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NCCN Guidelines Panel: Melanoma

On behalf of Castle Biosciences Inc., I respectfully request the NCCN Melanoma Panel review the enclosed information and consider inclusion of the DecisionDx-Melanoma test in the guidelines as a prognostic test that provides risk of metastasis stratification for cutaneous melanoma[1-3].

Specific Change:

In the NCCN Guidelines Version 1.2017 ME B footnote 3 and ME 1 to ME 3 footnote d note "*while there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low versus high risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside clinical study (trial)".*
We suggest the following changes:

- ME B footnote 3 and ME-1 to ME-3 footnote d "*gene expression profiling to differentiate melanomas at low (Class 1) versus high (Class 2) risk for metastasis may provide additional prognostic information beyond standard clinical and pathological staging*".

In addition, the discussion in MS-5 raises issues regarding: a) the development and validation sets being considered as relatively high-risk, b) confirmation in a large population of patients with average- to low- risk melanoma, c) the need for the test to be validated in the context of all known prognostic characteristics of localized melanoma, and d) the lack of overlap in gene signatures. As described in the rationale below, these issues have been addressed by recent studies and thus we suggest the discussion section be updated or deleted.

FDA Status: FDA clearance is not required for this test, as it is performed in the central laboratory of Castle Biosciences that is regulated under the Clinical Laboratory Improvement Amendments (CLIA).

Rationale: The DecisionDx-Melanoma is a validated 31-gene expression profile (GEP) test that classifies cutaneous melanoma patients as low (Class 1) or high (Class 2) risk for metastasis within 5 years of diagnosis. Three studies (n= 690) have shown that Class 2 patients have a significantly higher risk of metastasis than Class 1 patients, and that GEP is a significant predictor of metastatic risk independent from clinicopathologic features[1-3]. Within these studies, Zager et al[3] reported on a 334 patient population representative of the general melanoma population (n=523 in submitted manuscript). In addition, three independent, prospective studies (total n= 510) have confirmed performance of the test in contemporary patient cohorts[4-6]. In addition, an interim analysis of two prospective, multi-center registries with 322 patients found that 83% of distant metastases and 72% of melanoma-related deaths occurred in Class 2 patients[7]. Therefore, the DecisionDx-Melanoma test has now been validated in large retrospective and prospective cohorts with average- to low- risk melanoma[1-7].

DecisionDx-Melanoma has consistently been shown to be an independent, significant predictor of metastatic risk[1-7]. In a comparison with the AJCC Online Predictor Tool, which accounts for all prognostic variables used clinically, DecisionDx-Melanoma identified 81% of the cases with distant metastasis as Class 2, compared to 69% with the online predictor; used together, sensitivity for distant metastasis improved to 88%[8]. Furthermore, in 368 patients with known SLNB status from the combined retrospective cohorts[1-3], 70% of the distant metastases in SLNB-negative patients were identified as Class 2. DecisionDx-Melanoma provides prognostic information that

is independent from standard prognostic factors and improves detection of patients at high-risk of metastasis when used in combination with these factors.

The DecisionDx-Melanoma has been accepted by the Melanoma community, being utilized by 2,237 physicians for 10,777 patients since January 2016. Three studies have addressed the clinical impact of this test[9-11]. A multi-center study on 156 consecutively tested patients demonstrated that the DecisionDx-Melanoma results are used to: a) intensify management for Class 2 patients, including more frequent imaging, referrals and clinical visits and b) reduce the intensity of management for low-risk patients[9]. A second study found that, when physicians were confronted with 6 clinical scenarios, DecisionDx-Melanoma had a significant and appropriate impact on management decisions while remaining within established guidelines[10]. In addition, a single-center study of 91 patients found that sentinel lymph node biopsy (SLNB) negative Class 1 and 2 patients were managed differently, with Class 1 patients primarily followed by dermatology alone while more Class 2 patients had multidisciplinary management and more frequent recommendations for adjuvant therapy[11]. Therefore, the test results direct intense surveillance towards those patients that are at high-risk for distant metastatic recurrence (Class 2), while reducing the burden of surveillance for Class 1 patients which is consistent with the current NCCN framework for follow-up based upon an individual patient's risk of recurrence.

The 28 discriminant gene targets in the DecisionDx-Melanoma test were derived from published melanoma datasets with one criteria for gene selection being that genes were reported in more than one of these studies[12-19]. These discriminant genes have been shown to be involved in regulating essential cellular functions and they also overlap with other melanoma gene expression datasets beyond those used in the gene identification process[20-23]. Gene overlap includes: SPP1, DSC1, CLCA2, TRIM29, CXCL14, AQP3, SPRR1B, S100A8, KRT14, TACSTD2, KRT6B, TYRP1, PPL, and MGP. Thus, the DecisionDx-Melanoma gene set is well-supported by published evidence[10-21].

In ME-8 and ME-9 it is noted that follow up schedule should be influenced by a patient's conditional risk of recurrence, however, in ME-9, it is stated that imaging should be considered for patients with Stage IIB-IIIC melanoma (Category 2B). Unfortunately, current risk stratification based on pathological/clinical staging misses patients with biologically aggressive disease, who account for the large majority of those that die of melanoma[24-27]. These patients currently are not offered the benefit of surveillance. Several studies have shown that 80% of all distant melanoma recurrences can be identified by routine imaging, prior to the onset of symptoms and that patients who have early-detected distant metastatic recurrences have better outcomes[28-36]. In addition, there is strong evidence that melanoma patients who have lower tumor burden at the start of traditional and contemporary therapies have improved responses and survival outcome[37-45]. Therefore, routine surveillance imaging coupled with intensified clinical follow up, in high-risk patients is critical for early detection of metastasis to maximize the success of therapeutic interventions. A more detailed rationale is presented separately as an executive summary on the DecisionDx-Melanoma test.

The following cited literature is submitted in support of this proposed change:

1. Gerami P, et al. J Amer Acad Derm. 2015;72(5):780-785 e783. PMID: 25564571
2. Gerami P, et al. Clin Cancer Res. 2015;21(1):175-183. PMID: 25748297
3. Zager JS, et al. J Clin Oncol 34, 2016 (suppl; abstr 9581). ASCO 2016 Meeting / Submitted Manuscript
4. Greenhaw BN, et al. American College of Mohs Surgeons 2016 Meeting Abstract
5. Hsueh E, et al. J Clin Oncol, 2016. 34(suppl; abstr 9565). ASCO 2016 Meeting Abstract.
6. Renzetti M, et al. Society for Surgical Oncology 2017 Annual Meeting Abstract PT286
7. Hsueh EC, et al. J Clin Oncol 35, 2017 (suppl; abstr 9573). ASCO 2017 Meeting Abstract.
8. Ferris, L, et al. J Amer Acad Derm. 2017; 76(5): 818-825.e3. PMID: 28110997
9. Berger AC, et al. Curr Med Res Opin, 2016, Jun 3:1-6. [Epub ahead of print]
10. Farberg AS, et al. J Drugs Derm, 2017. 16(5): p. 611-616.
11. Schuitevoerder D, et al. Society for Surgical Oncology Annual Meeting. 2017: Seattle, WA.