, collagen type I alpha 1 chain gene; *DDx*, differential diagnosis; *DFSP*, dermatofibrosarcoma protuberans; *EWSR1*, EWS RNA binding protein 1 gene; *FCL*, follicle center lymphoma; *FISH*, fluorescence in situ hybridization; histology typical for CCS, monotonous spindled cells in a storiform pattern with honeycombing or entrapment of adnexal structures and/or adipocytes and extension into the subcutis; *HPV*, human papilloma virus; *IHC*, immunophenotype/immunohistochemistry; *ISH*, in situ hybridization; *KA*, keratoacanthoma; *MF*, mycosis fungoides; *MLH1*, mutL homolog 1; *MM*, melanoma; *MMR*, mismatch repair analysis; *MSH2*, mutS homolog 2; *MSH6*, mutS homolog 6; *MTS*, Muir-Torre syndrome; *NRAS*, NRAS proto-oncogene, GTPase gene; *PCLBCL*, primary cutaneous large B-cell lymphoma; *PCMZL*, primary cutaneous marginal zone lymphoma; *PCR*, polymerase chain reaction; *PDGFB*, platelet derived growth factor subunit B gene; *PMS2*, PMS1 homolog 2, mismatch repair system component; *qRT-PCR*, quantitative reverse-transcription polymerase chain reaction; *TCR*, T-cell receptor; *UA,* usually appropriate; *UAU*, usually appropriate to uncertain.

Table II. Appropriate use scores: clinical scenarios ranked rarely appropriate and rarely appropriate to uncertain (majority rarely appropriate)

Lymphoproliferative group: TCR beta and gamma appropriate use scores

Clinical scenario	Beta ratings	Gamma ratings	Commentary
Dermatitis; clinical findings rule out MF/CTCL; histology not diagnostic for MF	RA (2.8)	RA (2.8)	Congruent with current scientific evidence, testing is rarely appropriate in cases of dermatitis or pigmented purpuric patches with a nondiagnostic histology given the inherent limitations in sensitivity and specificity of clonality tests to reliably distinguish between early presentations of T-cell lymphoproliferative disorders and benign inflammatory dermatoses, such as lymphomatoid drug eruptions, lichen sclerosus, entities within the PL disease group, and pigmented purpuric eruptions. The high rate of false positives with clonality testing is reflected in the rarely appropriate recommendation for the clinical scenarios in which a diagnosis of LyP or PL is made histologically. Not surprisingly, panel raters believed that it was rarely appropriate to perform this assay in cases of new nodules in a patient with a known diagnosis of MF concerning for or suggestive of large cell transformation, regardless of CD30 positivity Although there was 1 clinical scenario in which panel raters utilized the OUT option during the rating process for both the beta and gamma clonality assays, this was considered to not be significant, as rating was completed by 88% of panel raters
Inflammatory/reactive/papular/papulonecrotic solitary/regional/generalized; clinical findings rule out LyP, PL, MF, CTCL; histology typical for LyP or PL	RA (2.1)	RA (2.1)	
Pigmented purpuric patches solitary/regional/generalized; clinical findings rule out MF/CTCL; histology not diagnostic for MF	RA (2.87) 2/16 OUT	RA (2.6) 2/16 OUT	
Nodules in patient with a history of MF; histology concerning for or suggestive of MF with $CD30^+$ large cell transformation	RA (2.8)	RA (2.8)	
Nodules in patient with a history of MF; histology concerning for or suggestive of MF without $CD30^+$ large cell transformation	RA (2.7)	RA (2.7)	

Lymphoproliferative group: B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores

Clinical scenario	IgH ratings	Commentary
≥1 erythematous concerning nodule; clinical findings rule out B-cell lymphoma (PCMZL or FCL); histology and IHC not diagnostic for cutaneous B-cell lymphoma	RA (2.7)	
New/evolving lesion in patient with a prior diagnosis of B-cell lymphoma (PCMZL or FCL); clinical findings rule out B-cell lymphoma; histology and IHC consistent with PCMZL or FCL	RA (2.6)	

Melanocytic group: FISH and CGH appropriate use scores

Clinical scenario	Patient type	FISH ratings	CGH ratings	qRT-PCR ratings	Commentary
Pathology definitive for MM	Adult/pediatric	RA (1.1/1.5) 1/16 OUT: pediatric patients	RA (1.2/1.4) 1/16 OUT: pediatric patient	RA (1.2/1.2)	In those cases in which the pathology is definitive for either MM or melanocytic nevus, testing with FISH, CGH, and qRT-PCR is rarely appropriate. This was not surprising, as histology is considered the criterion standard in the diagnosis of melanocytic lesions. Of note, inclusion of these clinical scenarios may be considered a proof of concept that the rounds of ratings yielded meaningful results
Pathology definitive for nevus	Adult/pediatric	RA (1.1/1.1)	RA (1.1/1.1)	RA (1.1/1.4)	

Other group: HPV appropriate use scores

Clinical scenario	ISH ratings	IHC ratings	Commentary
Adult; definitive for condyloma	RA (1.6) 1/16 OUT	RA (1.5) 1/16 OUT	Use of HPV, ISH, and IHC shows wide variability, and these tests are currently frequently performed and often at the request of clinicians. Although there are many commercially available type-specific probes and cocktails for the detection of HPV by ISH, type-specific probes for HPV 6, 11, 16, 18, 31, and 33 are the most commonly utilized by dermatopathologists. The availability of commercially available antibodies targeting HPV is much more limited, with only 2 currently available[11]
Subungual wart	RA (2.0) 1/16 OUT	RA (2.1) 1/16 OUT	
Nail bed, periungual, or nail matrix SCCIS or SCC	RA (2.6)	RA (2.2)	
SCCIS or SCC with verrucous features on digits	RA (2.9)	RA (2.2)	
History of HPV-induced lesion and SCC in the genital area	RAU (3.6)	RA (2.8)	Although most of the literature for detection of HPV centers on use of ISH in condylomas or lesions histologically concerning for condylomas in adults, consensus ratings found testing by ISH to be rarely appropriate to "majority rarely appropriate" for many of the scenarios ranked
SCC in the genital area and history of chronic dermatoses (ie, LSEA, LP)	RAU (3.2)	RA (2.7)	
Clinical impression and pathology consistent with verrucous carcinoma	RAU (3.3)	RA (2.3)	Most scenarios were ranked as rarely appropriate for the use of IHC in the detection of HPV. These ratings probably reflect the presence of only 2 articles exploring the use of IHC for detection of HPV
Immunosuppressed patients with SCCIS or SCC with verrucous features	RAU (3.3)	RA (2.6)	
SCCIS/undifferentiated intraepithelial dysplasia of the genital skin	Please refer to Table III	RA (2.8) 1/16 OUT	
SCC in the genital area	Please refer to Table IV	RA (2.8)	

Other group: MTS appropriate use scores

Clinical scenario	4-AB panel ratings	2-AB panel ratings	Commentary
Age >60 y; periocular sebaceous carcinoma	Please refer to Table IV	RA (3.0)	

Soft-tissue group: t(17:22) in dermatofibrosarcoma protuberans appropriate use scores

Clinical scenario	t(17:22) ratings	Commentary
Histology typical for DFSP; $CD34^+$	RA (1.4)	Ratings in this group were expected. Testing is typically not needed when a diagnosis can be made by histology and IHC or in situations in which testing for the translocation has been completed by another testing modality
Metastatic lesion with histology similar to prior DFSP	RA (2.9) 1/16 OUT	
Locally recurrent DFSP; positive translocation testing result by other molecular test	RA (1.6)	
Metastatic DFSP; positive translocation testing result by other molecular test	RA (1.7)	

