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Title: Appropriate Use Criteria in Dermatopathology: Initial Recommendations from the American Society of Dermatopathology

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ABSTRACT (194 words)

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

Objectives: The American Society of Dermatopathology (ASDP), with input from the American Academy of Dermatology (AAD) and the College of American Pathologists (CAP), 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 (CS) involving 12 ancillary studies (AS). Consensus was reached for 188 (89%) CS, with 93 (44%) considered "usually appropriate", 52 (25%) "rarely appropriate", and 43 (20%) "uncertain appropriateness".

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

Conclusions: The ultimate decision of when to order specific test rests with the physician and is one where the expected benefit exceeds the negative consequences. This publication outlines the recommendation of appropriateness - 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.

DISCLAIMER

The recommendations presented in this study were developed using the RAND Corp methodology (Santa Monica, CA) / University of California-Los Angeles (RAND/UCLA 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/study should or can be performed. Future literature may require changes to the recommendations based on additional information.

INTRODUCTION (Word count without disclaimer 6744)

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).

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 first step in 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 to 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 by each of the subgroups and developed using the RAND/UCLA Appropriateness Method (3). The goal in a health system is for inappropriate care to be reduced while necessary and appropriate care is increased or maintained. It is imperative to 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,

with emerging literature updates to the AUC will need to be made and are already planned by the ASDP.

MATERIALS AND METHODS (Figure 1)

The AUC process combines evidence-based medicine with clinical scenarios and expert judgment by engaging a rating panel in a modified Delphi exercise based on 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. The process begins by selection of tests or 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.

In total, 12 dermatopathology ancillary studies underwent the AUC process. These include 3 topics for the lymphoproliferative group: T-cell receptor (TCR) clonality assay for the beta chain by polymerase chain reaction (PCR), TCR clonality assay for the gamma chain by PCR, and B-cell receptor immunoglobulin heavy chain (IgH) clonality assay by PCR. The melanocytic group also examined 3 topics: fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH) and gene expression profiling by quantitative reverse transcription polymerase chain reaction (qRT-PCR) for melanocytic lesions. The other group explored 4 topics: human papilloma virus (HPV) in situ hybridization (ISH; HPV subtypes 6,11, 16, 18, 31, 33), HPV immunohistochemistry (IHC; Abcam HPV subtypes 1, 6, 11, 16, 18, 31 / Dako HPV subtypes 6, 11, 16, 18, 31, 33, 42, 51, 52, 56, and 58), and mismatch repair (MMR) protein IHC 4 antibody panel (MSH2, MLH1, MSH6, and PMS2) and MMR IHC 2 antibody panel (MSH2 and MLH1) in the screening for Muir-Torre syndrome (MTS). Finally, the soft tissue group explored 2 topics: t(17;22) *COL1A1-PDGFB* FISH assay in the diagnosis of dermatofibrosarcoma protuberans (DFSP) and dual color break-apart *EWSR1* FISH assay in differentiating melanocytic tumors and clear cell sarcoma (CSS).

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 developed clinical scenarios ("indications") to simulate situations most likely to be encountered in clinical 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 accordingly such that they comprised the most often encountered situations in dermatopathology practice. The clinical scenarios were not intended to be exhaustive but to at least represent 85% of anticipated scenarios. They were based on information that is readily available to dermatopathologists during routine practice (age, body site, histomorphology, etc.). Further specific information regarding definitions and clinical scenarios for each subgroup is summarized in table format (4, 5, 6, 7, 8, 9). Tables 1A-4B.

Evidence

The development of AUC 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 the year 2016, overlapping studies removed, and case series with 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, 11, 12, 13, 14).

Rating process

Seventeen panel raters were carefully selected for balance, expertise in a field and breadth of knowledge. Attempt to avoid selection of panel raters with any financial conflict of interest was made. Twelve panel raters (3 per topic) 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, non-dermatopathologists) and 2 representatives nominated by the College American Pathologists (both were pathologist and dermatopathologists) to incorporate the broader pathology perspective and a medical director from a regional Medicare carrier. The number of rating rounds was predetermined at 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 scenarios booklets. All panel raters rated all of the ancillary studies and all ratings were done independently by each panel rater, with the overarching objective being to converge in consensus. They were instructed to rate the appropriateness of each clinical scenarios 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 test/procedure independently, such that each test/procedure was rated on its own merits. During each round, panelists were asked to rate each clinical scenarios on a 9-point scale (shown below). A score of 9 to 7 indicated the test/procedure belonged to a category of "usually appropriate" where higher scores indicate greater agreement within the category. A score of 1 to 3 indicated the test/procedure is "rarely appropriate" in that specific clinical scenario while acknowledging clinician discretion may 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 to perform a test lies with the physician and takes into account not only the clinical scenario but also the individual patient. Scores in the rage of 4 to 6 were used to indicate "uncertain appropriateness" for

ordering the test/procedure in that clinical scenario. Scores in this mid-range generally indicated panel raters assessment that there was lack of scientific evidence for the test/procedure in general or for that individual clinical scenario. Insufficient scientific evidence could be due to the data being considered as emergent or underdeveloped.

RARELY APPROPRIATE ----------|		|--------- UNCERTAIN -------- |		| --------- USUALLY APPROPRIATE		
1	2	3	4	5	6	7	8	9
☐	☐	☐	☐	☐	☐	☐	☐	☐

The first-round rating was done individually without interaction with other panel raters or AUC Task Force members. Ratings were analyzed by two research team members who identified clinical scenarios where there was no apparent consensus. After the initial rating, an in-person moderated meeting of the panel raters occurred during the annual ASDP meeting in Chicago. During this meeting there was a discussion of clinical scenarios where consensus had not been achieved. The discussion was preceded by a literature review summary by an AUC Task Force member for each ancillary study for which AUC were being developed. The goal was to discuss the literature, draw from other experts in the field while also being mindful of not requesting ratings or influencing the panel to seek consensus. After the in-person meeting, the second-round rating was done individually and submitted to the research team within two weeks. 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. The third and final rating was completed individually, again within about two weeks of the teleconference sessions. One panelist withdrew from the project after the first-round; thus, the complete data for all three rounds was provided by 16 panel raters.

To facilitate the panel rater discussion and support categorization for each clinical scenarios the mean of ratings was calculated; the mean was adjusted by filtering/removing two scores – the highest and 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 <2.0 were classified as having reached 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).

During the in-person meeting, panel raters requested two additional options be allowed during the rating process: Unqualified (UQ), which was to be used if "as a dermatopathologist I do not have the expertise to decide if this is appropriate" and OUT, which was not an acronym but rather an indication that "assessment of appropriateness of 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 two options should be used sparingly.

