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Early Detection and Prognostic Assessment of Cutaneous Melanoma Consensus on Optimal Practice and the Role of Gene Expression Profile Testing

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Abstract

IMPORTANCE—Therapy for advanced melanoma has transformed during the past decade, but early detection and prognostic assessment of cutaneous melanoma (CM) remain paramount goals. Best practices for screening and use of pigmented lesion evaluation tools and gene expression profile (GEP) testing in CM remain to be defined.

OBJECTIVE—To provide consensus recommendations on optimal screening practices and prebiopsy diagnostic, postbiopsy diagnostic, and prognostic assessment of CM.

EVIDENCE REVIEW—Case scenarios were interrogated using a modified Delphi consensus method. Melanoma panelists (n = 60) were invited to vote on hypothetical scenarios via an

emailed survey (n = 42), which was followed by a consensus conference (n = 51) that reviewed the literature and the rationale for survey answers. Panelists participated in a follow-up survey for final recommendations on the scenarios (n = 45).

FINDINGS—The panelists reached consensus (70% agreement) in supporting a risk-stratified approach to melanoma screening in clinical settings and public screening events, screening personnel recommendations (self/partner, primary care provider, general dermatologist, and pigmented lesion expert), screening intervals, and acceptable appointment wait times. Participants also reached consensus that visual and dermoscopic examination are sufficient for evaluation and follow-up of melanocytic skin lesions deemed innocuous. The panelists reached consensus on interpreting reflectance confocal microscopy and some but not all results from epidermal tape stripping, but they did not reach consensus on use of certain pigmented lesion evaluation tools, such as electrical impedance spectroscopy. Regarding GEP scores, the panelists reached consensus that a low-risk prognostic GEP score should not outweigh concerning histologic features when selecting patients to undergo sentinel lymph node biopsy but did not reach consensus on imaging recommendations in the setting of a high-risk prognostic GEP score and low-risk histology and/or negative nodal status.

CONCLUSIONS AND RELEVANCE—For this consensus statement, panelists reached consensus on aspects of a risk-stratified approach to melanoma screening and follow-up as well as use of visual examination and dermoscopy. These findings support a practical approach to diagnosing and evaluating CM. Panelists did not reach consensus on a clearly defined role for GEP testing in clinical decision-making, citing the need for additional studies to establish the clinical use of existing GEP assays.

Melanoma management has transformed during the past decade, with therapeutic developments for advanced and adjuvant settings, but early detection remains a paramount goal given that early-stage melanoma is treated more easily. In clinical practice, various gene expression profile (GEP) assays are commercially available and widely used. However, to our knowledge, the GEP assays have not been validated in large multicenter prospective randomized clinical trials, and their use in clinical workflows remains poorly defined. Therefore, a group of melanoma experts participated in a modified Delphi process to develop a consensus statement on optimal practices for early detection and diagnostic and prognostic assessment of cutaneous melanoma (CM) (the clinical cases for dicussion and survey form for responses can be found in the Supplement).

While population-based skin cancer screening is unlikely to be cost-effective and may be associated with harms associated with overdiagnosis or misdiagnosis, failure to screen can be followed by missed detection of thicker melanomas that is associated with poor outcomes.[1,2] Screening higher-risk populations for melanomas that may be potentially lethal may be cost-effective and associated with fewer individuals needing to be screened per diagnosis of CM.[3,4] Unfortunately, the major skin cancer screening guidelines do not provide consistent guidance to support a risk-stratified approach to skin cancer screening.[3] In addition, there is a dearth of evidence to support screening by specific clinician types or for risk-based screening by individuals and/or their partners. We sought to develop consensus recommendations for a risk-based approach to melanoma screening.