Soft-tissue group: *EWSR1* FISH clear cell sarcoma appropriate use scores

Clinical scenario	*EWSR1* FISH ratings	Commentary
Age ≥50 y; nontypical location; tumor expressing melanocytic markers; with nontypical histology for CCS, involving reticular dermis, subcutis, or aponeurosis. No history of MM but with what appears to be cutaneous metastasis of MM from unknown primary	RA (2.2)	For clinical scenarios in which a typical histology of CCS is lacking, older individuals and occurrence of CCS on nontypical locations testing for *EWSR1* FISH was generally not recommended (majority rarely appropriate/rarely appropriate). Likewise, testing was rarely appropriate if the tumor has undergone testing to detect the translocation by another modality
Recurrent/metastatic CCS with translocation testing by other method positive	RA (1.9)	

Continued

Table II. Cont'd

Soft-tissue group: *EWSR1* FISH clear cell sarcoma appropriate use scores		
Clinical scenario	***EWSR1* FISH ratings**	**Commentary**
Age ≥50 y; typical location; tumor with nontypical histology for CCS expressing melanocytic markers, involving reticular dermis, subcutis, or aponeurosis. No history of MM	RAU (3.4)	
Age <50 y; nontypical location; tumor expressing melanocytic markers; with nontypical histology for CCS, involving reticular dermis, subcutis, or aponeurosis. No history of MM but with what appears to be cutaneous metastasis of MM from unknown primary	RAU (3.2)	
Metastatic tumor with histology similar to previous CCS	RAU (3.2)	

RA indicates mean' scores of 3.0 or lower, and RAU (majority rarely appropriate) indicates mean' scores between 3.1 and 3.9 with a standard deviation less than 2.0. Please refer to the Supplemental Tables for complete wording of the clinical scenarios and associated definitions.

AB, Antibody; *CCS*, clear cell sarcoma; *CGH*, comparative genomic hybridization; *CTCL*, cutaneous T-cell lymphoma; *DFSP*, dermatofibrosarcoma protuberans; *EWSR1*, EWS RNA binding protein 1 gene; *FCL*, follicle center lymphoma; *FISH*, fluorescence in situ hybridization; histology typical for CCS, monotonous spindled cells in a storiform pattern with honeycombing or entrapment of adnexal structures and/or adipocytes and extension into the subcutis; *HPV*, human papilloma vius; *IHC*, immunophenotype/immunohistochemistry; *ISH*, in situ hybridization; *LP*, lichen planus; *LSEA*, lichen sclerosus et atrophicus; *LyP*, lymphomatoid papulosis; *MF*, mycosis fungoides; *MM*, melanoma; *MTS*, Muir-Tore syndrome; *PCMZL*, primary cutaneous marginal zone lymphoma; *PCR*, polymerase chain reaction; *PL*, pityriasis lichenoides; *qRT-PCR*, quantitative reverse-transcription polymerase chain reaction; *RA*, rarely appropriate; *RAU*, rarely appropriate to uncertain; *SCC*, squamous cell carcinoma; *SCCIS*, squamous cell carcinoma in situ; *TCR*, T-cell receptor.

knowledge. Every attempt to avoid selection of panel raters with any financial conflicts of interest was made. Twelve panel raters (3 per topic) representing a cross-section of academics and private practice physicians were chosen for their expertise in each of the 4 subgroups and then approved by the Chair of the AUC committee. Additionally, there were 2 representatives nominated by the American Academy of Dermatology to incorporate the dermatologists' perspective (both were dermatologists, nondermatopathologists), 2 representatives nominated by the College of American Pathologists (both were pathologists and dermatopathologists) to incorporate the broader pathology perspective, and a medical director from a regional Medicare carrier. The number of rating rounds was predetermined to be 3. Panel raters received the literature review tables for all of the ancillary studies that included a general summary by test/procedure, concise individual article summaries, and the exact citations. They were also provided with clinical scenario booklets. All panel raters rated all of the ancillary studies and all ratings were done individually by each panel rater, with the overarching objective being to converge in consensus. They were instructed to rate the appropriateness of each clinical scenario using their own best expert clinical judgement and the available literature. They were specifically instructed to not consider cost during rating and to rate each independently, such that each test/procedure was rated on its own merits. During each round, panelists were asked to rate each clinical scenario on a 9-point scale (Fig 2). The category nomenclature was chosen to reflect the fact that the ultimate decision to perform a test lies with the physician and takes into account not only the clinical scenario but also the individual patient. One panelist withdrew from the project after the first-round; thus, the complete data for all 3 rounds was provided by 16 panel raters.

To facilitate panel rater discussion and support categorization for each clinical scenario, the mean of ratings was calculated; the mean was adjusted by filtering/removing 2 scores, the highest and the lowest, to minimize the impact of outlying raters (mean'). A mean' of ≥7.0 was classified as "usually appropriate." A mean' of ≤3.0 was classified as "rarely appropriate." Clinical scenarios with a mean' between 3.1 and 6.9 that had a standard deviation (SD) ≥2.0 were designated as not having reached consensus. It was determined by the research team that a SD ≥2.0 on the 9-point scale captured wide variation in rater scores. The clinical scenarios with a mean' of ≥4.0 and ≤6.0 with a SD

Table III. Appropriate use scores: clinical scenarios ranked uncertain

Lymphoproliferative group: TCR beta and gamma appropriate use scores

Clinical scenario	Beta ratings	Gamma ratings	Commentary
Clinically reactive entities; histology and IHC concerning for or suggestive of MF	U (6.0)	U (3.6)	This rating may be reflective of the high false-positive rate with these assays

Lymphoproliferative group: B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores

Clinical scenario	IgH ratings	Commentary
There were no scenarios ranked U for this assay. Please refer to Tables I, II, and IV		