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 reach 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 "UQ" was recorded in detail during the third round. Important to note, all panel raters felt they had the expertise to rate all clinical scenarios as "UQ" was never used. The use of the "OUT" rating, indicating that consultation with the clinician may be necessary to determine the appropriateness of ordering the ancillary studies, was considered meaningful if e3 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 5A-8B summarize appropriateness ratings for each ancillary study by group.

DISCUSSION

Lymphoproliferative group

Additional testing is commonly considered when dealing with a cutaneous lymphoid infiltrate. In examining the literature, evidence for the use of T-cell clonality assays was generally more extensive than that for the B-cell clonality assays.

TCR clonality assays

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 where the histology and immunophenotype is "concerning", "suspicious" or "suggestive of" MF, if a folliculotropic infiltrate is encountered, and for clone comparison. 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 (i.e., angioimmunoblastic T cell lymphoma), secondary cutaneous infiltrates are often not histologically atypical in appearance. In addition, some specialized immunohistochemical stains (i.e., PD-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 T cell receptor in the germline configuration or if the patient has synchronous primary lymphomas. Congruent with current scientific evidence testing is "rarely appropriate" in cases of dermatitis or pigmented purpuric patches with a non-diagnostic 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 pityriasis lichenoides 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 lymphomatoid papulosis or pityriasis lichenoides is made histologically and the “uncertain appropriateness” recommendation for clinical reactive entities displaying histology and IHC "concerning", "suspicious" or "suggestive of" MF. Not surprisingly, panel raters felt it was "rarely appropriate" to perform this assay in cases of new nodules in a patient with a known diagnosis of MF "concerning", "suspicious" or "suggestive of" large cell transformation, regardless of CD30 positivity. 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 where 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 and the patients’ previous biopsies. Ratings also yielded a recommendation of "no consensus" in the scenario of an erythrodermic patient with non-diagnostic histology, which may in general reflect poor global experience with early Sézary syndrome.

Although there was one clinical scenario where 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.

IgH clonality assay

In looking at the results for B-cell clonality assays, there were 6 clinical scenarios where testing for the 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," "suspicious of" or "suggestive of" either primary cutaneous marginal zone lymphoma (PCMZL), follicle center lymphoma (FCL). These entities tend to be difficult to diagnose based primarily on 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 is often absent even in grade 2 FCL. While in FCL with a diffuse pattern, the presence of sheets of B cells is concerning for lymphoma, again, 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 where the clonality assay was being used for clone comparison. Testing was recommended by the majority of panel raters in cases where the clinical impression was of a single lesion suggestive of a non-neoplastic process or of dermatitis, but the histology showed a B-cell predominant infiltrate. Conversely, there were 2 clinical scenarios ranked "rarely appropriate": when single or multiple nodules are found and the clinical impression is rule out B-cell lymphoma (PCMZL or FCL), but the histology and immunohistochemistry results are "not diagnostic" for cutaneous B-cell lymphoma and in patients with a pre-existing diagnosis of cutaneous B-cell lymphoma (either PCMZL or FCL) and when a diagnosis of PCMZL or FCL can be made on histologic grounds. There was

"no consensus" for 2 scenarios, which included cases where the history is unknown, but the histology and immunophenotype of the infiltrate are "consistent with" with PCMZL or FCL and when other more aggressive cutaneous B-cell lymphomas other than PCLBCL, LT are considered in the diagnosis. The latter 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.

Melanocytic group

FISH and CGH

Regarding melanocytic lesions, ratings indicate that in most scenarios where 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 where the pathology is definitive for melanoma or melanocytic nevus, expert rating found that it is "usually appropriate" to perform FISH or CGH on melanocytic lesions when the diagnosis is in question. In those cases where the pathology is definitive for either a melanoma or melanocytic nevus, testing with FISH and CGH is "rarely appropriate." This was not surprising as histology is considered the "gold 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. 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. The consensus rating for FISH in the same clinical scenario was of uncertain appropriateness. Pouryazdanparast et al. described the utility in epithelioid blue nevi and blue nevi cutaneous metastasis (15) and Gammon et al. explored FISH in distinguishing cellular blue nevi from blue nevus-like melanoma showing a 100% sensitivity and specificity (16). While these studies utilized a FISH probe set different than the one defined by the group in this analysis, there was overlap of at least of 2 of the probes used - the RREB1 and 6p25 probes.

There was "no consensus" on the value of FISH for situations where the pathology is suggestive or suspicious for melanoma where the differential diagnosis is between sclerosing desmoplastic nevus and desmoplastic melanoma, 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 (17).

The "OUT" rating was used once in 3 clinical scenarios by the panel raters when rating FISH and CGH, with 94% of panel raters participating. Scenarios rated for FISH and CGH independently showed the same number of "OUT" ratings and when they were considered in pediatric versus adult patients the use of "OUT" was similar.

qRT-PCR

Consensus ratings in most of the clinical scenarios using qRT-PCR were of "appropriateness uncertain" with the exception being those cases where a diagnosis can be made on histologic grounds. While validation studies and studies exploring unequivocal cases had been published when the AUC process began (18, 19), only one study was available exploring the test in ambiguous lesions (20) at the time of rating. In addition, the possibility of limited clinical experience with the test may have played a role in the rating result. Since the completion of process, additional studies have been reported in the literature, including one dealing with diagnostic challenging case (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 AUC are subsequently and expectedly updated.

Other group

HPV ISH and IHC

Use of HPV, ISH and IHC show wide variability and are tests that 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).

While 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 scenarios ranked. Only in pediatric cases where pathology is suggestive of condyloma, did experts feel 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% (23,24,25,26), which may be the reason for the recommendation. However, there was "no consensus" in a similar scenario of a pediatric patient, but with histology definitive for condyloma. This rating may be because HPV 2, which is not typically detected by ISH, is the most common subtype of HPV found in this age group (27).

Most scenarios were ranked as "rarely appropriate" for the use of IHC in the detection of HPV. These ratings likely reflect the presence of only 2 articles exploring the use of IHC for detection of HPV.

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 where the pathology is "suggestive of" a condyloma in an adult, in situations when the pathology is definitive or “suggestive of” a condyloma in the pediatric population, and in cases where the pathology is “consistent with” a seborrheic keratosis of the genital skin, perineum, lower abdomen, or inner thighs. 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.