Best practices also need to be delineated for diagnosing CM. The appropriate roles remain to be defined for prebiopsy diagnostic tools in evaluating whether a suspicious pigmented lesion warrants biopsy. In addition, the histological diagnosis of a subset of CM can be challenging owing to a lack of precise or reproducible histological criteria distinguishing between lethal and indolent melanocytic neoplasms. This is associated with substantial discordance or interobserver variability in evaluating lesions ranging from dysplastic nevi with moderate atypia through T1a melanoma.[5–7] For postbiopsy diagnosis, molecular techniques, diagnostic GEP testing, next-generation sequencing, and immunohistochemical assessment for preferentially expressed antigen in melanoma (*PRAME*), among other markers, are available to aid in histopathologic assessment, but questions remain regarding their diagnostic accuracy.[8,9] Postbiopsy, molecular tools to enhance diagnostic accuracy and prognostic assessment would benefit clinical decision-making and potentially improve patient outcomes.

In 2020, the Melanoma Prevention Working Group (MPWG) published a consensus statement on the use of available GEP tests for prognostication in CM.[10] The MPWG concluded that GEP testing might be associated with improved risk stratification and clinical decision-making in the right setting, but its use was limited in patients with early-stage disease, highlighting the need for performance measures in large, prospectively enrolled independent cohorts. The state of GEP testing in melanoma contrasts with advances in breast cancer, in which prospectively validated evidence supporting GEP testing allows personalized treatment approaches for localized forms of estrogen-dependent breast cancers.[11] Since the 2020 MPWG publication,[10] clinical experience with GEP testing has grown, not only for prognostication but also for diagnosis. Therefore, panelists considered scenarios involving 2 GEP tests commercially available in 2021: a prebiopsy GEP test (epidermal tape stripping) that assessed 2 genes, *LINC00518* (*LINC*) and *PRAME*,[12] which has since been augmented to include a third gene, telomerase reverse transcriptase (*TERT*); a 23-gene diagnostic GEP test performed on biopsied specimens (diagnostic GEP)[13]; and the 31-gene prognostic GEP assay[2] (the more recent DiffDx [Castle Biosciences] and i31-ROR tests were not included in the Delphi process).

Methods

Members of the MPWG and primary care clinicians with a stated interest in melanoma detection and GEP testing were invited to participate in the consensus meeting sponsored by the Melanoma Research Foundation. Three dermatologists with expertise in pigmented lesion diagnosis and management (S.A.L., J.A.S., and M.K.S.) led the discussions for recommendations on (1) screening; (2) lesion assessment; and (3) GEP testing. A panel chair with experience in melanoma therapeutics (J.M.K.) oversaw the entire effort. The conduct of a consensus conference did not require institutional review board or human participants committee approval. Hypothetical case scenarios were developed to query clinicians for management recommendations using a modified Delphi approach.[14] The first survey was sent in October 2021 to 60 individuals who had completed a conflict of interest disclosure. The 42 survey respondents included 29 academic dermatologists, 4 surgical oncologists, 7 medical oncologists, 1 primary care physician, and 1 community dermatologist. Consensus was defined as 70% agreement or greater.[15] The panel then hosted

a half-day virtual consensus conference in November 2021, at which 51 attending panelists were queried about their approach (and supporting data) for each of the clinical case scenarios, focusing on scenarios in which consensus was not reached. All attendees were subsequently surveyed for their final recommendations regarding the discrepant scenarios, with 45 responses received (75% participation rate). These methods were used to derive consensus-based recommendations, not to develop guidelines.

Results

Screening Personnel Recommendations

Panelists considered various melanoma risk factors and were queried regarding which medical specialty should optimally administer screening for individuals of different risk categories (Table 1[16–26]). Although access to care was considered a critical issue in melanoma diagnosis, there was no consensus among the panelists regarding acceptable wait times for an appointment, factors that would be associated with more rapid access, or effective strategies to improve patient access to care. There was consensus that a general dermatologist (GD) would be the most appropriate clinician to screen higher-risk individuals with severe skin sun damage, exposure to ultraviolet radiation through indoor tanning, systemic immunosuppression, or a personal history of nonmelanoma skin cancer. There was also consensus that a pigmented lesion evaluation (PLE) expert would be the most appropriate clinician to screen individuals with a genetic risk for melanoma whenever possible. Following the conference, additional consensus was reached that GDs would be most appropriate to screen patients with a personal history of melanoma.