Melanocytic group: FISH and CGH appropriate use scores

Clinical scenario	Patient type	FISH ratings	CGH ratings	qRT-PCR ratings	Commentary
Pathology suggestive of MM (DDx nevoid MM vs benign melanocytic nevus)	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.9/4.9)	Consensus ratings in most of the clinical scenarios using qRT-PCR were of appropriateness uncertain, with the exception being those cases in which a diagnosis could be made on histologic grounds. Although validation studies and studies exploring unequivocal cases had been published when the AUC process began,[18,19] only 1 study exploring the test in ambiguous lesions was available at the time of rating.[20] In addition, the possibility of limited clinical experience with the test may have played a role in the rating result. Since the completion of the AUC process, additional studies have been reported in the literature, including 1 dealing with diagnostically challenging cases[21] and another that correlates with clinical outcome.[22] Thus, recommendations for the appropriateness of qRT-PCR in the studied clinical scenarios are expected to change as the AUCs are subsequently and expectedly updated
Pathology suggestive of MM (DDx nevoid cutaneous metastasis vs benign melanocytic nevus)	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.6/4.4)	
Pathology suggestive of MM (DDx MM arising within nevus/dysplastic nevus)	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.7/4.6)	
Pathology suggestive/suspicious for MM (DX cong nevus with proliferative nodule vs MM)	Adult/pediatric	Please refer to Table I	Please refer to Table I	(4.8/4.8)	
Pathology suggestive/suspicious for MM (DDx atypical Spitz vs spitzoid MM)	Adult/pediatric	Please refer to Table I	Please refer to Table I	(4.9/4.8)	
Pathology suggestive/suspicious for MM; incompletely sampled (DDx unclassified Spitz vs Spitzoid MM)	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.9/4.7)	
Pathology suggestive/suspicious for MM (DDx severely atypical melanocytic proliferation vs MM on cosmetically sensitive area and SS)	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (5.1/4.9)	
Light microscopy not definitive	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (5.2/4.9)	
Partial biopsy; light microscopy not definitive	Adult/pediatric			U (4.9/4.6)	
DDx nevus vs metastasis; light microscopy not definitive	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.6/4.3)	
DDx nevus vs metastasis; partial biopsy; light microscopy not definitive	Adult/pediatric	Please refer to Table I	Please refer to Table I	U (4.4/4.2)	
Pathology suggestive of MM (DDx atypical blue nevus vs benign blue nevus)	Adult/pediatric	U (4.4/4.3)	Please refer to Tables I and IV	U (4.4/4.4)	In regard to the utility of FISH in dermal melanocytosis, Pouryazdanparast et al described the utility in epithelioid blue nevi and cutaneous melanoma metastases simulating blue nevi,[15] and Gammon et al explored use of FISH in distinguishing cellular blue nevi from blue nevus-like melanoma, showing 100% sensitivity and
Pathology suggestive of MM (DDx blue nevus-like cutaneous metastasis vs benign blue nevus)	Adult: 4.9/pediatric: Please refer to Table IV		Please refer to Table I	U (4.6/4.3)	
Pathology suggestive of MM (DDx malignant blue nevus vs benign blue nevus)	Adult/pediatric	Please refer to Table IV	Please refer to Table I	U (4.7/4.4)	

Continued

Table III. Cont'd

Melanocytic group: FISH and CGH appropriate use scores

Clinical scenario	Patient type	FISH ratings	CGH ratings	qRT-PCR ratings	Commentary
Pathology suggestive of MM; incompletely sampled (DDx sclerosing desmoplastic nevus vs desmoplastic MM)	Adult/pediatric	Please refer to Table IV	Please refer to Table I	U (4.4/4.4)	specificity.[16] Although these studies utilized a FISH probe set different from that defined by the group in this analysis, there was overlap of at least 2 of the probes used—the RREB1 and 6p25 probes

Other group: HPV appropriate use scores

Clinical scenario	ISH ratings	IHC ratings	Commentary
Age <25 y; pathologic findings consistent with seborrheic keratosis of genital skin, perineum, lower abdomen, or inner thigh	Please refer to Table I	U (3.6) 3/16 OUT	A significant number of panel raters utilized the OUT rating in scenarios dealing with the use of ISH and IHC for the detection of HPV. The scenario in this grouping with a significant number of OUT ratings was when the pathology is suggestive of a condyloma in an adult. This likely reflects the psychosocial implications surrounding a diagnosis of HPV, especially in the genital area and in children, emphasizing the importance of direct communication between dermatopathologist and clinician before performing these tests
Adult; suggestive of condyloma	U (6.3) 3/16 OUT	U (5.2) 2/16 OUT	
SCCIS/undifferentiated intraepithelial dysplasia of the genital skin	U (3.7) 1/16 OUT	Please refer to Table II	

Other group: MTS appropriate use scores

Clinical scenario	4-AB panel ratings	2-AB panel ratings	Commentary
Age >60 y; BCC with sebaceous differentiation	U (5.0)	U (4.6)	
Age >60 y; 1 sebaceous tumor of the head and neck	Please refer to Table IV	U (4.9) 1/16 OUT	

Soft-tissue group: t(17:22) in dermatofibrosarcoma protuberans appropriate use scores

Clinical scenario	t(17:22) ratings	Commentary
Metastatic lesion with histology different from that of prior DFSP	U (6.5)	This rating may speak to the need for further research exploring this topic

Soft-tissue group: *EWSR1* FISH clear cell sarcoma appropriate use scores

Clinical scenario	*EWSR1* FISH ratings	Commentary
There were no scenarios ranked U for this assay. Please refer to Tables I, II, and IV		

U indicates mean' scores from 4.0 to 6.0 with a standard deviation less than 2.0. Please refer to the Supplemental Tables for complete wording of the clinical scenarios and associated definitions. *AB*, Antibody; *AUC*, appropriate use criteria; *BCC*, basal cell carcinoma; *CGH*, comparative genomic hybridization; *DDx*, differential diagnosis; *DFSP*, dermatofibrosarcoma protuberans; *EWSR1*, EWS RNA binding protein 1 gene; *FISH*, fluorescence in situ hybridization; *IHC*, immunophenotype/immunohistochemistry; *ISH*, in situ hybridization; *MF*, mycosis fungoides; *MM*, melanoma; *MTS*, Muir-Torre syndrome; *PCR*, polymerase chain reaction; *qRT-PCR*, quantitative reverse-transcription polymerase chain reaction; *TCR*, T-cell receptor.

Table IV. Appropriate use scores: clinical scenarios with no consensus

Lymphoproliferative group: TCR beta and gamma appropriate use scores

Clinical scenario	Beta ratings	Gamma ratings	Commentary
Erythroderma; clinical findings rule out MF/CTCL/Sézary disease; histology not diagnostic for MF	NC (5.6)	NC (5.8)	Surprisingly, there was no consensus to perform clonality studies in the scenario of a new or evolving lesion in a patient with a history of MF in which the histology and immunophenotype is consistent with MF. It may be inferred that in this clinical scenario it would be more appropriate to compare clones between the current biopsy specimen and the patients' previous biopsy specimens. Ratings also yielded a recommendation of no consensus in the scenario of an erythrodermic patient with nondiagnostic histology, which may in general reflect poor global experience with early Sézary syndrome
New/evolving lesion in a patient with a history of MF; clinical findings rule out MF; histology and IHC consistent with MF	NC (3.4)	NC (3.1)	

Lymphoproliferative group: B-cell receptor (IgH) gene rearrangement by PCR appropriate use scores

Clinical scenario	IgH ratings	Commentary
Unknown history; histology and IHC consistent with PCMZL or FCL	NC (6.6)	The latter rating in this grouping may be related to the lack of clarity among some panel raters for this scenario and the scarcity of literature pertaining to the use of clonality assays for more aggressive and rarer lymphomas
Other more aggressive cutaneous B-cell lymphoma other than PCLBCL LT (eg, IVL or cutaneous plasmablastic lymphoma)	NC (5.2)	

Melanocytic group: FISH and CGH appropriate use scores

Clinical scenario	Patient type	FISH ratings	CGH ratings	qRT-PCR ratings	Commentary
Pathology suggestive of MM (DDx atypical blue nevus vs benign blue nevus)	Adult/pediatric	Please refer to Table III	Please refer to Table I NC (6.8)	Please refer to Table III	
Pathology suggestive of MM (DDx blue nevus-like cutaneous metastasis vs benign blue nevus)	Adult/pediatric	Adult: Please refer to Table III / Pediatric: NC (5.1)	Please refer to Table I	Please refer to Table III	
Pathology suggestive of MM (DDx malignant blue nevus vs benign blue nevus)	Adult/pediatric	NC (4.6/4.8)	Please refer to Table I	Please refer to Table III	
Pathology suggestive of MM; incompletely sampled (DDx of sclerosing desmoplastic nevus vs desmoplastic MM)	Adult/pediatric	NC (6.4/6.2)	Please refer to Table I	Please refer to Table III	There was no consensus on the value of FISH for situations in which the pathology is suggestive of MM when the differential diagnosis is between sclerosing desmoplastic nevus and desmoplastic MM in partially sampled lesions. However, in this specific scenario CGH was rated usually appropriate. This may relate to Gerami et al in 2011, which showed a low sensitivity but high specificity in this subset with FISH[19]

