Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-1, ME-2, ME-3, ME-B External request: Submission from Castle Biosciences, Inc (06/28/19) to consider inclusion of DecisionDx-Melanoma in the guidelines as a molecular prognostic feature that provides metastasis risk stratification and informs management decisions for patients with cutaneous melanoma, including the identification of patients at low risk for a positive sentinel lymph node (SLN). Suggest changing Footnote d, on pages ME-1 to ME-3 as follows: "Gene expression profiling to differentiate melanomas at low (Class 1) versus high (Class 2) risk for metastasis has been shown to provide additional information on individual risk of recurrence beyond standard clinical and pathological staging, which may inform management decisions." (Also see ME-C for additional request)	Based on a review of data and discussion, the panel did not support making the proposed footnote language change. However, the panel supported adding the following language: o Footnote d revised: "~~While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low versus high risk for metastasis, routine (baseline) prognostic genetic testing of primary cutaneous melanomas (before or following sentinel lymph node biopsy [SLNB]) is not recommended outside of a clinical study (trial). Newer prognostic molecular techniques should not replace standard staging procedures~~. *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 SLNB) requires further prospective investigation in large, contemporary data sets of unselected patients See Principles of Molecular Testing (ME-C*)." (Also for ME-2, ME-3)	0	25	0	4
ME-4, ME-5, ME-6, ME-12, ME-14 Internal request Panel discussion comment to add a footnote to adjuvant dabrafenib/trametinib for resected stage III disease regarding providing other BRAF/MEK inhibitor combination options to patients who may have a toxicity to dabrafenib/trametinib.	Based on a review of data and discussion, the panel vote and consensus supported adding the following footnote "In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations could be considered" to the recommendation of dabrafenib/trametinib in the settings below: o Adjuvant treatment for newly-diagnosed resected stage III melanoma (sentinel node positive) (ME-4) o Adjuvant treatment for newly-diagnosed Stage III (clinically positive node[s]), after wide local excision and complete therapeutic lymph node dissection. (ME-5) o Adjuvant treatment for newly-diagnosed Stage III (clinical satellite /in-transit) with no evidence of disease after surgery (ME-6) o Adjuvant treatment for local satellite/in-transit recurrence in patients who have no evidence of disease after surgery (ME-12) o Adjuvant treatment for completely resected nodal recurrence (ME-13)	21	3	0	5

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(ME-4A, ME-5, ME-6A, ME-12A, ME-13A, ME-14A, ME-15A) Internal Request: Panel member comment to consider adding other BRAF/MEK inhibitor combinations as options for adjuvant therapy for resected stage III disease in patients who cannot tolerate dabrafenib/trametinib.	Based on a review of data and discussion, the panel vote and consensus supported adding new footnote cc: "In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations can be considered" to the adjuvant treatment option of dabrafenib/trametinib.	25	0	0	4
ME-5, ME-13A Internal Request Institutional Review comments and panel comments to (1) include the option of neoadjuvant therapy for resectable stage III with clinically positive nodes and resectable nodal recurrence, and (2) allow for neoadjuvant therapy to be used outside of a formal clinical trial provided that there is multidisciplinary review.	Based on a review of data and discussion, the panel vote and consensus supported revising footnote dd as follows: "In patients with ~~borderline~~ *extensive* resectable *nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain* ~~lymphadenopathy or very high risk of recurrence after lymphadenectomy~~, *recommend multidisciplinary tumor board review to* consider ~~a clinical trial~~ of neoadjuvant systemic therapy *preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (See ME-15)*."	25	0	0	4
ME-10 and ME-A External request Submission from Myriad Genetic Laboratories, Inc to adjust the current content regarding genetic testing for inherited melanoma risk to improve consistency and provide additional clinical relevance by making changes to the Guideline language as follows: o On pages ME-10 and ME-A (1 of 7) use the same list of relevant genes: *CDKN2A, CDK4, BAP1, TERT, MITF, MC1R*.	Based on a review of data and discussion, the panel vote supported including making on the following changes: o To a bullet on ME-10, Common Follow-up Recommendations for All Patients: "Testing for other genes that can harbor melanoma-predisposing mutations (eg, ***MC1R***, *CDK4, TERT, MITF,* ***BRCA2****, BAP1 [especially for uveal melanoma]*) may be warranted." [Note that CDKN2A testing remains in a different bullet on ME-10: "Consider genetic counseling referral for p16/CDKN2A mutation testing…"] o To a bullet on ME-A 1 of 2, Risk Factors For Development of Single Or Multiple Primary Melanomas, under Genetic predisposition: "Presence of germline mutations or polymorphisms predisposing to melanoma (including CDKN2a, CDK4, MC1R, ***BRCA2***, BAP1 *[especially for uveal melanoma]*, and potentially other genes)."	25	0	0	4