As shown in Table 1, panelists did not reach consensus on several questions in the October 2021 survey, so the conference devoted time to review data on risk factors, relative risk, and population risk for CM. There was a shift toward acceptance of primary care physicians (PCPs) for administering screening for the general population, with most panelists suggesting self-screening in the general population. For individuals with a personal history of actinic keratosis, blistering or peeling sunburns, or a fair complexion, panelists recommended screening by a PCP or GD. For individuals with more than 40 melanocytic nevi or 2 or more clinically atypical nevi, panelists recommended screening by a GD or PLE.

A pattern of recommendations for risk-stratified screening emerged, as shown in Table 1 and the eFigure in the Supplement. Panelists suggested that general or lower-risk populations (relative risk [RR] <2) can be appropriately screened by a PCP, or regular self or partner examinations. Those at moderate risk (RR, 2 to <5) could be appropriately screened by a PCP or a GD, those at high risk (RR, 5–10) by a GD or PLE, and those at ultra-high risk (RR >10) by a PLE. The shift in recommendation from PCP to GD or PLE in the moderate-risk settings of multiple nevi, atypical/dysplastic nevi, or immunocompromised status was associated with factors beyond RR alone. For example, in the setting of multiple nevi or clinically atypical nevi, specialized equipment (eg, total body photography) and experience were recommended to avoid excessive biopsy specimens or failing to identify suspicious lesions against a backdrop of multiple lesions. In immunocompromised patients,

melanoma may behave more aggressively, and the likelihood of developing keratinocyte carcinomas that can be deadly[27] shifted recommendations for more vigilant monitoring.

Recommendations for Public Screening

Risk Stratification—Cost-free skin cancer screenings have been conducted in the US since the mid-1980s.[28] Given the scenario that a local dermatology practice is hosting a free skin cancer screening event, panelists were asked to select attendees who would be highly likely, somewhat likely, and least likely to benefit. Individuals selected as highly likely to benefit are shown in Table 2, representing those with the highest risk profiles. However, certain genetic, phenotypic, and environmental risk factors that are known to play an important role in individual risk were not identified as important for population-based screenings. This was because they are either too rare (eg, carriers of the *CDKN2A* variant) or they were not believed to be of sufficient absolute risk to justify more intensive screening.

Role of PLE Tools in the Prebiopsy Setting—The panel was queried about use of pigmented lesion imaging and evaluation (Table 3). Among the 42 respondents, 34 (81%) reported experience with dermoscopy, 6 of 42 (14%) with RCM, 6 of 42 (14%) with 2-gene epidermal tape stripping, 2 of 42 (5%) with *TERT* epidermal tape stripping, and 0 with electrical impedance spectroscopy. Panelists reached consensus that visual and dermoscopic examination is sufficient to evaluate patients with no new, changing, or unusual skin lesions or with a new lesion that is not visually concerning. Respondents (39 of 42 [93%]) agreed that 3 months was the appropriate time frame for reevaluation after a dermoscopic photograph for monitoring of a flat, slightly changed lesion, in the absence of additional change. Although reflectance confocal microscopy (RCM) was not commonly used by panelists, they reached consensus in management of lesions evaluated by RCM, with 32 of 42 (76%) indicating that a clinically suspicious lesion with likely benign RCM findings would not need a biopsy and could be followed with repeated visual examination. Most agreed that lesions found to be clinically suspicious for cancer on RCM results (91%) or showing RCM features of cancer (93%) should be biopsied. Most respondents (36 of 42 [86%]) were not currently using epidermal tape stripping routinely in their practice, and some panelists believed that clinical use was limited by low specificity. Posed a hypothetical situation in which epidermal tape stripping had been used to evaluate a suspicious lesion, the panelists reached consensus that *PRAME*+ and *LINC*+ (or *PRAME*+ only) lesions should be biopsied.