Other group: HPV appropriate use scores

Clinical scenario	ISH ratings	IHC ratings	Commentary
Pediatric; suggestive of condyloma	Please refer to Table I	NC (5.7) 4/16 OUT	In looking at ISH, there was no consensus for the clinical scenario of a pediatric patient with histology definitive for condyloma. There were also

Continued

Table IV. Cont'd

Other group: HPV appropriate use scores			
Clinical scenario	**ISH ratings**	**IHC ratings**	**Commentary**
Pediatric; definitive for condyloma	NC (6.0) 4/16 OUT	NC (4.1) 3/16 OUT	a significant number of panel raters who utilized the OUT rating in scenarios dealing with the use of ISH and IHC for the detection of HPV. The scenarios with a significant number of OUT ratings were those in which the pathology was suggestive of or definitive for a condyloma in the pediatric population. This may be because HPV type 2, which is not typically detected by ISH, is the most common subtype of HPV found in this age group[27]
SCC in the genital area	NC (3.9)	Please refer to Table II	

Other group: MTS appropriate use scores			
Clinical scenario	**4-AB panel ratings**	**2-AB panel ratings**	**Commentary**
Age >60 y; periocular sebaceous carcinoma	NC (3.5)	Please refer to Table II	
Age >60 y; 1 sebaceous tumor of the head and neck	NC (5.1) 1/16 OUT	Please refer to Table III	
Age >60 y; 1 sebaceous tumor non−head and neck	NC (6.7) 1/16 OUT	Please refer to Table I	

Soft-tissue group: t(17:22) in dermatofibrosarcoma protuberans appropriate use scores		
Clinical scenario	**t(17:22) ratings**	**Commentary**
Histology typical for DFSP; CD34 not uniformly reactive	NC (3.2)	The lack of consensus for the first 2 clinical scenarios in this grouping was not expected
Histology typical for DFSP; $CD34^+$; but subcutis not visualized	NC (4.7)	
Limited cytologic and/or architectural histology evaluation; $CD34^+$	NC (6.0) 7/16 OUT	The lack of consensus for the last clinical scenario in this grouping is not surprising. The frequent use of the OUT rating option (by 44% of panel raters) in the last scenario in this grouping, where the sample provided for evaluation is limited both cytologically and architecturally, likely underscores the importance of a discussion to ascertain the feasibility of obtaining more tissue before performing the test

Soft-tissue group: *EWSR1* FISH clear cell sarcoma appropriate use scores		
Clinical scenario	***EWSR1* FISH ratings**	**Commentary**
Age <50 y; typical location; tumor with nontypical histology for CCS expressing melanocytic markers, involving reticular dermis, subcutis, or aponeurosis. No history of MM	NC (6.3)	

NC indicates mean' scores between 3.1 and 6.9 that had a standard deviation of 2.0 or more. Please refer to the Supplemental Tables for complete wording of the clinical scenarios and associated definitions.

AB, Antibody; *CCS*, clear cell sarcoma; *CGH*, comparative genomic hybridization; *CTCL*, cutaneous T-cell lymphoma; *DDx*, differential diagnosis; *DFSP*, dermatofibrosarcoma protuberans; *EWSR1*, EWS RNA binding protein 1 gene; *FCL*, follicle center lymphoma; *FISH*, fluorescence in situ hybridization; histology typical for CCS, monotonous spindled cells in a storiform pattern with honeycombing or entrapment of adnexal structures and/or adipocytes and extension into the subcutis; *IHC*, immunophenotype/immunohistochemistry; *ISH*, in situ hybridization; *IVL*, intravascular lymphoma; *MF*, mycosis fungoides; *MM*, melanoma; *MTS*, Muir-Torre syndrome; *NC*, no consensus; *PCLBCL LT*, primary cutaneous large B-cell lymphoma, leg type; PCMZL, primary cutaneous marginal zone lymphoma; *PCR*, polymerase chain reaction; *qRT-PCR*, quantitative reverse-transcription polymerase chain reaction; *SCC*, squamous cell carcinoma; *TCR*, T-cell receptor.

<2.0 were classified as having reached a consensus of "uncertain appropriateness." Clinical scenarios with a 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 a mean' between 3.1 and 3.9 were classified as "majority rarely appropriate" (rarely appropriate to uncertain).

RESULTS

A total of 211 clinical scenarios were rated. Consensus was reached for 188 (89%) scenarios while no consensus was reached for 23 (11%) scenarios. A consensus of "usually appropriate" was reached in 78 (37%) scenarios with an additional 15 (7%) scenarios where the majority of ratings were "usually appropriate" ("majority usually appropriate"), consensus of "rarely appropriated" was reached in 45 (21%) scenarios with an additional 7 (3%) scenarios where the majority of ratings were rarely appropriate ("majority rarely appropriate"), while consensus for uncertain appropriateness was reached in 43 (20%) scenarios.

Number of times raters used the options "OUT" and unqualified (UQ) was recorded in detail during the third round. Of note, all panel raters felt they had the expertise to rate all clinical scenarios (UQ was never used). The use of the "OUT" rating, indicating that consultation with the clinician might be necessary to determine the appropriateness of ordering the ancillary studies, was considered meaningful if ≥3 panel raters used it and only occurred in a total of 9 clinical scenarios. Scenarios that were rated more than once for separate ancillary tests had complementary "OUT" numbers. Tables I-IV summarize the appropriateness ratings by appropriateness category with added commentary.[15-49]

DISCUSSION

This paper summarizes the first set of AUC in dermatopathology and represents the first AUC developed for pathology and the second AUC developed for dermatology by using the RAND/UCLA methodology. The intent of these AUC is to provide guidance and clarification for use of a test in a particular clinical scenario. Although some of the scenarios specifically address adequacy of the sampled specimen, discretion and clinical judgement should be used regarding suitability of the test for a specific specimen. These guidelines may provide the foundation for studies exploring overuse and underuse of tests and ancillary studies and serve as a model for further efforts in the field.

Evidence review was at the crux of expert judgement in ranking each scenario. Therefore, as new literature emerges, the AUC developed here will need to be updated and may be revised. Importantly, scenarios that resulted in "no consensus" and consensus around "uncertain appropriateness" are areas in which the body of evidence is controversial or underdeveloped. It is hoped that in addition to providing a guide for those using these tests and procedures for diagnosis of skin biopsy specimens that the results of this process will highlight areas of needed and potential research.

The concept of appropriate and necessary care is essential for a health care system to be efficient and just. The development and implementation of AUC is necessary to address ambiguous approaches in utilizing ancillary studies with policy makers, health care organizations, and the public.