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ME-10 and ME-A (continued) o Proposed change on ME-10 and ME-A 1 to use the same list of relevant malignancies suggestive of inherited risk on both pages: cutaneous and uveal melanoma, pancreatic cancer, astrocytoma, mesothelioma and kidney. o Add additional content to the last bullet point on page ME-10 regarding the importance of genetic testing: "Identification of a germline mutation in a melanoma patient can provide important information about risk for additional primary melanomas, as well as the risk for other cancers. This information can guide management recommendations for prevention and early detection in the patient and relatives." o Adjust the wording in the last bullet point on page ME-11 from "Consider referral to a genetic counselor…." To "Consider genetic counseling…."	Based on a review of data and discussion, the panel vote supported the following changes on ME-10, Common Follow-up Recommendations for All Patients: • A bullet was added: "*Clinical and family history can identify patients in whom multigene testing might indicate an increased genetic risk for cutaneous and uveal melanoma, astrocytoma**, mesothelioma**, and cancers of the **breast**, pancreas, and **kidney**. This information can guide recommendations for surveillance and early detection in the patient and his/her relatives*." • The subsequent sub-bullet modified: "Consider *genetic counseling* referral ~~to a genetics counselor~~ for p16/CDKN2A mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family." The panel did not change the malignancies listed on ME-A (1 of 7), Risk Factors For Development of Single Or Multiple Primary Melanomas, under Genetic predisposition: "Family history of cutaneous melanoma (especially if multiple), pancreatic cancer, astrocytoma, uveal melanoma, and/or mesothelioma."	25	0	0	4
o Add Leachman et al. (citation 1 below) to the references for genetic testing, as this is a recent, comprehensive discussion of hereditary risk for melanoma. (Leachman SA, et al. Identification, genetic testing, and management of hereditary melanoma. Cancer Metastasis Rev. 2017 Mar;36(1):77-90.)	Based on a review of data and discussion, the panel consensus was not to add the noted reference to the algorithm, but may be considered for the Discussion text (update in progress).	0	25	0	4
ME-12 Institutional review comment from panel member: Panel member request to consider the addition of ipilimumab for the adjuvant treatment of resected local satellite/in-transit recurrence for patients with prior exposure to anti-PD-1, due to similar risk as those with nodal recurrence.	Based on a review of data and discussion, the panel vote supported the inclusion of ipilimumab if prior exposure to anti-PD-1 therapy (category 2A). It was preference stratified as "Useful in certain circumstances".	22	2	1	4

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ME-13, ME-14 and ME-15 Internal request Institutional review comments regarding the adjuvant treatment option "high-dose ipilimumab for patients with prior exposure to anti-PD-1 therapy" (category 1 for resected nodal recurrence [ME-13 and ME-14], category 2A for resected distant metastatic disease [ME-15]): o Remove "high-dose" because recent data suggests that 3 mg/kg is equally effective; keep footnotes describing dosing considerations o Reassess the category 1 designation because the randomized controlled trial did not evaluate adjuvant high-dose ipilimumab for patients with prior exposure to anti-PD-1 therapy	Based on the discussion, the panel consensus was to remove "high-dose" from the adjuvant ipilimumab recommendation for resected nodal recurrence and for resected distant metastatic disease. Based a review of data and discussion, the panel consensus was that adjuvant high-dose ipilimumab for resected nodal recurrence in patients with prior exposure to anti-PD-1 therapy is not supported by high-level evidence and the category was changed from a category 1 to a category 2A recommendation.	25 1	0 23	0 1	4 4
ME-15 Internal request For adjuvant treatment of limited (resectable) distant metastatic disease, in patients with NED after resection: • Institutional review comment to consider including dabrafenib/trametinib combination as an option • Panel member comment to include all BRAF/MEK inhibitor combinations as options.	Based on a review of data and discussion, the panel vote supported the inclusion of the following BRAF/MEK inhibitor combinations as adjuvant treatment options for completely resected stage IV melanoma: o Dabrafenib/trametinib (category 2B) o Vemurafenib/cobimetinib (category 2B) o Encorafenib/binimetinib (category 2B) These options were preference stratified as "Other regimens (for patients with BRAF V600-activating mutation)"	13	12	0	4

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ME-C (1 of 7) External request Submission from DermTech, Inc (6/27/19) to review the enclosed Pigmented Lesion Assay (PLA) data for inclusion of non-invasively obtained molecular risk factors to support clinicians in their biopsy decisions and efforts to rule out primary cutaneous melanoma. Under the bullet "Pre-diagnostic technologies to inform decision about whether to biopsy" consider changing the following language "NCCN Guidelines for Cutaneous Melanoma focus on the management of cutaneous melanoma following pathology diagnosis. As such, emerging molecular technologies for pre-diagnostic biopsy purposes (e.g. non-invasive genomic adhesive patch testing) are not within the guidelines' purview" to: "The NCCN Guidelines for Cutaneous Melanoma generally focus on the management of cutaneous melanoma following pathology diagnosis. However, molecular technologies for pre-diagnostic biopsy purposes (e.g. non-invasive genomic adhesive patch testing) have demonstrated clinical validity and utility and can also be considered to support clinicians in their biopsy decisions," and cite the 14 provided key peer reviewed manuscripts published in leading dermatology journals that are all fully available and in the public domain.	Based on a review of data and discussion, the panel did not support making the proposed change to the guidelines due to insufficient data. The panel consensus supported removing the bullet "Pre-diagnostic technologies to inform decision about whether to biopsy" and the corresponding sub-bullet "NCCN Guidelines for Cutaneous Melanoma focus on the management of cutaneous melanoma following pathology diagnosis. As such, emerging molecular technologies for pre-diagnostic biopsy purposes (e.g. non-invasive genomic adhesive patch testing) are not within the guidelines' purview" from the algorithm portion of the Guidelines and moving it to the Discussion section. See submission for references.	0	25	0	4