Panelists agreed that clinically suspicious, raised lesions should be biopsied and not monitored given the possibility of nodular melanoma. Generally, for lesions that remained concerning to the expert after prebiopsy diagnostic testing, biopsy remained the mainstay recommendation. The panelists did not reach consensus on use of the tools for many other scenarios (Table 3).

Postbiopsy Diagnostic Tools—In the setting of atypical Spitzoid lesions, the 2018 World Health Organization melanoma classification has indicated the use of *BRAF-V600E* variant testing, which if present, excludes a Spitzoid melanoma.[29] However, because

Spitzoid lesions and severely dysplastic melanocytic nevi remain diagnostic challenges, panelists were queried regarding their preferred approach to these atypical lesions.

Panelists reported using the following diagnostic tests routinely in practice: 11 of 42 (26%) use fluorescence in situ hybridization, 12 of 42 (29%) comparative genomic hybridization, 2 of 42 (5%) diagnostic GEP, and 3 of 42 (7%) whole-exome sequencing. Results of their application in clinical scenarios are shown in Table 4. A Spitzoid lesion scenario was presented with a lesional thickness (1.5 mm in this question) that would typically trigger consideration of sentinel lymph node biopsy (SLNB) in unambiguous primary CM. In the pediatric setting, there was no consensus regarding use of any of the modalities discussed. In the setting of a 6-year-old patient, a wide range of next steps was selected, with only 12 of 42 (29%) favoring wide local excision (WLE) and 7 of 42 (17%) favoring WLE and SLNB. In an older (16-year-old) pediatric patient, more respondents favored WLE plus SLNB (17 of 42 [41%]) vs WLE alone (8 of 42 [19%]), while in the adult patient with an atypical Spitzoid proliferation, WLE with SLNB was favored, and this reached consensus (33 of 42 [79%]). For the histologic differential diagnosis of dysplastic nevus vs melanoma, there was no consensus among the aforementioned options, although 27 of 45 respondents (60%) favored treating the lesion as melanoma (excision), whereas 7 of 45 (16%) favored evaluation by fluorescence in situ hybridization and 5 of 45 (11%) favored no further treatment.

Postbiopsy Prognostic Tools—While many questions remain about the use prognostic GEP testing in assisting with management decisions,[30,31] 1 area in which consensus was reached among the panel was that the 31-gene prognostic GEP testing result alone would not outweigh routine histopathologic features to inform selection of patients for SLNB. Panelists supported an approach that favors histopathologic vs GEP testing for SLNB. As shown in Table 4, the panelists consistently recommended WLE plus SLNB for individuals who meet histopathologic criteria for SLNB, even in the setting of a low-risk (class 1) 31-gene GEP testing result. Panelists were not queried regarding various SLNB risk calculators/nomograms or other GEP testing (ie, Merlin Assay 8-GEP; DecisionDx i-31-GEP) purported to predict SLN positivity.

Questions also arose regarding the use of prognostic GEP testing to inform the routine use of radiographic modalities in the initial and follow-up assessment of asymptomatic patients with primary melanoma. Panelists did not reach consensus on using GEP testing to inform imaging decisions with discordant histological vs molecular risk scores. Specifically, in a patient with transected stage IA melanoma, negative SLNB result, and class 2B high-risk GEP testing result, only 18 of 45 (40%) recommended adding routine imaging at baseline or in follow-up. In a patient with stage IIB desmoplastic melanoma with negative SLNB and class 1 GEP testing results, 12 of 42 (29%) did not recommend any routine imaging, whereas 9 of 42 (21%) recommended a positron emission tomography/computed tomography (CT) scan at baseline, and 9 of 42 (21%) recommended positron emission tomography/CT (or CT) scans in follow-up.