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Supplemental Table I. Ancillary studies chosen by each subgroup for the AUC process

AUC Task Force group	Ancillary studies chosen for AUC process
Lymphoproliferative group	TCR clonality assay for beta chain by PCR
	TCR clonality assay for gamma chain by PCR
	B-cell receptor IgH clonality assay by PCR
Melanocytic group	FISH for melanocytic lesions
	CGH for melanocytic lesions
	qRT-PCR for melanocytic lesions
Other group	HPV ISH (HPV subtypes 6,11, 16, 18, 31, 33)
	HPV IHC (Abcam HPV subtypes 1, 6, 11, 16, 18, 31; Dako HPV subtypes 6, 11, 16, 18, 31, 33, 42, 51, 52, 56, 58)
	MMR protein IHC 4-antibody panel (MSH2, MLH1, MSH6, PMS2) in the screening for MTS
	MMR IHC 2-antibody panel (MSH2, MLH1) in the screening for MTS
Soft tissue group	t(17;22) *COL1A1-PDGFB* FISH assay in the diagnosis of DFSP
	Dual-color break-apart *EWSR1* FISH assay in differentiating melanocytic tumors and CCS

AUC, Appropriate use criteria; *CCS*, clear cell sarcoma; *CGH*, comparative genomic hybridization; *DFSP*, dermatofibrosarcoma protuberans; *FISH*, fluorescence in situ hybridization; *HPV*, human papilloma virus; *IgH*, immunoglobulin heavy chain; *IHC*, immunohistochemistry; *ISH*, in situ hybridization; *MMR*, mismatch repair; *MTS*, Muir-Torre syndrome; *PCR*, polymerase chain reaction; *qRT-PCR*, quantitative reverse transcription PCR; *TCR*, T-cell receptor.

Supplemental Table II. Lymphoproliferative definitions and T-cell receptor clonality clinical scenarios

Definitions

Specific clinical entities in B-cell and T-cell subgroups categorized according to the 2008 World Health Organization classification were further examined.[4]

- Diagnostic for mycosis fungoides:
  - Presence of nearly all typical histopathologic diagnostic features of mycosis fungoides (atypical lymphocytes with hyperchromatic, cerebriform nuclei surrounded by clear haloes, epidermotropism of solitary lymphocytes or clusters of atypical lymphocytes in the absence of spongiosis, epidermal lymphocytes larger than dermal lymphocytes)
  - Loss of 1 or more important T-cell markers (CD2, CD5, CD7) within the neoplastic T-cell infiltrate along the dermoepidermal junction and/or in the epidermis
  - Nearly all neoplastic cells express CD4 or CD8 (significant predominance)

- Consistent with mycosis fungoides:
  - Histopathologic diagnostic criteria of mycosis fungoides are present
  - Epidermotropic atypical lymphocytes:
    - Predominantly immunoreactive for CD2, CD3, CD4, CD5, and CD7 (partial)
    - Predominantly immunoreactive for CD4 or CD8
    - Loss of 1 or more mature T-cell markers (CD2, CD3, CD5, CD7)

- Concerning for, suspicious of, or suggestive of mycosis fungoides:
  - Presence of 1 or more typical histopathologic diagnostic features of mycosis fungoides
    - Atypical lymphocytes with hyperchromatic, cerebriform nuclei surrounded by clear haloes
    - Epidermotropism of solitary lymphocytes or clusters of atypical lymphocytes in absence of spongiosis
    - Epidermal lymphocytes larger than dermal lymphocytes
    - Perivascular distribution of atypical lymphocytes (bare underbelly sign)
    - Papillary dermal fibrosis
  - Normal immunophenotypic features: T-cell lymphoid infiltrate along the dermoepidermal junction and/or in the epidermis that is immunoreactive for CD2, CD3, CD5, and CD7 (partial or no loss) with a normal CD4:CD8 ratio

- Not diagnostic for mycosis fungoides:
  - Limited/minimal/scant T-cell lymphoid infiltrate along the dermoepidermal junction and/or within the superficial dermal perivascular space
  - Absence of lymphocyte epidermotropism or folliculotropism
  - Absence of lymphocyte atypia
  - Absence of papillary dermal fibrosis
  - Normal immunophenotypical features: T-cell lymphoid infiltrate along the dermoepidermal junction and/or in the epidermis that is immunoreactive for CD2, CD3, CD5, and CD7 (partial or no loss) with a normal CD4:CD8 ratio

- Lymphomatoid papulosis:
  - Wedge-shaped mixed infiltrate of small and large lymphocytes with eosinophils and neutrophils, numerous CD30-positive large lymphocytes
  - Or, scant-to-moderate mixed infiltrate with small and large lymphocytes with epidermotropism
  - Or, dense diffuse infiltrate of large atypical CD30-positive lymphocytes

- Pityriasis lichenoides:
  - Mixed lichenoid and spongiotic dermatitis with mounds of parakeratosis, extravasated erythrocytes; large cells are present
  - Or, wedge shaped superficial and deep dermal lymphocytic infiltrate with extravasated erythrocytes (lymphocytic vasculitis), epidermal necrosis, parakeratosis, lichenoid reaction pattern; large cells are present

Clinical scenarios

1. Solitary or generalized scaly patches or plaques that are clinically concerning for mycosis fungoides (clinical impression: ruled out mycosis fungoides or cutaneous T-cell lymphoma) and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of mycosis fungoides
2. Clinical presentation of erythroderma with clinical impression of ruled out mycosis fungoides, cutaneous T-cell lymphoma, or Sézary syndrome and that is not diagnostic for mycosis fungoides
3. Clinical presentation of dermatitis with clinical impression of ruled out mycosis fungoides or cutaneous T-cell lymphoma and that is not diagnostic for mycosis fungoides

Continued

Supplemental Table II. Cont'd

4. Inflammatory/reactive papular or papulonecrotic eruption (solitary, regional, or generalized) with clinical impression of lymphomatoid papulosis or pityriasis lichenoides, ruled out mycosis fungoides or cutaneous T-cell lymphoma and histopathologic and immunophenotypic features typical for lymphomatoid papulosis or pityriasis lichenoides
5. The development of T-cell cutaneous infiltrate that is not diagnostic for mycosis fungoides but is present in patient with history of mycosis fungoides with a known T-cell clone (comparison of past and present clones)
6. The development of T-cell cutaneous infiltrate in patient with history of systemic T-cell lymphoma
7. A cutaneous T-cell infiltrate with a folliculotropic rather than epidermotropic T-cell infiltrate
8. Pigmented purpuric patches (solitary, regional, or generalized) and clinical impression of ruled out mycosis fungoides or cutaneous T-cell lymphoma and histopathologic and immunophenotypic features that are not diagnostic for mycosis fungoides
9. Clinically reactive entities (see references for individual diagnoses) with histologically and immunophenotypically concerning for, suspicious of, or suggestive of mycosis fungoides
10. Pre-existing diagnosis of mycosis fungoides and new or evolving lesions similar to original lesions with clinical impression of ruled out mycosis fungoides in setting of pre-existing mycosis fungoides and histopathologic and immunophenotypic features consistent with mycosis fungoides
11. Development of nodules in patient with mycosis fungoides which are histologically concerning for, suspicious of, or suggestive of large cell transformation with CD30 positivity
12. Development of nodules in patient with mycosis that is histologically concerning for, suspicious of, or suggestive of large cell transformation without CD30 positivity

Supplementary Table III. Lymphoproliferative definitions and B-cell receptor (IgH) clonality clinical scenarios

Definitions

Specific clinical entities in B-cell and T-cell subgroups categorized according to the 2008 World Health Organization classification were further examined.[4]

- Consistent with cutaneous marginal zone lymphoma or follicle center lymphoma:
  - Histopathologic diagnostic criteria of cutaneous marginal zone lymphoma or follicle center lymphoma are present
  - Predominance of B cells
  - B cells cannot be explained by normal architecture (ie, confined to lymphoid follicles)
  - No light-chain restriction is present by protein immunohistochemistry (kappa and lambda) or mRNA chromogenic in situ hybridization (kappa and lambda)