Guideline Page and Request	Panel Discussion/References	Vote			
		YES	NO	ABSTAIN	ABSENT
ME-C (1 of 7) External request: Submission from Myriad Genetic Laboratories, Inc (06/28/19) to: o Remove the term "Emerging" from the section title "Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication." o Replace the existing paragraph regarding "Diagnostic testing for indeterminate melanocytic neoplasms following histopathology" with language proposed in the submission: o Testing for melanocytic neoplasms that remain diagnostically equivocal despite clinical and histopathologic evaluation: ▪ Most melanocytic neoplasms can be diagnosed accurately and definitively as either benign nevus or malignant melanoma through clinical inspection by a dermatologist combined with microscopic examination by a dermatopathologist. For cases in which this method does not yield a definitive diagnosis, ancillary diagnostic techniques may be used. Ancillary tests to differentiate benign from malignant melanocytic neoplasms include comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), and immunohistochemistry (IHC). Because ancillary tests are intended as adjuncts and not as replacements for clinical and histopathologic examination, they must always be interpreted within the context of the clinical and histopathologic findings.	o Based on a review of data and discussion, the panel did not support removing the term "emerging" from the subtitle "Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication." o Based on a review of data and discussion, the panel did not support making the proposed changes to diagnostic testing for indeterminate melanocytic neoplasms following histopathology. However, the panel supported adding the following language: ▪ Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. Ancillary methods to ~~detect genetic alterations in these lesions~~ *aid in benign versus malignant differentiation* include molecular cytogenetics (eg, comparative genomic hybridization [CGH]), ~~other cytogenetic techniques (eg~~, fluorescence in situ hybridization [FISH]~~)~~, gene expression profiling (GEP), *next generation sequencing (NGS)*, and immunohistochemistry (IHC), among others. ~~For example, CGH studies have demonstrated that unlike benign nevi, melanomas have aberrations frequently involving chromosomes 6, 7, 9, and 10[4] that may be detected with the abovementioned methods~~. 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. ~~Although they may provide complementary information to inform a better understanding of the biologic behavior of melanocytic neoplasms of uncertain biologic potential as assessed by histology alone, these tests cannot replace the gold standard of diagnostic histopathologic examination by an expert dermatopathologist. They may be used on a case-by-case basis in ambiguous melanocytic tumors; however, their utility is still under evaluation, and more data are needed before they can be routinely recommended. Measurement of chromosomal aberrations and separation of melanocytic neoplasms based on reproducible association of pathogenetically relevant genetic alterations should be further evaluated as a diagnostic tool in ambiguous melanocytic neoplasms and remains investigational at this time~~. *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*."	0 0	25 25	0 0	4 4

Guideline Page and Request	Panel Discussion/References	Vote			
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ME-C (1 of 7) External request: Submission from Castle Biosciences, Inc (06/28/19) to consider inclusion of DecisionDx-Melanoma in the guidelines as a molecular prognostic feature that provides metastasis risk stratification and informs management decisions for patients with cutaneous melanoma, including the identification of patients at low risk for a positive sentinel lymph node (SLN). Consider adding a new sub-bullet under "Prognostic Testing" as follows "The clinically available 31-gene expression profile test for melanoma prognosis can independently classify cutaneous melanoma into separate categories based on risk of metastasis. As with other risk stratification factors, this information can be used to inform follow-up schedules, use of surveillance imaging, specialty referrals and SLNB decisions."	Based on a review of data and discussion, the panel did not support adding the proposed language to the Guidelines. The panel agreed to change the following sub-bullet under "prognostic testing": "Various (mostly retrospective) studies of ~~a~~ prognostic ~~31-~~GEP test*ing* suggest ~~that class 2 assignment is~~ *its role as* an independent predictor of worse outcome, though not ~~as significant as~~ *superior to* Breslow thickness or SLN status."	0	25	0	4
ME-H (1 of 7) External Request: Submission from Merck & Co (11/29/18) to: Consider 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 guidelines, including section ME-H, based on the longer follow-up data from KEYNOTE-029 presented at SMR 2018.	Based on review of the data and discussion, the panel did not support adding pembrolizumab in combination with low-dose ipilimumab as an option for first-line systemic therapy for metastatic or unresectable disease. See submission for references.	10	14	1	4