Discussion

Panelists agreed that risk stratification is important to maximize screening detection of potentially lethal melanomas and minimize risks of overdiagnosis or misdiagnosis. The recommendations based on risk levels were consistent with access to specialized experts with increasing risk. Furthermore, there was an ultimate goal of risk-stratifying populations by melanoma lethality (eg, greater in White men older than 50 years and with lower socioeconomic status) and a need for better diagnostic and prognostic markers to reduce overdiagnosis and misdiagnosis.

Absolute risk was discussed in association with stratifying populations for recommendations, although to our knowledge the absolute risk level needed to justify screening has not been established. Panelists believed that public skin cancer screenings should prioritize absolute risk vs relative or lifetime risk for stratification and should target people 50 years or older, those with prior history of CM, and those with a skin lesion of concern. The American Academy of Dermatology is formulating a proposal to move American Academy of Dermatology–sponsored screenings toward a risk-stratified model. While the US Public Health Task Force does not currently recommend routine public skin cancer screenings,[3] the panelists emphasized the effect of public screenings for health promotion and education and that low-risk individuals can develop CM. Strategies for enriching higher-risk populations for screening include targeted promotion to those demographic groups as well as individuals of lower socioeconomic status, regardless of race and ethnicity.

Limitations

The limitations of this consensus statement included our inability to review all relevant data, including proprietary industry data. There was a lack of uniform experience with the technologies discussed. However, the panelists had a working knowledge of the data to support these technologies. Another limitation was that the Delphi method did not modify the case scenarios in subsequent rounds of consensus building, which may have improved consensus. Another limitation affecting the consensus process was lack of data on the association of clinician type and delay times with melanoma outcomes, although these data may become available from emerging studies of the association of COVID-19 restrictions with melanoma outcomes.[32]

The panelists discussed molecular tests and emphasized the importance of focusing on the intention of tests and baseline risk of the tested population when establishing the validity and use of molecular tests in practice. For example, for epidermal tape stripping, the panelists expressed concern that widespread use of the test by nondermatologists may be associated with overbiopsy of benign lesions, given the low pretest probability of melanoma in the primary care setting. The test was believed to be most appropriately used in assessing melanocytic lesions that are concerning for melanoma in adults, a scenario for which the test has been validated.

The panelists' recommendation against using the 31-gene prognostic GEP testing assay for making clinical decisions regarding SLNB is consistent with the current guidelines of

the National Comprehensive Cancer Network,[31] which indicate that GEP testing to assess risk of metastasis should not replace pathologic staging procedures and that "currently available GEP tests should not be used to determine SLNB eligibility." The panelists did not reach consensus on imaging recommendations for thin melanoma with a negative SLNB result but high-risk GEP testing score. This survey was conducted before the publication of several sentinel node metastasis risk prediction tools.[33,34] Research is moving forward with integrated clinicopathologic and gene expression profile models and outcomes-based studies, and a newer version of the 31-GEP (i31-GEP) assay was not included in the analysis. Panelists noted that recommendations may change with new data and that prognostic GEP testing in special circumstances (eg, poor surgical candidates) was not addressed but represents a situation in which clinicians may consider using the test.

Panelists emphasized the importance of conducting GEP testing studies in the intended target patient population. The development path taken to date has used different clinical end points and data sets in prognostically heterogeneous patient populations. Prospective studies in defined patient subsets (eg, specific T categories, SLNB-negative vs SLNB-positive) were strongly favored. In addition, given the limited use of purely prognostic assays, panelists recommended prospective trials in which patient care (such as the use of either routine radiographic monitoring or systemic adjuvant therapy in molecularly defined high-risk patient subsets) is altered based on GEP testing results to demonstrate clinical use.

Conclusions

For this consensus statement, panelists reached consensus on several open questions associated with early detection and prognostic assessment of CM. The group agreed on a risk-stratified approach to melanoma screening and for screening intervals and acceptable wait times for appointments. There was consensus that self-examinations and partner examinations are important screening adjuncts for all populations. The group did reach consensus on not using prognostic GEP testing to drive clinical decision-making regarding SLNB based on the available knowledge at the time the surveys were conducted. The panelists await future, well-designed prospective studies to determine if use of these and newer technologies improves the care of patients with melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

What are the recommended methods for early detection and prognostic assessment of cutaneous melanoma?