MTS MMR IHC

MTS is a clinical variant of Lynch syndrome defined by the synchronous or metachronous occurrence of at least one sebaceous neoplasm or keratoacanthoma and at least one 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 who are 70 or under (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 where germline mutation analysis is also available point to a high false positive rate presumably from nonheritable molecular events within the lesion (30,31,32).

The average age of presentation of sebaceous neoplasms in MTS is 53 years old; however, the range is broad (21 to 88). Of note, these neoplasms can present before (22%), concurrently (6%) or after (56%) the internal malignancy (33). An age >60 years old 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 the preponderance of literature employing a panel of MLH1 and MSH2, this was chosen as the 2-antibody panel to be rated. However, a panel employing 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-antibody and 2-antibody 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 where multiple sebaceous neoplasms were encountered and scenarios where the patient had a history of a 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 clinical scenarios.

Soft tissue group

t(17;22) FISH assay for DFSP

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 alfa 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, or *COL1A1* break-apart FISH (35,36,37,38,39,40). 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 that has an overall sensitivity of 95% (range 91-100%). The sensitivity of the COL1A1 break-apart probe is likely in the same range; however, there is only one study that explicitly mentioned this probe being identified (41,42,43,44). Given the high sensitivity of FISH and the therapy potential if the translocation is detected, it is not surprising that the two scenarios where the test was found to be "usually appropriate" were situations when

the histology of the tumor is not typical for DFSP and the tumor is CD34 reactive and situations where tyrosine kinase therapy is being considered.

The scenarios where the histology is not typical for DFSP and the tumor is CD34 reactive but the subcutis is not visualized were found to be "majority usually appropriate." Although, this may suggest a bias from panel raters that it may be more appropriate to discuss the case with the clinician and depending on clinical circumstances obtain a larger sample of the tumor to visualize deeper structures, this was not reflected using the "OUT" option. The frequent use of the "OUT" option (44% of panel raters) in the scenario 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 prior to performing as the test. The lack of consensus for this scenario is thus not surprising. Similarly, this may be the case when the tissue has not been processed in a standard manner since these tumors are usually large and accessible.

Interestingly, expert ratings found it "majority usually appropriate" to perform FISH in scenarios when only fibrosarcoma-like areas are visualized and when the clinician is requesting further confirmation of the diagnosis. Perhaps the latter recommendation by panel raters considers that the clinician may be planning to use targeted therapy and is also reflected by 3 panel raters using the "OUT" option. Conversely, it is not surprising that results show testing to be "rarely appropriate" when the histology and IHC are supportive for a diagnosis of DFSP, a metastatic lesion is encountered with a similar histology to a prior DFSP, or in situations where testing for the translocation has been completed by another testing modality.

Although overall the "OUT" option was not used frequently for scenarios dealing with the use of FISH in the diagnosis of DFSP, there was one scenario in this group that had the highest number of "OUT" ratings of all 211 clinical scenarios. This was the scenario dealing with utility of the test in cases where the tissue available for evaluation is limited.

EWSR1 FISH assay for CSS

CCS is a very rare aggressive soft tissue sarcoma showing neuroectodermal and melanocytic differentiation (45,46). It typically occurs in individuals <50 years of age 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 where 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 if 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 for situations where 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. For CS where a typical histology of CCS is lacking, older individuals and occurrence of CCS on non-typical 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.

Overall conclusions

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 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 over and under use of tests/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 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 where the body of evidence is controversial and/or underdeveloped. It is the hope that in addition to providing a guide for those using these tests/procedures for diagnosis of skin biopsy specimens, that the results of this process will also highlight areas of needed and potential research.

The concept of appropriate and necessary care is essential for a healthcare 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, healthcare organizations and the public.

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Figure legend(s)

Figure 1. Process overview taken by the ASDP AUC Task Force in the development of the dermatopathology AUC.

Title: Appropriate Use Criteria in Dermatopathology: Initial Recommendations from the American Society of Dermatopathology

1. **Running Title:** Appropriate Use Criteria in Dermatopathology
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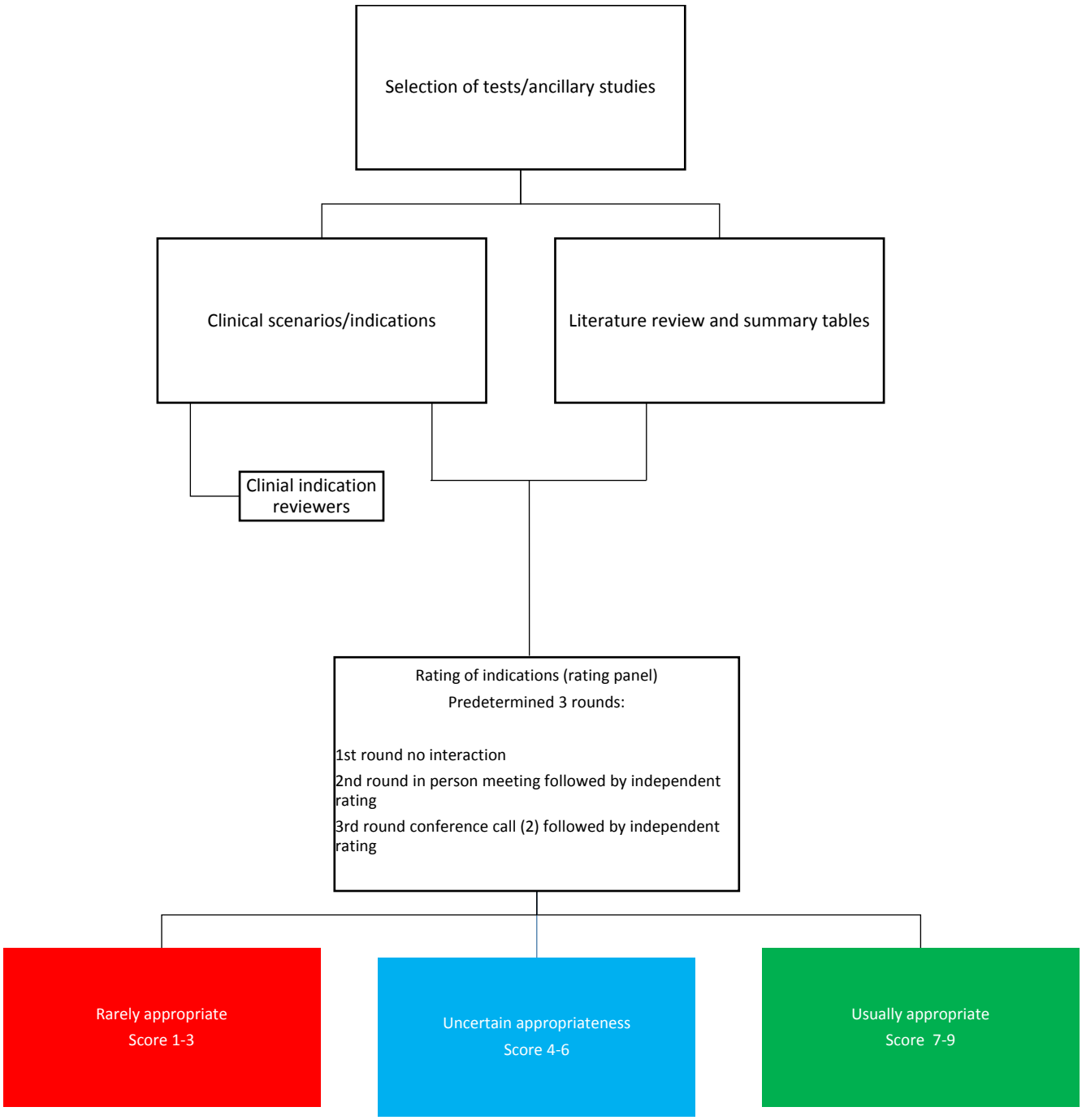

