Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-1, ME-2, ME-3 External request: Submission from Castle Biosciences (06/17/20) to consider the following suggested changes to footnote d on ME-1, ME-2, ME-3: "Prognostic gene expression profiling (**31-**GEP) to differentiate melanomas at low versus high risk for metastasis may provide information on individual risk of recurrence, as an adjunct to standard AJCC staging. ~~However,~~ **T**he currently available prognostic molecular techniques should not replace pathologic staging procedures.~~, and the use of GEP testing according to specific melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients.~~"	Based on a review of the data and discussion, the panel did not support the changes proposed in the submissions. However, the panel supported the following language revisions (as shown in italics): Footnote d revised: ~~Prognostic gene expression profiling (GEP) to differentiate melanomas at low versus high risk for metastasis may provide information on individual risk of recurrence, as an adjunct to standard AJCC staging. However, the currently available prognostic molecular techniques should not replace pathologic staging procedures, and the use of GEP testing according to specific melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients~~. *The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup. See Principles of Molecular Testing (ME-C).* (Also for ME-2A, ME-3) Supporting References: • Marchetti MA, Bartlett EK, Dusza SW, Bichakjian CK. Use of a prognostic gene expression profile test for T1 cutaneous melanoma: Will it help or harm patients? J Am Acad Dermatol 2019;80:e161-e162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30586612. • Marchetti MA, Coit DG, Dusza SW, et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and Meta-analysis. JAMA Dermatol 2020;156:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32745161 . • Bellomo D, Arias-Mejias SM, Ramana C, et al. Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma. JCO Precis Oncol 2020;4:319-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32405608.	1	22	1	7

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
	• Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. J Am Acad Dermatol 2020;83:745-753. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32229276. • Chan WH, Tsao H. Consensus, Controversy, and Conversations About Gene Expression Profiling in Melanoma. JAMA Dermatol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32745178. • Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. JAMA Dermatol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32725204. • Kovarik CL, Chu EY, Adamson AS. Gene Expression Profile Testing for Thin Melanoma: Evidence to Support Clinical Use Remains Thin. JAMA Dermatol 2020;156:837-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32293654.				
ME-11 Common Follow-Up Recommendations For All Patients External request: Submission from Myriad (06/09/20) • Under the last bullet (pertaining to multigene testing): Add the following sentence to the first sub-bullet – "Multigene panel testing that includes *CDKN2A* is also recommended for all patients if they have a first-degree relative diagnosed with pancreatic cancer (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)." • Add *PTEN* to the list of genes in the second sub-bullet.	Based on a review of the data and discussion, the panel did not use the exact language proposed in the submission. However, the panel supported the following on ME-11: • Added bullet: *Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first degree relative diagnosed with pancreatic cancer (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)*. • Revised bullet: Testing for other genes that can harbor melanoma-predisposing mutations (~~eg, MC1R, CDK4, TERT, MITF, BRCA2, BAP1 [especially for uveal melanoma]~~ *See ME-A 1 of 2*) may be warranted. [Note: *PTEN* was added to the list of genes on ME-A] See Submission for references.	22	1	1	7

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-11 External requests 1. Submission from DermTech, Inc., (06/16/20): Recommend the Pigmented Lesion Assay ("PLA") as a useful pre-diagnostic tool that supports a clinician's decision of whether or not to biopsy in the assessment of pigmented skin lesions suspicious of melanoma (changed from "requires further investigation)". 2. Submission from Dermatologic Surgery Center of Washington (06/21/20): Recommend deleting the last sentence of second bullet to replace with: "*The clinical utility of pre-diagnostic biopsy-guiding noninvasive genomic patch testing is established, and the use of this technology is warranted to support biopsy decisions*." 3. Submission from SUNY Downstate (06/22/20): Recommend the following changes to the second bullet: … ~~The clinical utility of novel/emerging diagnostic imaging and molecular technologies (e.g. non-invasive genomic patch testing) requires further investigation~~. … Prediagnostic molecular genomic patch testing to help guide biopsy decisions on pigmented skin lesions should be considered. 4. Submission from University of Pittsburgh (06/23/20): Recommend deleting the last sentence of the second bullet regarding pre-diagnostic clinical modalities. Based on the evidence available, please correct to: "*Pre-diagnostic noninvasive genomic patch testing should be considered to guide biopsy decisions*." 5. Northwestern University Feinberg School of Medicine, Department of Dermatology (06/23/20): The pigmented lesion assay should be considered as a non-invasive test to guide the decision to perform a surgical biopsy in a difficult to assess melanocytic lesion	Based on a review of the data and discussion, the panel did not support the changes proposed in the submissions. However, the panel supported the following language revision in bullet 2 on ME-11 (shown in italics): "~~Pre-diagnostic clinical modalities (ie, total body photography and sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. The clinical utility of novel/emerging diagnostic imaging and molecular technologies (eg, noninvasive genomic patch testing) requires further investigation~~. *Available, noninvasive pre-biopsy imaging and molecular technologies have not been prospectively compared for diagnostic accuracy*. Prediagnostic clinical modalities (ie, total-body photography and sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. *Prediagnostic noninvasive genomic patch testing may also be helpful to guide biopsy decisions."* See Submissions for references.	1	22	1	7