Findings

In this consensus statement, via a modified Delphi method, melanoma experts supported a risk-stratified approach to various aspects of melanoma screening as well as the use of visual and dermoscopic examination, the interpretation of reflectance confocal microscopy, and some uses of epidermal tape stripping. They did not, based on available evidence, reach consensus on the role for gene expression profile testing in clinical decision-making.

Meaning

The study results suggest that a risk-stratified approach to melanoma screening may be most appropriate; the role of molecular-based diagnostic and prognostic tests in cutaneous melanoma is evolving.

Table 1.

Melanoma Risk Classification and Type of Individual Screening Recommended

Category and supporting references	Consensus reached?	Recommended screening personnel, No./total No. (%)			
		Self/partner sufficient	PCP	GD	PLE
General population or low risk					
Risk unstratified, encompasses general population (RR of 1) and low-risk individuals (RR <2)	No[a]	24/42 (57)[b]	15/42 (36)	3/42 (7)	0
Phenotypic characteristics					
Fair complexion (eg, light hair, skin, eye color, and/or freckles), RR, 1.5–3.64[16]	No[a]	3/42 (7)[c]	20/42 (48)	19/42 (45)	0
Sun exposure					
Personal history of blistering/peeling sunburn, RR of 2.02[16]	No[a]	1/42 (2)	12/42 (29)	29/42 (69)	0
Severely sun-damaged skin, RR, 1.77–4.28[16,17]	Yes, first round	0	11/42 (26)	31/42 (74)	0
Substantial prior UV radiation exposure, history of indoor tanning, RR, 1.7–6.0[18,19]	Yes, first round	0	11/42 (26)	30/42 (71)	1/42 (2)
Personal history of skin cancer or other relevant condition					
History of actinic keratosis, RR of 4.28[16]	No[a]	1/42 (2)	18/42 (43)	23/42 (55)	0
History of nonmelanoma skin cancer, RR of 4.28[16]	Yes, first round	0	8/42 (19)	32/42 (76)	2/42 (5)
History of melanoma, RR, 8.2–13.4[20]	Yes, second round[a]	0	3/42 (7)	30/42 (71)	9/42 (21)
Immunocompromised, RR, 2.0–5.0[21,22]	Yes, first round	0	1/42 (2)	33/42 (79)	8/42 (19)
Family history of melanoma					
Family history of melanoma (or melanoma syndrome-related cancer) in 3 or more relatives, RR up to 35–70[23,24]	Yes, first round	0	0	8/42 (19)	34/42 (81)
Melanocytic nevi					
Numerous (>40) or atypical nevi (RR 2.56)[25]	No[a]	0	0	15/42 (36)	27/42 (64)
Genotype					
CDKN2A (or other high-penetration gene) variant carrier, RR, 35–70[26]	Yes, first round	0	0	7/42 (17)	35/42 (84)

Abbreviations: GD, general dermatologist; PCP, primary care physician; PLE, pigmented lesion expert; RR, relative risk; UV, ultraviolet.

[a] Results listed from the follow-up survey, initiated after the consensus conference.

[b] Included 16.7% indicating no screening necessary.

[c] Included 2.4% indicating no screening necessary.

Table 2.

Patient Factors Making Patients Highly Likely to Benefit From Public Skin Cancer Screenings

Patient factor	Respondents indicating the patient is highly likely to benefit from screening, No./total No. (%)
History of melanoma	38/41 (93)
New or changing mole	37/42 (88)
Unusual mole	36/43 (84)[a]
Numerous large or atypical moles	30/43 (70)[a]
Family history of melanoma	25/43 (58)[a]
Male sex, age >55 y	22/43 (51)[a]
Immunosuppression	20/43 (47)[a]
Red hair or numerous freckles	15/43 (35)[a]
Personal history of keratinocyte carcinoma	14/43 (33)[a]
History of sunburn and/or tanning salon use	12/43 (28)[a]
Lightly pigmented complexion, hair, or eyes	5/43 (12)[a]

[a]Results listed from the follow-up survey, initiated after the consensus conference.