Table 1A. Lymphoproliferative Definitions and Clinical Scenarios T-cell Receptor Clonality

Definitions:

Specific clinical entities in B-cell and T-cell subgroups categorized according to the 2008 World Health Organization (WHO) 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 one or more important T cell marker (CD2, CD5 and/or CD7) within the neoplastic T-cell infiltrate along the dermoepidermal junction and/or in the epidermis
  - Nearly all neoplastic cells express CD4 OR CD8 (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 one or more mature T-cell markers (CD2, CD3, CD5, CD7)

- "Concerning for", "suspicious of" or "suggestive of" mycosis fungoides:
  - Presence of one 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 the absence of spongiosis
    - Epidermal lymphocytes larger than dermal lymphocytes
    - Perivascular distribution of atypical lymphocytes (‘bare underbelly’ sign)
    - 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

- "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/plaques that are clinically concerning for mycosis fungoides (clinical impression: rule 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 rule 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 rule out mycosis fungoides or cutaneous T-cell lymphoma and that is "not diagnostic for" mycosis fungoides.
4. Inflammatory/reactive papular or papulonecrotic eruption (solitary, regional or generalized) with clinical impression of lymphomatoid papulosis (LyP) or pityriasis lichenoides (PL), rule out mycosis fungoides or cutaneous T-cell lymphoma and histopathologic and immunophenotypic features typical for LyP or PL .
5. The development of T-cell cutaneous infiltrate that is "not diagnostic for" mycosis fungoides but is present in a patient with a history of mycosis fungoides with a known T-cell clone (comparison of past and present clones).
6. The development of a T-cell cutaneous infiltrate in a patient with a 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 rule 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 rule out mycosis fungoides in setting of pre-existing mycosis fungoides and histopathologic and immunophenotypic features "consistent with" mycosis fungoides.
11. Development of nodules in a 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 a patient with mycosis which are histologically "concerning for", "suspicious of" or "suggestive of" large cell transformation without CD30 positivity.

Table 1B. Lymphoproliferative Definitions and Clinical Scenarios B-cell receptor (IgH) Clonality

Definitions:

Specific clinical entities in B-cell and T-cell subgroups categorized according to the 2008 World Health Organization (WHO) 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 (i.e., 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 one 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 and T cell infiltrate)

- "Concerning for", "suspicious of" or "suggestive of" follicle center lymphoma:
  - Presence of one or more typical histopathologic features of follicle center lymphoma (Grenz zone, predominance of cleaved cells (centrocytes) and/or large non-cleaved cells (centroblasts), nodular infiltrate composed of disorganized follicles, 'bottom heavy' infiltrate, follicle like structures without tingible body macrophages, diffuse infiltrate of monotonous small cleaved or large non cleaved lymphocytes)
  - Normal immunophenotypical features (mixed B and T cell infiltrate, B cells confined to follicles, high Ki67 proliferative rate within follicles, lack of Bcl-6+, CD10+ B cells outside of follicles)

- "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 (less than 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 one 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 –rule 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 –rule 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 rule out cutaneous B-cell lymphoma (cutaneous marginal zone or follicle center lymphoma) and that is "not diagnostic for" cutaneous B-lymphoma.
6. Clinical presentation of a solitary lesion, suggestive of a non-neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B-cells immunophenotypically.
7. Clinical presentation of a dermatitis, suggestive of a non-neoplastic process clinically, that has a diffuse infiltrate of lymphocytes and has a predominance of B-cells immunophenotypically.
8. Unknown history, but histopathologic and immunophenotypic features "consistent with" cutaneous marginal zone lymphoma or follicle center lymphoma.
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 rule 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 –rule 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 a B-cell cutaneous infiltrate that is not diagnostic for cutaneous B-cell lymphoma in a patient with a history of cutaneous B-cell lymphoma with a known B-cell clone (comparison of past and present clones).
12. The development of a B-cell cutaneous infiltrate in a patient with a 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.

Table 2. Melanocytic Definitions and Clinical Scenarios

Definitions:

- Nevoid melanoma: Lesion of malignant melanocytes with some histologic features which 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 which 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 which 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 which closely mimic architectural and cytologic features of a benign blue nevus or blue nevus subtype
- Blue nevus-like melanoma (malignant blue nevus): Lesion of malignant melanocytes which closely mimic architectural and cytologic features of benign blue nevus or arises within a histologically recognizable benign blue nevus remnant
- 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 which have any of the following: marked architectural asymmetry, dysmaturation, ulceration, increased mitotic rate or increased and/or atypical mitoses in the deep portion of the lesion, marked cytologic atypia
- Incompletely sampled unclassified Spitz tumor: Lesion of Spitzoid melanocytes which is partially sampled to the degree it is not able to be subclassified and with atypical features
- Spitzoid melanoma: Lesion of malignant melanocytes with some histologic features which closely mimic architectural and cytologic features of a benign Spitz nevus
- Sclerosing (desmoplastic) nevus: Lesion of benign melanocytes which may be ovoid, dendritic or Spitzoid occurring within a distinctive eosinophilic stroma with overall architectural symmetry and without significant cytologic atypia or mitotic activity
- Desmoplastic melanoma: Lesion of malignant melanocytes with a predominantly spindled shaped, prominent desmoplasia and frequent neurotropism
- Pathology suggestive of /suspicious for melanoma = atypical melanocytic proliferation
- Pediatric patient is < 18 years of age