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
(recommend deleting the last sentence of bullet point number 2).					
ME-C (1 of 7) External Request: Submission from Myriad Genetic Laboratories (06/22/20) Modify the existing bullet regarding diagnostic testing from Principles ff Molecular Testing as indicated below: "Ancillary tests to differentiate benign from malignant melanocytic neoplasms include gene expression profiling (GEP), comparative genomic hybridization (CGH), single nucleotide polymorphism (SNP) array, fluorescence in situ hybridization (FISH), and immunohistochemistry (IHC). These tests may facilitate interpretation of cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests are adjuncts and not replacements for clinical and histopathologic examination and should therefore be interpreted within the context of the clinical and histopathologic findings."	Based on a review of the data and discussion, the panel did not support the changes proposed in the submission. However, the panel supported the following language revisions under "Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication", First Bullet; First arrow sub-bullet (shown in italics): "Melanocytic neoplasms of uncertain biologic potential unique challenge to pathologists and treating clinicians. ~~Ancillary methods to aid in benign versus malignant differentiation include molecular cytogenetics (eg, comparative genomic hybridization [CGH]), fluorescence in situ hybridization [FISH]), gene expression profiling (GEP), next-generation sequencing (NGS), and immunohistochemistry (IHC), among others. While limited reports on the intermediate category of melanocytic neoplasia show evolutionary pathogenic genetic alteration during melanoma progression, there are insufficient data from histologically ambiguous melanocytic neoplasms. Because ancillary tests are intended as adjuncts, and not replacements, for clinician and expert dermatopathologist examination, they should always be interpreted within the context of the clinical and histopathologic findings~~. *Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate interpretation of cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and be interpreted within the context of these findings."* See Submission for references.	1	22	1	7