- Concerning for, suspicious of, or suggestive of cutaneous marginal zone lymphoma:
  - Presence of 1 or more typical histopathologic features of cutaneous marginal zone lymphoma (grenz zone, predominance of plasma cells, bottom heavy infiltrate, superficial and deep perivascular and periadnexal infiltrate, nodular infiltrate with periphery of plasma cells and numerous monocytoid B cells, diffuse infiltrate of monotonous lymphocytes)
  - Normal immunophenotypical features (mixed B-cell and T-cell infiltrate)

- Concerning for, suspicious of, or suggestive of follicle center lymphoma:
  - Presence of 1 or more typical histopathologic features of follicle center lymphoma (grenz zone, predominance of cleaved cells (centrocytes) and/or large noncleaved cells (centroblasts), nodular infiltrate composed of disorganized follicles, bottom-heavy infiltrate, follicle-like structures without tangible body macrophages, diffuse infiltrate of monotonous small cleaved or large noncleaved lymphocytes)
  - Normal immunophenotypic features (mixed B-cell 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)

- Not diagnostic for cutaneous B-cell lymphoma (cutaneous marginal zone lymphoma or follicle center lymphoma):
  - Grenz zone is absent and there is epidermal involvement by lymphocytes
  - Scant (<200 lymphoid cells) infiltrate
  - Minimal number of B cells within a nodular or diffuse infiltrate
  - No light-chain restriction as measured by protein immunohistochemistry (kappa and lambda); No light-chain restriction as measured by mRNA chromogenic in situ hybridization (kappa and lambda)

- Concerning for, suspicious of, or suggestive of cutaneous diffuse large B cell lymphoma, leg type:
  - Presence of 1 or more typical histopathologic features of large B-cell lymphoma, leg type
    - Grenz zone, predominance of large immunoblastic cells
    - Diffuse infiltrate, necrosis, and easily observable mitotic activity in neoplastic-appearing cells
  - Predominance of B cells on immunohistochemistry

Clinical scenarios

1. Solitary or multiple erythematous nodules that are clinically concerning for cutaneous B-cell lymphoma (clinical impression, ruled out B-cell lymphoma) and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of cutaneous marginal zone lymphoma
2. Solitary or multiple erythematous nodules that are clinically concerning for cutaneous B-cell lymphoma (clinical impression, ruled out B-cell lymphoma) and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of follicle center lymphoma
3. Clinical presentation of solitary or multiple nodules with clinical impression of cutaneous lymphoid hyperplasia and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of cutaneous marginal zone lymphoma
4. Clinical presentation of solitary or multiple nodules with clinical impression of cutaneous lymphoid hyperplasia and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of follicle center lymphoma
5. Clinical presentation of solitary or multiple nodules with clinical impression of ruled out cutaneous B-cell lymphoma (cutaneous marginal zone or follicle center lymphoma) and that is not diagnostic for cutaneous B-cell lymphoma
6. Clinical presentation of a solitary lesion, suggestive of a nonneoplastic process clinically that has a diffuse infiltrate of lymphocytes and a predominance of B cells immunophenotypically
7. Clinical presentation of dermatitis suggestive of a nonneoplastic process clinically that has a diffuse infiltrate of lymphocytes and a predominance of B cells immunophenotypically
8. Unknown history, but histopathologic and immunophenotypic features consistent with cutaneous marginal zone lymphoma or follicle center lymphoma

Continued

Supplementary Table III. Cont'd

9. Pre-existing diagnosis of cutaneous B-cell lymphoma (cutaneous marginal zone lymphoma or follicle center lymphoma) and new or evolving lesions similar to original lesions with clinical impression of ruled out cutaneous B-cell lymphoma and histopathologic and immunophenotypic features consistent with cutaneous marginal zone lymphoma or follicle center lymphoma
10. Solitary or multiple erythematous nodules that are clinically concerning for an aggressive B-cell lymphoma (clinical impression of ruled out B-cell lymphoma, leg type) and that are histologically and immunophenotypically concerning for, suspicious of, or suggestive of cutaneous diffuse large B-cell lymphoma, leg type.
11. The development of B-cell cutaneous infiltrate that is not diagnostic for cutaneous B-cell lymphoma in a patient with history of cutaneous B-cell lymphoma with a known B-cell clone (comparison of past and present clones)
12. The development of B-cell cutaneous infiltrate in patient with history of any systemic B-cell lymphoma
13. Other more aggressive cutaneous B-cell lymphomas other than cutaneous diffuse large B-cell lymphoma, leg type, such as intravascular large B-cell lymphoma or cutaneous plasmablastic lymphoma

Supplementary Table IV. Melanocytic definitions and clinical scenarios

Definitions

- Nevoid melanoma: lesion of malignant melanocytes with some histologic features that closely mimic architectural and cytologic features of a benign compound or intradermal nevus
- Nevoid cutaneous metastatic melanoma: lesion of metastatic malignant melanoma with some histologic features that closely mimic architectural and cytologic features of a benign compound or intradermal nevus
- Benign melanocytic nevus: lesion of benign melanocytes with either a compound or intradermal configuration
- Atypical blue nevus: lesion of spindled melanocytes with or without an admixed epithelioid component that have any of the following: pronounced cytologic atypia or hyperchromasia, necrosis, increased mitotic rate or dysmaturation
- Blue nevus-like cutaneous metastatic melanoma: lesion of metastatic malignant melanoma composed of spindled and pigmented melanocytes that 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 that closely mimic architectural and cytologic features of benign blue nevus or arises within a histologically recognizable benign blue nevus remnant
- Benign blue nevus: lesion of benign spindled melanocytes occurring within a fibrotic stroma, subtypes include cellular, deep penetrating and epithelioid
- Congenital nevus with proliferative nodule: nodular lesion of atypical epithelioid or spindled melanocytes occurring within a pre-existing congenital nevus
- Atypical spitz tumor: lesion of spitzoid melanocytes that 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
- Incompletely sampled unclassified spitz tumor: lesion of spitzoid melanocytes that is partially sampled to the degree it is not able to be subclassified and with atypical features
- Spitzoid melanoma: lesion of malignant melanocytes with some histologic features that closely mimic architectural and cytologic features of a benign Spitz nevus
- Sclerosing (desmoplastic) nevus: lesion of benign melanocytes that might be ovoid, dendritic, or spitzoid occurring within a distinctive eosinophilic stroma with overall architectural symmetry and without significant cytologic atypia or mitotic activity
- Desmoplastic melanoma: lesion of malignant melanocytes with a predominantly spindled-shaped, prominent desmoplasia and frequent neurotropism
- Pathology suggestive of or suspicious for melanoma: atypical melanocytic proliferation
- Pediatric patient is $<$18 years of age
- Adult patient is $\geq$18 years of age
- Fluorescence in situ hybridization panel includes
  - RREB1 (6p25)
  - MYC (8q24)
  - CDKN2A p16 (9p21)
  - CCND1 (11q13)
- The 23 genes included in qualitative reverse transcription PCR testing are
  - PRAME: a single gene involved in cell differentiation
  - S100A7, S100A8, S100A9, S100A12, and PI3: a group of genes involved in multiple cell signaling pathways
  - CCL5, CD38, CXCL10, CXCL9, IRF1, LCP2, PTPRC, and SELL: involved in tumor immune response signaling
  - Nine housekeeping genes that are measured to normalize RNA expression for analysis