Table 3.

Use of Current Lesion Imaging and Evaluation Tools to Detect Melanoma

Clinical scenario	Recommending imaging or evaluation tool, No./total No. (%)						
	Visual +/− dermoscopic examination result	Dermoscopic photography for monitoring	RCM	Prebiopsy diagnostic GEP (epidermal tape stripping)	Electrical impedance profile	Biopsy alone (excision if noted)	Biopsy + diagnostic GEP
Patient with no new, changing, or unusual skin lesions	42/42 (100)	0	0	0	0	0	0
Patient with new, but not visually concerning, lesion(s)	40/42 (95)	0	1/42 (2)	1/42 (2)	0	0	0
Patient with a new and visually concerning lesion[a]	23/42 (55)	0	2/42 (5)	0	0	0	0
Patient with a preexisting lesion that is changing[a]	18/42 (43)	0	4/42 (10)	1/42 (2)	0	19/42 (45)	0
Patient with facial lesion, new or changing[a]	13/42 (31)	0	14/42 (33)	0	0	15/42 (36)	0
19-y-old Woman with many atypical nevi whose mother died of melanoma, concerned about 2 large moles on leg and shoulder[b]	32/42 (76)	38/42 (90); total body photo plus dermoscopy	16/42 (37)[a]	7/42 (16)[a]	1/42 (2)[a]	18/42 (42); remove the lesions via excisional biopsy[a]	NA
Patient with slight change from total body photography but no overt features of melanoma on dermoscopy results[a]	1/42 (2)	21/42 (47)	4/42 (9)	1/42 (2)	0	18/42 (40)	0
Amelanotic nodule on the scalp of an 87-y-old man	0	1/42 (2)	0	0	0	39/42 (93)	2/42 (5)
Man (age 50 y) with actinic keratoses who presented with a 7-mm ill-defined brown lesion on the forehead demonstrating asymmetrical follicular openings on dermoscopy results[a]	0	8/45 (18)	11/45 (24)			25/45 (56)	
If lesion is examined with RCM and shows suspicious features[a]	0	0	3/45 (7)[c]	1/45 (2)	0	18/45 (40)[d] (partial); 24/45 (53) (excisional)	0
If lesion is diagnosed as lentigo maligna; treated with 3 excisions but did not histologically clear at 1 margin; then treated with imiquimod[a]	23/45 (51); monitor	0	17/45 (38)			5/45 (11); after imiquimod	

	Recommending imaging or evaluation tool, No./total No. (%)						
Clinical scenario	**Visual +/− dermoscopic examination result**	**Dermoscopic photography for monitoring**	**RCM**	**Prebiopsy diagnostic GEP (epidermal tape stripping)**	**Electrical impedance profile**	**Biopsy alone (excision if noted)**	**Biopsy + diagnostic GEP**
35-y-old Woman, history of melanoma, with a lesion that has been present for 10 y has recently changed (tape stripping performed)							
LINC+, PRAME+, TERT as next-step option	0	1/42 (2)	0	0	0	39/42 (93)	2/42 (5)
LINC-, PRAME+, TERT as next-step option	0	1/42 (2)	3/42 (7)	1/42 (2)	0	35/42 (84)	2/42 (5)
LINC+, PRAME-, TERT as next-step option[a]	1/45 (2)	10/45 (22)	2/45 (4)	0	1/45 (2)	30/45 (67)	1/45 (2)
LINC-, PRAME-, TERT as next-step option[a]	4/45 (9)	27/45 (60)	4/45 (9)	0	0	10/45 (22)	0
Acral lesion: 70-y-old Black man with mottled pigmentation across plantar foot who presents with 1 ill-defined 1.5-cm darker area with a homogenous pattern on dermoscopy[a]	0	5/43 (12)	3/43 (7)	0)	0	21/43 (49) Partial biopsy; 10/43 (23) multiple scouting biopsies; 3/43 (7) excisional surgical biopsy	1/43 (2) (Excisional surgical)
This acral lesion is diagnosed as in situ but only partially biopsied[a]	15/43 (35) Additional scouting biopsies; 8/43 (19) complete excision of clinically evident area; 20/43 (47) excision with 5-mm margin	NA	NA	NA	NA	NA	NA
This acral lesion diagnosed with multiple excisions but unable to obtain a clear positive margin[a]	20/43 (47) Monitor; 4/43 (9) refer for radiation therapy; 4/43 (9) refer for adjuvant therapy; 15/43 (35) for other (including imiquimod and Mohs surgery); 0/45 (0) amputation	NA	NA	NA	NA	NA	NA