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-C (1 of 7) External Request Submission from Castle Bioscience (06/17/20) Consider the following suggested changes under "Prognostic Testing": • Bullet 1: "Commercially available GEP tests ~~are marketed as being able to~~ **can** classify cutaneous melanoma into separate categories based on risk of metastasis. ~~However, it remains unclear whether~~ **Five prospective studies and two meta-analyses have shown** that **the 31-GEP** ~~these~~ tests ~~provide~~**s** clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors. ~~or multivariable nomograms that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status. Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established.~~ **Three clinical use studies showed that physicians use 31-GEP results to adjust management in agreement with individual risk of recurrence."** • Bullet 2: "Various ~~(mostly~~ **prospective and** retrospective studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, ~~though not superior~~ **in addition** to Breslow thickness or SLN status. ~~It remains unclear whether this GEP profile is reliably predictive of outcome across the risk spectrum of melanoma. Prospective validation studies (as have been performed in breast cancer) are required to more accurately define~~ **To date, two retrospective and one prospective studies have reported on** the clinical utility of molecular testing ~~prior to widespread implementation of GEP for prognostication of~~	Based on a review of the data and discussion, the panel did not support the changes proposed in the submissions. However, the panel supported the following language revisions under "Prognostic Testing" (as shown in italics): • Arrow sub-bullet 1: "Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on risk of metastasis. However, it remains unclear whether these *GEP* ~~tests~~ *platforms* provide clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors or multivariable nomograms that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status. Furthermore, the impact of current GEP tests on treatment outcomes or follow-up schedules has not been established." • Arrow sub-bullet 2: "Various (mostly retrospective) studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, though not superior to Breslow thickness or SLN status. It remains unclear whether ~~this GEP profile is~~ *available GEP platforms are* reliably predictive of outcome across the risk spectrum of melanoma. Prospective validation studies (as have been performed in breast cancer) are required to more accurately define the clinical utility of molecular testing prior to widespread implementation of GEP for prognostication of cutaneous melanoma, and in particular to determine its role in guiding surveillance imaging, SLNB, and adjuvant treatment decisions. Existing and emerging GEP platforms and other prognostic techniques should also be compared with optimized contemporary multivariable phenotypic models (ie, the AJCC 8th edition melanoma risk calculator/prognostic tool in development)." Supporting References: • Marchetti MA, Bartlett EK, Dusza SW, Bichakjian CK. Use of a prognostic gene expression profile test for T1 cutaneous melanoma: Will it help or harm patients? J Am Acad Dermatol 2019;80:e161-e162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30586612. • Marchetti MA, Coit DG, Dusza SW, et al. Performance of Gene Expression Profile Tests for Prognosis in Patients With Localized Cutaneous Melanoma: A Systematic Review and	1	22	1	7

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
~~cutaneous melanoma, and in particular determine its role in guiding~~ **showing that physicians use results to guide** surveillance imaging, SLNB, and adjuvant treatment decisions. ~~E~~ **When available, e**xisting and emerging GEP platforms and other prognostic techniques should also be compared with optimized contemporary multivariable phenotypic models~~ (i.e., the AJCC 8th edition melanoma risk calculator/prognostic tool in development)~~."	Meta-analysis. JAMA Dermatol 2020;156:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32745161. • Bellomo D, Arias-Mejias SM, Ramana C, et al. Model Combining Tumor Molecular and Clinicopathologic Risk Factors Predicts Sentinel Lymph Node Metastasis in Primary Cutaneous Melanoma. JCO Precis Oncol 2020;4:319-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32405608. • Greenhaw BN, Covington KR, Kurley SJ, et al. Molecular risk prediction in cutaneous melanoma: A meta-analysis of the 31-gene expression profile prognostic test in 1,479 patients. J Am Acad Dermatol 2020;83:745-753. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32229276. • Chan WH, Tsao H. Consensus, Controversy, and Conversations About Gene Expression Profiling in Melanoma. JAMA Dermatol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32745178. • Grossman D, Okwundu N, Bartlett EK, et al. Prognostic Gene Expression Profiling in Cutaneous Melanoma: Identifying the Knowledge Gaps and Assessing the Clinical Benefit. JAMA Dermatol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32725204. • Kovarik CL, Chu EY, Adamson AS. Gene Expression Profile Testing for Thin Melanoma: Evidence to Support Clinical Use Remains Thin. JAMA Dermatol 2020;156:837-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32293654.				

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-I (1 of 8) External request: Submission from Merck & Co (07/21/20): Request the inclusion of pembrolizumab in combination with low dose ipilimumab as a first-line treatment recommendation in patients with unresectable or metastatic melanoma in the appropriate sections of the NCCN Cutaneous Melanoma Guidelines including page ME-I 1 of 7 based on the longer follow-up data from KEYNOTE-029 recently published in Clinical Cancer Research.	• Based on the review of the data in the noted reference, the panel consensus was to include pembrolizumab/low-dose ipilimumab as a first-line systemic therapy option for unresectable or metastatic melanoma This is a category 2B, (Other recommended) recommendation. • The following corresponding footnote was also added: "*Dosing used in KEYNOTE-029: Pembrolizumab 2 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks (Q3W) for four doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision*." Reference • Carlino MS, Menzies AM, Atkinson V, et al. Long-term follow-up of standard dose pembrolizumab plus reduced-dose ipilimumab in patients with advanced melanoma: KEYNOTE-029 Part 1B. Clin Cancer Res 2020;26:5086-5091.	17 20	5 2	2 2	7 7