Clinical scenarios

1. Adult patient with pathology definitive for melanoma
2. Adult patient with pathology suggestive of or suspicious for melanoma: nevoid melanoma vs benign melanocytic nevus
3. Adult patient with pathology suggestive of or suspicious for melanoma: nevoid cutaneous metastatic melanoma vs benign melanocytic nevus
4. Adult patient with pathology suggestive of or suspicious for melanoma: melanoma arising within a nevus/dysplastic nevus
5. Adult patient with pathology suggestive of or suspicious for melanoma: atypical blue nevus vs benign blue nevus
6. Adult patient pathology suggestive of or suspicious for melanoma: blue nevus-like cutaneous metastatic melanoma vs benign blue nevus
7. Adult patient with pathology suggestive of or suspicious for melanoma: blue nevus-like melanoma (malignant blue nevus) vs benign blue nevus
8. Adult with pathology suggestive of or suspicious for melanoma: congenital nevus with proliferative nodule vs melanoma

Continued

Supplementary Table IV. Cont'd

9. Adult patient with pathology suggestive of or suspicious for melanoma: atypical spitz tumor vs spitzoid melanoma
10. Adult patient with pathology suggestive of or suspicious for melanoma: incompletely sampled unclassified spitz tumor vs spitzoid melanoma
11. Adult patient with pathology suggestive of or suspicious for melanoma: sclerosing (desmoplastic) nevus incompletely sampled vs desmoplastic melanoma
12. Adult patient with pathology suggestive of 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
13. Adult patient with pathology definitive for nevus
14. Distinction of nevus from primary melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters
15. Distinction of nevus from primary melanoma in an adult patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters
16. Distinction of nevus from metastatic melanoma in an adult patient when the morphologic findings are ambiguous by light microscopic parameters
17. Distinction of nevus from metastatic melanoma in an adult patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters
18. Pediatric patient with pathology definitive for melanoma
19. Pediatric patient with pathology suggestive of or suspicious for melanoma: nevoid melanoma vs benign melanocytic nevus
20. Pediatric patient with pathology suggestive of or suspicious for melanoma: nevoid cutaneous metastatic melanoma vs benign melanocytic nevus
21. Pediatric patient with pathology suggestive of or suspicious for melanoma: melanoma arising within a nevus/dysplastic nevus
22. Pediatric patient with pathology suggestive of or suspicious for melanoma: atypical blue nevus vs benign blue nevus
23. Pediatric patient with pathology suggestive of or suspicious for melanoma: blue nevus-like cutaneous metastatic melanoma vs benign blue nevus
24. Pediatric patient with pathology suggestive of or suspicious for melanoma: blue nevus-like melanoma (malignant blue nevus) vs benign blue nevus
25. Pediatric patient with pathology suggestive of or suspicious for melanoma: congenital nevus with proliferative nodule vs melanoma
26. Pediatric patient with pathology suggestive of or suspicious for melanoma: atypical spitz tumor vs spitzoid melanoma
27. Pediatric with pathology suggestive of or suspicious for melanoma: incompletely sampled unclassified spitz tumor vs spitzoid melanoma
28. Pediatric with pathology suggestive of or suspicious for melanoma: sclerosing (desmoplastic) nevus incompletely sampled vs desmoplastic melanoma
29. Pediatric patient with pathology suggestive of 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
30. Pediatric patient with pathology definitive for nevus
31. Distinction of nevus from primary melanoma in a pediatric patient when the morphologic findings are ambiguous by light microscopic parameters
32. Distinction of nevus from primary melanoma in a pediatric patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters
33. Distinction of nevus from metastatic melanoma in a pediatric patient when the morphologic findings are ambiguous by light microscopic parameters
34. Distinction of nevus from metastatic melanoma in a pediatric patient when the partial nature of the biopsy precludes optimal assessment by light microscopic parameters

Supplementary Table V. HPV definitions and HPV clinical scenarios

Definitions[5-7]

- Adult patient: age >14 years
- Pediatric patient: age ≤14 years
- Condyloma: histopathologic findings to include all of the following: epidermal acanthosis, hyperkeratosis, round parakeratosis, coarse keratohyaline granules, vacuolated keratinocytes, including true koilocytes
- Pathology suggestive of condyloma: histopathologic findings do not include all of the features defined above for condyloma and might also include pseudo horn cysts
- Age of 25 years was chosen as although seborrheic keratosis have been reported in patients under this age, they are rare and increase in prevalence with increasing age
- Squamous cell carcinoma in situ or undifferentiated intraepithelial dysplasia of the anogenital skin
  - The terminology used for premalignant and malignant dysplasia of the genitourinary tract has been confusing with older terminology, including Bowen disease, erythroplasia of Queyrat, bowenoid papulosis, multifocal Bowen disease, severe dysplasia, and carcinoma in situ.
    - Newer terminology in the vulva has been replaced with undifferentiated usual type of VIN. This is defined as atypia involving two thirds to full thickness of the epidermis (previously defined as VIN2 and VIN 3, respectively). VIN1 is not regarded as flat condyloma
    - The terminology is likewise confusing on the penis, with some proposing a similar nomenclature: undifferentiated penile intraepithelial neoplasia (PeIN).
  - Histologically undifferentiated intraepithelial neoplasia (VIN3 and PeIN3) demonstrates full thickness cytologic atypia, increased mitotic figures, and dyskeratosis. It can have the presence of hypergranulosis +/- partially vacuolated cells
- Squamous cell carcinoma of genital skin
  - For this purpose, divided into squamous cell carcinoma arising in the background of a chronic dermatosis (ie, lichen sclerosis et atrophicus, lichen planus) or squamous cell carcinoma arising in a background of undifferentiated VIN or PeIN
  - Various histologies have been reported with some including verrucous carcinoma and others offering a more complex separation with the introduction of terms such as warty (condylomatous) squamous cell carcinoma, papillary squamous cell carcinoma, and low-grade verruciform carcinoma
- Verrucous carcinoma
  - The term used here encompasses verrucous carcinoma, well-differentiated epidermoid squamous cell carcinoma, epithelioma cuniculatum, and giant condyloma of Buschke-Löwenstein that clinically present as a warty, exophytic plaque in the oropharynx, lower limb (typically sole of foot), and anogenital region, respectively.
  - Histopathologic findings should include all the following: exoendophytic architecture, hyperkeratosis, keratinocytes with abundant pale pink cytoplasm, large bulbous rete ridges with pushing boarder
- Subungual wart: includes clinical lesions involving the hyponychium, distal nail bed or proximal nail fold that might be causing subungual hyperkeratosis or onycholysis and have histologic findings that include parakeratosis, papillomatosis, and the presence of koilocytes in the most superficial layers
- Verrucous features are any of the following histologic features: epidermal papillomatosis, coarse keratohyaline granules, vacuolated keratinocytes.
- HPV-induced lesion of the genital skin includes condyloma or undifferentiated intraepithelial neoplasia.