Abbreviations: GEP, gene expression profiling; *LINC, LINC00518;* NA, not applicable; *PRAME,* preferentially expressed antigen in melanoma; RCM, reflectance confocal microscopy; *TERT*, telomerase reverse transcriptase.

[a]Results listed from the follow-up survey, initiated after the consensus conference.

[b]Respondents were asked to select all that applied (so more than 1 selection was possible).

[c]To define margins for excision of the entire lesion.

[d]Partial biopsy of the suspicious area identified by RCM; excisional biopsy of the clinically defined pigmented lesion. No panelist recommended excision with 5 to 10mmclinical margin/staged excision/Mohs micrographic surgery (definitive treatment).

Table 4.

Postbiopsy and Diagnostic and Prognostic Assessment of Melanoma

| | Next step in management, No./total No. (%) | | | | | | |
Case scenario	FISH	CGH	Postbiopsy diagnostic GEP[c]	Postbiopsy prognostic GEP[d]	WES	WLE	WLE + SLNB
Differentiation of Spitz nevus vs Spitzoid melanoma: 1.5-mm deep lesion, nonulcerated							
6-y-old Boy[a]	9/42 (21)	10/42 (24)	1/42 (2)	1/42 (2)	2/42 (5)	12/42 (29)	7/42 (17)
16-y-old Boy[a]	6/42 (14)	10/42 (24)	0	0	1/42 (2)	8/42 (19)	17/42 (41)
50-y-old Man	2/42 (5)	2/42 (5)	1/42 (2)	0	0	4/42 (10)	33/42 (79)
Differentiation of dysplastic nevi vs melanoma: 45-y-old woman, 9-mm diameter lesion on the back, equivocal dermatopathology on biopsy[a]	7/45 (16)	1/45 (2)	4/45 (9)	1/45 (2)	0	27/45 (60)[b]	NA
50-y-old Man, 0.9-mm thick, recurrent melanoma, nonulcerated, 1 mitosis/mm^2	NA	NA	0	1/42 (2)	0	6/42 (14)	35/42 (83)
With low risk (Class 1) 31-Gene Prognostic GEP-Result						11/42 (26)	30/24 (71); topical imiquimod, 2%
87-y-old Man with 4.5-mm thick desmoplastic, neurotropic nonulcerated melanoma on the scalp, 1 mitosis/mm^2	NA	NA	0	0	0	9/42 (21)	33/42 (79)
With low-risk (class 1) 31-gene prognostic GEP result						11/42 (26)	31/42 (74)

Abbreviations: CGH, comparative genomic hybridization; FISH, fluorescence in situ hybridization; GEP, gene expression profile; NA, not assessed; SLNB, sentinel lymph node biopsy; WES, whole-exome sequencing; WLE, wide local excision.

[a]Results listed from the follow-up survey, initiated after the consensus conference.

[b]An additional 5 of 45 (11%) would follow the biopsy site with no additional treatment as of last follow-up.

[c]Postbiopsy diagnostic GEP, Myriad/Castle MyPath (23-gene diagnostic GEP).

[d]Postbiopsy prognostic GEP, Castle DecisionDx GEP (31-gene prognostic GEP).