- Adult patient is ≥ 18 years of age
- Fluorescence in-situ hybridization panel includes:
    - RREB1 (6p25)
    - MYC (8q24)
    - CDKN2A p16 (9p21)
    - CCND1 (11q13)
- The 23 genes included in qRT-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 or suspicious for melanoma: Nevoid melanoma vs. benign melanocytic nevus.
3. Adult patient with pathology suggestive or suspicious for melanoma: Nevoid cutaneous metastatic melanoma vs. benign melanocytic nevus.
4. Adult patient with pathology suggestive or suspicious for melanoma: Melanoma arising within a nevus/dysplastic nevus.
5. Adult patient with pathology suggestive or suspicious for melanoma: Atypical blue nevus vs. benign blue nevus.
6. Adult patient pathology suggestive or suspicious for melanoma: Blue nevus-like cutaneous metastatic melanoma vs. benign blue nevus.
7. Adult patient with pathology suggestive or suspicious for melanoma: Blue nevus-like melanoma (malignant blue nevus) vs. benign blue nevus.
8. Adult with pathology suggestive or suspicious for melanoma: Congenital nevus with proliferative nodule vs. melanoma.
9. Adult patient with pathology suggestive or suspicious for melanoma: Atypical Spitz tumor vs. Spitzoid melanoma.
10. Adult patient with pathology suggestive or suspicious for melanoma: Incompletely sampled unclassified Spitz tumor vs. Spitzoid melanoma
11. Adult patient with pathology suggestive or suspicious for melanoma: Sclerosing (desmoplastic) nevus incompletely sampled vs desmoplastic melanoma.
12. Adult patient with pathology suggestive or suspicious for melanoma: Severely atypical compound melanocytic proliferation vs melanoma on cosmetically sensitive areas and special sites, including digits, acral, genital, ears, scalp

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 or suspicious for melanoma: Nevoid melanoma vs. benign melanocytic nevus.
20. Pediatric patient with pathology suggestive or suspicious for melanoma: Nevoid cutaneous metastatic melanoma vs. benign melanocytic nevus.
21. Pediatric patient with pathology suggestive or suspicious for melanoma: Melanoma arising within a nevus/dysplastic nevus.
22. Pediatric patient with pathology suggestive or suspicious for melanoma: Atypical blue nevus vs. benign blue nevus.
23. Pediatric patient with pathology suggestive or suspicious for melanoma: Blue nevus-like cutaneous metastatic melanoma vs. benign blue nevus.
24. Pediatric patient with pathology suggestive or suspicious for melanoma: Blue nevus-like melanoma (malignant blue nevus) vs. benign blue nevus.
25. Pediatric patient with pathology suggestive or suspicious for melanoma: Congenital nevus with proliferative nodule vs. melanoma.
26. Pediatric patient with pathology suggestive or suspicious for melanoma: Atypical Spitz tumor vs. Spitzoid melanoma.
27. Pediatric with pathology suggestive or suspicious for melanoma: Incompletely sampled unclassified Spitz tumor vs. Spitzoid melanoma.
28. Pediatric with pathology suggestive or suspicious for melanoma: Sclerosing (desmoplastic) nevus incompletely sampled vs desmoplastic melanoma.
29. Pediatric patient with pathology suggestive or suspicious for melanoma: Severely atypical compound melanocytic proliferation vs melanoma on cosmetically sensitive areas and special sites, including digits, acral, genital, ears, scalp.
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.

Table 3A. Other Definitions and Clinical Scenarios Human Papilloma Virus

Definitions: (5,6,7)

- Adult patient: Age greater than 14 years
- Pediatric patient: Age equal to or less than 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 may also include pseudo horn cysts
- Age of 25 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/ 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's disease, erythroplasia of Queyrat, bowenoid papulosis, multifocal Bowen's disease, severe dysplasia and carcinoma in situ
        - Newer terminology in the vulva has been replaced with "undifferentiated usual type of vulvar intraepithelial neoplasia (VIN)." This is defined as atypia involving 2/3 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 (SCC) of genital skin
    - For this purpose, divided into SCC arising in the background of a chronic dermatoses (i.e., lichen sclerosis et atrophicus (LSEA), lichen planus (LP)) OR SCC 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 encompass 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: exo-endophytic architecture, hyperkeratosis, keratinocytes w/ 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 may 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: defined as having 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. Pt 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 (i.e., LSEA, LP).
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 (e.g., organ transplant and HIV patients) with squamous cell carcinoma in situ or squamous cell carcinoma with verrucous features.

Table 3B. Other Definitions and Clinical Scenarios Muir-Torre Syndrome

Definitions: (8,9)

- Age 60: There are some articles that suggest age 50 instead of 60 as a cut off, this may be because sebaceous neoplasms present at a mean age of 53
- 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 over the age of 60 with a periocular sebaceous carcinoma.
2. A patient over the age of 60 with a single sebaceous tumor on the head and neck.
3. A patient over the age of 60 with a single sebaceous tumor on a site other than the head and neck.
4. A patient over the age of 60 with multiple (greater than or equal to 2) sebaceous tumors.
5. A patient over the age of 60 with a basal cell carcinoma with sebaceous differentiation.
6. A patient over the age of 60 with a keratoacanthoma with sebaceous differentiation.
7. A patient over the age of 60 with a cystic sebaceous neoplasm.
8. A patient over the age of 60 with a MTS-associated neoplasm and/or a personal history of a MTS-associated visceral malignancy.

Table 4A. Definitions and Clinical Scenarios for Dermatofibrosarcoma Protuberans

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
- Non-typical histomorphology of DFSP: refers to variant histomorphology such as fibrosarcomatous, giant cell fibroblastoma, myxoid, epithelioid or non-specific spindled cell histomorphology.