Clinical scenarios

1. Adult patient, pathology definitive for condyloma
2. Adult patient, pathology suggestive of condyloma
3. Pediatric patient, pathology definitive for condyloma
4. Pediatric patient, pathology suggestive of condyloma
5. Patient under 25 years of age with pathologic findings consistent with seborrheic keratosis of genital skin, perineum, lower abdomen, or inner thighs
6. Patient with squamous cell carcinoma in situ/undifferentiated intraepithelial dysplasia of the genital skin
7. Patient with a squamous cell carcinoma in the genital area
8. Patient with a history of an HPV-induced lesion and a squamous cell carcinoma in the genital area
9. Patient with a squamous cell carcinoma in the genital area and a history of a chronic dermatoses (ie, lichen sclerosis et atrophicus, lichen planus)
10. Patient with clinical impression and pathology consistent with verrucous carcinoma
11. Patient with a subungual wart
12. Patient with nail bed, periungual, or nail matrix squamous cell carcinoma in situ/squamous cell carcinoma
13. Patient with squamous cell carcinoma in situ or squamous cell carcinoma with verrucous features on digits
14. Immunosuppressed patients (eg, organ transplant and HIV patients) with squamous cell carcinoma in situ or squamous cell carcinoma with verrucous features

HPV, Human papilloma virus; *PeIN*, penile intraepithelial neoplasia; *VIN*, vulvar intraepithelial neoplasia.

Supplementary Table VI. MTS definitions and clinical MTS scenarios

Definitions[8,9]

- Age 60 years: some articles suggest 50 years of age instead of 60 years of age as a cut off, this might be because sebaceous neoplasms present at a mean age of 53 years
- MTS—associated sebaceous neoplasm: sebaceous adenoma, sebaceoma, sebaceous epithelioma, sebaceous carcinoma
- MTS-associated neoplasm: MTS-associated sebaceous neoplasms, cystic sebaceous neoplasm, basal cell carcinoma with sebaceous differentiation, keratoacanthoma with sebaceous differentiation
- MTS-associated visceral malignancy: colorectal adenocarcinoma (most common), genitourinary carcinoma (second most common), breast, hematologic, endometrial and gastric carcinoma (less common)

Clinical scenarios

1. A patient >60 years of age with a periocular sebaceous carcinoma
2. A patient >60 years of age with a single sebaceous tumor on the head and neck
3. A patient >60 years of age with a single sebaceous tumor on a site other than the head and neck
4. A patient >60 years of age with multiple (greater than or equal to 2) sebaceous tumors
5. A patient >60 years of age with a basal cell carcinoma with sebaceous differentiation
6. A patient >60 years of age with a keratoacanthoma with sebaceous differentiation
7. A patient >60 years of age with a cystic sebaceous neoplasm
8. A patient >60 years of age with an MTS-associated neoplasm or personal history of a MTS-associated visceral malignancy

MTS, Muir-Torre syndrome.

Supplemental Table VII. Definitions and clinical scenarios for DFSP

Definitions

- Typical histomorphology of DFSP: monotonous spindled cells in a storiform pattern with honeycombing or entrapment of adnexal structures and/or adipocytes and extension into the subcutis
- Nontypical histomorphology of DFSP: refers to variant histomorphology, such as fibrosarcomatous; giant cell fibroblastoma; myxoid, epithelioid, or nonspecific spindled cell histomorphology

Clinical scenarios

1. Tissue with sampling down to subcutis with typical histomorphology of DFSP and $CD34^+$ by immunohistochemistry
2. Tissue with sampling down to subcutis with typical histomorphology of DFSP and CD34 immunohistochemistry not uniformly reactive
3. Tissue with sampling down to subcutis with nontypical histomorphology of DFSP and $CD34^+$ by immunohistochemistry
4. Superficial, $CD34^+$ tumor with typical histomorphology of DFSP except that good honeycombing of fat is not seen due to superficial sampling
5. Superficial, $CD34^+$ tumor with nontypical histomorphology for DFSP (SD5)
6. Superficial, $CD34^+$ tumor with scant tumor sampling as to limit cytologic and/or architectural evaluation
7. High-grade spindle cell tumor (fibrosarcomatous transformation) and no areas of typical histomorphology of DFSP
8. Metastatic tumor with histomorphology similar to previously diagnosed primary DFSP
9. Metastatic tumor with histomorphology distinct from previously diagnosed primary DFSP
10. Patient with locally recurrent DFSP in which testing for translocation by another established molecular technique (RT-PCR, FISH, cytogenetics) was previously positive
11. Patient with metastatic DFSP in which testing for translocation by another established molecular technique (RT-PCR, FISH, cytogenetics) was previously positive in the primary tumor
12. Patients for which tyrosine kinase therapy is being considered in the treatment plan
13. Patient with tissue that has been decalcified or processed with fixative other than 10% formalin
14. Patient with a pathologic diagnosis of DFSP by hematoxylin-eosin stain with $CD34^+$ immunohistochemistry but where the treating physician is requesting molecular studies (RT-PCR, FISH, cytogenetics) to be performed to further confirm the diagnosis

DFSP, Dermatofibrosarcoma protuberans; *FISH*, fluorescence in situ hybridization; *RT-PCR*, reverse transcription PCR.

Supplemental Table VIII. Clear cell sarcoma clinical scenarios and definitions clear cell sarcoma

Definitions

- Melanocytic markers: S100, Melan-A/MART-1, HMB45, MiTF, SOX10
- Typical histologic features of clear cell sarcoma: relatively uniform (nonpleomorphic) nuclei, large central nucleoli, nested appearance divided by fibrous septations, scattered osteoclast-like giant cells, little or no conspicuous melanin, no epidermal component

Clinical scenarios

1. Patient <50 years of age with acral tumor with typical histologic features of clear cell sarcoma expressing melanocytic markers and involving deep dermis, subcutis, or aponeurosis; no past history of melanoma
2. Patient <50 years of age with acral tumor without typical histologic features of clear cell sarcoma expressing melanocytic markers and involving deep dermis, subcutis, or aponeurosis; no history of melanoma
3. Patient ≥50 years of age with acral tumor with typical histologic features of clear cell sarcoma expressing melanocytic markers and involving deep dermis, subcutis, or aponeurosis; no history of melanoma
4. Patient ≥50 years of age with acral tumor without typical histologic features of clear cell sarcoma expressing melanocytic markers and involving deep dermis, subcutis, or aponeurosis; no history of melanoma
5. Patient <50 years of age with nonacral site tumor expressing melanocytic markers without typical histologic features of clear cell sarcoma and involving deep dermis, subcutis, or aponeurosis; no history of melanoma but with what appears to be a cutaneous metastasis of melanoma from an unknown primary
6. Patient ≥50 years of age with nonacral site tumor expressing melanocytic markers without typical histologic features of clear cell sarcoma and involving deep dermis, subcutis, or aponeurosis; no history of melanoma but with what appears to be a cutaneous metastasis of melanoma from an unknown primary
7. Patient with dermal-based tumor expressing melanocytic markers and demonstrating typical histologic features of clear cell sarcoma; history of invasive melanoma at another anatomic site
8. Patient with an acral tumor in the dermis or subcutis that has typical histologic features of clear cell sarcoma and expresses melanocytic markers but also has an overlying intraepidermal in situ component
9. Patient with a nonacral tumor in the dermis or subcutis that has typical histologic features of clear cell sarcoma and expresses melanocytic markers but also has an overlying intraepidermal in situ component
10. Patient with metastatic tumor with histomorphology similar to previously diagnosed primary clear cell sarcoma
11. Patient with metastatic tumor with histomorphology distinct from previously diagnosed primary clear cell sarcoma
12. Patient with recurrent or metastatic clear cell sarcoma in which testing for translocation by another established technique (reverse transcription PCR, fluorescence in situ hybridization, cytogenetics) was previously positive
13. Patient with primary or metastatic tumor expressing melanocytic markers in which *BRAF* or *NRAS* mutation has been detected
14. Patient with tissue that has been decalcified or processed with fixative other than 10% formalin