Clinical Scenarios:

1. Tissue with sampling down to subcutis with typical histomorphology of dermatofibrosarcoma protuberans and CD34+ by immunohistochemistry.
2. Tissue with sampling down to subcutis with typical histomorphology of dermatofibrosarcoma protuberans and CD34 immunohistochemistry not uniformly reactive.
3. Tissue with sampling down to subcutis with non-typical histomorphology of dermatofibrosarcoma protuberans and CD34+ by immunohistochemistry.
4. Superficial, CD34+ tumor with typical histomorphology of dermatofibrosarcoma protuberans except that good honeycombing of fat is not seen due to superficial sampling.
5. Superficial, CD34+ tumor with non-typical histomorphology for dermatofibrosarcoma protuberans. (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 dermatofibrosarcoma protuberans.
8. Metastatic tumor with histomorphology similar to previously diagnosed primary dermatofibrosarcoma protuberans.
9. Metastatic tumor with histomorphology distinct from previously diagnosed primary dermatofibrosarcoma protuberans.
10. Patient with locally recurrent dermatofibrosarcoma protuberans in which testing for translocation by another established molecular technique (RT-PCR, FISH, cytogenetics) was previously positive.
11. Patient with metastatic dermatofibrosarcoma protuberans 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 dermatofibrosarcoma protuberans by hematoxylin and eosin with CD34+ immunohistochemistry but where the treating physician is requesting molecular studies (RT-PCR, FISH, cytogenetics) to be performed to further confirm the diagnosis.

Table 4B. Soft Tissue 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 (non-pleomorphic) 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 less than 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 less than 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 past history of melanoma.
3. Patient greater than or equal to 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.
4. Patient greater than or equal 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 past history of melanoma.
5. Patient less than 50 years of age with NON-acral site tumor expressing melanocytic markers, WITHOUT typical histologic features of clear cell sarcoma, and involving deep dermis, subcutis or aponeurosis. No past history of melanoma but with what appears to be a cutaneous metastasis of melanoma from an unknown primary.
6. Patient greater than or equal to 50 years of age with NON-acral site tumor expressing melanocytic markers, WITHOUT typical histologic features of clear cell sarcoma, and involving deep dermis, subcutis or aponeurosis. No past history of melanoma but with what appears to be a cutaneous metastasis of melanoma from an unknown primary.
7. Patient less than 50 years of age with dermal based tumor expressing melanocytic markers and demonstrating typical histological features of clear cell sarcoma. No in situ component identified. No history of melanoma.
8. Patient less than 50 years of age with dermal based tumor expressing melanocytic markers and demonstrating typical histological features of clear cell sarcoma. No in-situ component identified. Patient has past history of invasive melanoma at another anatomic site.
9. Patient with an acral tumor in the dermis/subcutis that has typical histologic features of clear cell sarcoma and expresses melanocytic markers, but also has an overlying intra-epidermal in-situ component.

10. Patient with a non-acral tumor in the dermis/subcutis that has typical histologic features of clear cell sarcoma and expresses melanocytic markers but also has an overlying intra-epidermal in-situ component.
11. Patient with metastatic tumor with histomorphology similar to previously diagnosed primary clear cell sarcoma.
12. Patient with metastatic tumor with histomorphology distinct from previously diagnosed primary clear cell sarcoma.
13. Patient with recurrent or metastatic clear cell sarcoma in which testing for translocation by another established technique (RT-PCR, FISH, cytogenetics) was previously positive.
14. Patient with primary or metastatic tumor expressing melanocytic markers in which BRAF or NRAS mutation has been detected.
15. Patient with tissue that has been decalcified or processed with fixative other than 10% formalin.

Table 5A. Lymphoproliferative T-cell Clonality Beta and Gamma Appropriate Use Scores

Clinical Scenario (refer to Table 1A for complete wording of the clinical scenarios and associated definitions)	**Beta Ratings**	**Gamma Ratings**
e 1 scaly patches / plaques concerning for MF; histology and IHC "concerning", "suspicious" or "suggestive of" MF	UA (8.0)	UA (7.9)
Erythroderma; clinical r/o MF / CTCL / Sézary dz; histology "not diagnostic" for MF	NC (5.6)	NC (5.8)
Dermatitis; clinical r/o MF / CTCL; histology "not diagnostic" for MF	RA (2.8)	RA (2.8)
Inflam / react / papular / papulonecrotic solitary / regional / generalized; clinical r/o LyP, PL, MF, CTCL; histology typical for LyP or PL	RA (2.1)	RA (2.1)
Histology of a T-cell infiltrate "not diagnostic for MF" in pt w/ Hx MF and known clone (comparison of past and present clone)	UA (7.1)	UA (7.1)
T-cell infiltrate in pt w/ Hx systemic T-cell lymphoma	UAU (6.8)	UAU (6.9)
Histology of a folliculotropic T- cell infiltrate	UA (7.1)	UA (7.2)
Pigmented purpuric patches solitary / regional / generalized; clinical r/o MF / CTCL; histology "not diagnostic" for MF	RA (2.7) 2/16 OUT	RA (2.6) 2/16 OUT
Clinical reactive entities; histology and IHC "concerning", "suspicious" or "suggestive of" MF	U (6.0)	U (3.6)
New / evolving lesion in pt w/ Hx of MF; clinical r/o MF; histology and IHC "consistent with" MF	NC (3.4)	NC (3.1)
Nodules in patient w/ Hx of MF; histology "concerning", "suspicious" or "suggestive of" MF w/ CD30+ large cell transformation	RA (2.8)	RA (2.8)
Nodules in patient w/ Hx of MF; histology "concerning", "suspicious" or "suggestive of" MF w/out CD30+ large cell transformation	RA (2.7)	RA (2.7)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: MF - mycosis fungoides; IHC - immunophenotype; r/o - rule out; CTCL - cutaneous T-cell lymphoma; dz - disease; inflam - inflammatory; react - reactive; LyP - lymphomatoid papulosis; PL - pityriasis lichenoides; pt - patient; w/ - with; Hx - history

Table 5B. Lymphoproliferative B-cell receptor (IgH) gene rearrangement by PCR Appropriate Use Scores

Clinical Scenario (refer to Table 1B for complete wording of the clinical scenarios and associated definitions)	**IgH Ratings**
e 1 erythematous concerning nodules; clinical r/o B-cell lymphoma; histology and IHC "concerning for", "suspicious of", or "suggestive of" PCMZL	UA (7.8)
e 1 erythematous concerning nodules; clinical r/o B-cell lymphoma; histology and IHC "concerning for", "suspicious of", or "suggestive of" FCL	UA (8.1)
e 1 nodules; clinical CLH; histology and IHC "concerning for", "suspicious of", or "suggestive of" PCMZL	UA (8.2)
e 1 nodules; clinical CLH; histology and IHC "concerning for", "suspicious of", or "suggestive of" FCL	UA (8.2)
e 1 erythematous concerning nodules; clinical r/o B-cell lymphoma (PCMZL or FCL); histology and IHC "not diagnostic" for cutaneous B cell lymphoma	RA (2.7)
1 lesion; clinical s/o non-neoplastic process; B-cell predominant infiltrate	UAU (6.6)
Dermatitis; clinical s/o non-neoplastic process; B-cell predominant infiltrate	UAU (6.9)
Unknown Hx; histology and IHC "consistent with" PCMZL or FCL	NC (6.6)
New / evolving lesion in pt w/ prior ddx of B-cell lymphoma (PCMZL or FCL); clinical r/o B-cell lymphoma; histology and IHC "consistent with" PCMZL or FCL	RA (2.6)
e 1 nodules; clinical concerning for aggressive B-cell lymphoma r/o B-cell lymphoma, leg type; histology and IHC "concerning for", "suspicious of", or "suggestive of" PCLBCL, LT	UA (7.7)
Cutaneous B cell infiltrate not diagnostic for B-cell lymphoma but in a patient w/ Hx of B cell lymphoma known clone (comparison of past and present clones)	UA (7.9)
Cutaneous B-cell infiltrate in a patient w/ Hx of any systemic B cell lymphoma	UAU (6.8)
Other more aggressive cutaneous B-cell lymphoma other than PCLBCL, LT (e.g. IVL or cutaneous plasmablastic lymphoma)	NC (5.2)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: r/o - rule out; IHC - immunophenotype; PCMZL - primary cutaneous marginal zone lymphoma; FCL - follicle center lymphoma; s/o - suggestive of; Hx - history of; w/ - with; PCLBCL, LT - primary cutaneous large B-cell lymphoma, leg type; IVL - intravascular lymphoma

Table 6. Melanocytic Appropriate Use Scores

Clinical Scenario (refer to Table 2 for complete wording of the clinical scenarios and associated definitions)	Patient type	FISH Ratings	CGH Ratings	qRT-PCR Ratings
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 patients	RA (1.2/1.2)
Pathology suggestive / suspicious for MM (DDx nevoid MM vs benign melanocytic nevus)	Adult / Pediatric	UA (7.4/7.8)	UA (7.7/7.9)	U (4.9/4.9)
Pathology suggestive / suspicious for MM (DDx nevoid cutaneous met vs benign melanocytic nevus)	Adult / Pediatric	UA (7.3/7.7)	UA (7.8/7.9)	U (4.6/4.4)
Pathology suggestive / suspicious for MM (DDx MM arising w/in nevus/ dysplastic nevus)	Adult / Pediatric	UA (7.0/7.5)	UA (7.7/7.6)	U (4.7/4.6)
Pathology suggestive / suspicious for MM (DDx atypical blue nevus vs benign blue nevus)	Adult / Pediatric	U (4.4/4.3)	UA (7.0) / NC (6.8)	U (4.4/4.4)
Pathology suggestive / suspicious for MM (DDx blue nevus-like cut met vs benign blue nevus)	Adult / Pediatric	U (4.9) / NC (5.1)	UA (7.6/7.6)	U (4.6/4.3)
Pathology suggestive / suspicious for MM (DDx malignant blue nevus vs benign blue nevus)	Adult / Pediatric	NC (4.6/4.8)	UA (7.4/7.6)	U (4.7/4.4)
Pathology suggestive / suspicious for MM (DDx cong nevus with prolif nodule vs MM)	Adult / Pediatric	UA (7.6/7.7)	UA (7.9/7.9)	U (4.8/4.8)
Pathology suggestive / suspicious for MM (DDx atypical Spitz vs Spitzoid MM)	Adult / Pediatric	UA (7.6/7.1)	UA (7.7/7.9)	U (4.9/4.8)
Pathology suggestive / suspicious for MM; incompletely sampled (DDx	Adult /	UA (7.6/7.1)	UA (7.2/7.6)	U (4.9/4.7)

unclassified Spitz vs Spitzoid MM)	Pediatric			
Pathology suggestive / suspicious for MM; incompletely sampled (DDx sclerosing desmoplastic nevus vs desmoplastic MM)	Adult / Pediatric	NC (6.4/6.2)	UA (7.0/7.3)	U (4.4/4.4)
Pathology suggestive / suspicious for MM (DDx severely atypical mel prolif vs MM on cosmetically sensitive areas and SS)	Adult / Pediatric	UA (7.5/7.8)	UA (7.6/7.8)	U (5.1/4.9)
Pathology definitive for nevus	Adult / Pediatric	RA (1.1/1.1)	RA (1.1/1.1)	RA (1.1/.4)
Light microscopy not definitive	Adult Pediatric	UA (7.8/7.9)	UA (7.9/8.0)	U (5.2/4.9)
Partial bx; 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	U (4.9/4.6)
DDx nevus vs met; light microscopy not definitive	Adult / Pediatric	UA (7.5/7.6)	UA (7.9/7.9)	U (4.6/4.3)
DDx nevus vs met; partial bx; light microscopy not definitive	Adult / Pediatric	UA (7.5/7.4) 1/16 OUT - Adult patient; 1/16 OUT - Pediatric patient	UA (7.3/7.5) 1/16 OUT - Adult patient; 1/16 OUT - Pediatric patient	U (4.4/4.2)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: FISH - florescent in situ hybridization; CGH - florescent in situ hybridization; qRT-PCR - quantitative reverse transcription polymerase chain reaction; MM - melanoma; DDx - differential diagnosis; vs -

versus; met - metastasis; w/in - within; cut - cutaneous; cong - congenital; prolif - proliferative; mel - melanocytic; SS - special sites; bx - biopsy;

Table 7A. HPV Appropriate Use Scores

Clinical Scenario (refer to Table 3A for complete wording of the clinical scenarios and associated definitions)	**ISH Ratings**	**IHC Ratings**
Adult; definitive for condyloma	RA (1.6) 1/16 OUT	RA (1.5) 1/16 OUT
Adult suggestive of condyloma	U (6.3) 3/16 OUT	U (5.2) 2/16 OUT
Pediatric; definitive for condyloma	NC (6.0) 4/16 OUT	NC (4.1) 3/16 OUT
Pediatric; suggestive of condyloma	UA (7.5) 4/16 OUT	NC (5.7) 4/16 OUT
Age < 25; pathologic findings c/w seborrheic keratosis of genital skin, perineum, lower abdomen, or inner thighs	UAU (6.7) 4/16 OUT	U (3.6) 3/16 OUT
SCCIS/ undifferentiated intraepithelial dysplasia of the genital skin	U (3.7) 1/16 OUT	RA (2.8) 1/16 OUT
SCC in the genital area	NC (3.9)	RA (2.8)
Hx HPV induced lesion and a SCC in the genital area	RAU (3.6)	RA (2.8)
SCC in the genital area and Hx chronic dermatoses (ie LSEA, LP)	RAU (3.2)	RA (2.7)
Clinical impression and pathology c/w verrucous carcinoma	RAU (3.3)	RA (2.3)
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 w/ verrucous features on digits	RA (2.9)	RA (2.2)
Immunosuppressed patients with SCCIS or SCC with verrucous features	RAU (3.3)	RA (2.6)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: ISH - in situ hybridization; IHC - immunohistochemistry; c/w - consistent with; SCCIS - squamous cell carcinoma in situ; SCC - squamous cell carcinoma; LSEA - Lichen sclerosus et atrophicus; LP - lichen planus

Table 7B. Muir-Torre Syndrome Appropriate Use Scores

Clinical Scenario (refer to Table 3B for complete wording of the clinical scenarios and associated definitions)	**4 AB Panel Ratings**	**2 AB Panel Ratings**
Age >60; periocular sebca	NC (3.5)	RA (3.0)
Age >60; 1 seb tumor H&N	NC (5.1) 1/16 OUT	U (4.9) 1/16 OUT
Age >60; 1 seb tumor non-H&N	NC (6.7) 1/16 OUT	UAU (6.9) 1/16 OUT
Age >60; multiple seb tumors	UA (7.2)	UA (7.2)
Age >60; BCC w/ seb diff	U (5.0)	U (4.6)
Age >60; KA w/ seb diff	UA (7.1)	UAU (6.6)
Age >60; cystic seb neoplasm	UA (7.3)	UAU (6.9)
Age >60; MTS assoc. neoplasm &/or visceral malignancy	UA (7.3) 1/16 OUT	UAU (6.9)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: MTS - Muir-Torre syndrome; sebca - sebaceous carcinoma; seb - sebaceous; H&N - site head and neck; seb diff - sebaceous differentiation; assoc - associated

Table 8A. t(17:22) in Dermatofibrosarcoma Protuberans Appropriate Use Scores

Clinical Scenario (refer to Table 4A for complete wording of the clinical scenarios and associated definitions)	**t(17:22) Ratings**
Histology typical for DFSP; CD34+	RA (1.4)
Histology typical for DFSP; CD34 not uniformly reactive	NC (3.2)
Histology not typical for DFSP; CD34+	UA (7.2)
Histology typical for DFSP; CD34+; but SQ not visualized	NC (4.7)
Histology not typical for DFSP; CD34+; SQ not visualized	UAU (6.5)
Limited cytological and / or architectural histology evaluation; CD34+	NC (6.0) 7/16 OUT
Fibrosarcoma-like (high grade) histology; no histology typical for DFSP	UAU (6.9)
Met lesion with histology similar to prior DFSP	RA (2.9) 1/16 OUT
Met lesion with histology different from prior DFSP	U (6.5)
Locally recurrent DFSP; + translocation testing by other molecular test	RA (1.6)
Met DFSP; + translocation testing by other molecular test	RA (1.7)
Tyrosine kinase therapy is being considered	UA (7.2) 1/16 OUT
Tissue that has been decalcified or processed w/ fixative other than 10% formalin	UAU (6.6)
Histology typical for DFSP; CD34+; treating MD requesting cytogenetics to confirm diagnosis	UAU (6.3) 3/16 OUT

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: DFSP - dermatofibrosarcoma protuberans; histology typical - monotonous spindled cells in a storiform pattern with "honeycombing" or entrapment of adnexal structures and / or adipocytes and extension into the subcutis; SQ - subcutis; Met - metastatic; w/ - with

Table 8B. *EWSR1* FISH Clear Cell Sarcoma Appropriate Use Scores

Clinical Scenario (refer to Table 4B for complete wording of the clinical scenarios and associated definitions)	***EWSR1* FISH Ratings**
Age < 50; typical location; tumor w/ histology typical for CCS, expressing melanocytic markers, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma	UA (8.3)
Age < 50; typical location; tumor w/ non-typical histology for CCS expressing melanocytic markers, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma	NC (6.3)
Age e 50; typical location; tumor w/ histology typical for CCS, expressing melanocytic markers, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma	UA (8.1)
Age e 50; typical location; tumor w/ non-typical histology for CCS expressing melanocytic markers, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma	RAU (3.4)
Age < 50; non-typical location; tumor expressing melanocytic markers; w/ non-typical histology for CCS, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma but w/ what appears to be cut met of MM from unknown primary	RAU (3.2)
Age e 50; non-typical location; tumor expressing melanocytic markers; w/ non-typical histology for CCS, involving deep dermis, SQ or aponeurosis. No Hx of Melanoma but w/ what appears to be cut met of MM from unknown primary	RA (2.2)
Dermal tumor expressing melanocytic markers and demonstrating typical histology of CCS. Pt has Hx 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)
Non-typical location; tumor in dermis / subcutis; histology typical for CCS expressing melanocytic markers, but also has an intraepidermal in situ component	UA (7.4)
Met tumor w/ histology similar to previous CCS	RAU (3.2)
Met tumor w/ histology different from previous CCS	UA (7.3)
Recurrent / Met CCS w/ translocation testing by other method positive	RA (1.9)
Primary or Met tumor expressing melanocytic markers; BRAF or NRAS mutation detected	UAU (6.3)
Tissue that has been decalcified or processed w/ fixative other than 10% formalin	UA (7.0)

Usually appropriate indications (UA; mean' scores of $\geq$7.0) are colored dark green; Usually appropriate to uncertain ("majority usually appropriate") indications (UAU; mean' scores between 6.1 and 6.9 and SD <2.0) and colored light green; Rarely appropriate indications (RA; mean' scores of $\leq$3.0) are colored dark red; Rarely appropriate to uncertain (majority rarely appropriate) indications (RAU; mean' scores between 3.1 and 3.9 and SD <2.0); Uncertain appropriateness indications (U; mean' scores of $\geq$4.0 and $\leq$6.0 with a SD <2.0) are colored blue; No consensus (NC; mean' scores between 3.1 and 6.9 that had a standard deviation (SD) $\geq$2.0) are colored white

Abbreviations: CCS -clear cell sarcoma; w/ - with; typical location - deep soft tissue of tendon, aponeuroses and fascial structures of the distal extremities; SQ - subcutis; Hx - history; MM - malignant melanoma; Met - metastatic; typical histology - Tumor with a distinctly nested growth pattern that is divided by fibrous septations. Cells have a relatively uniform nucleus and large central nucleoli. Scattered osteoclast-like giant cells can be seen. There is little to no melanin appreciated.