Submitted by:
Federico A. Monzon, MD, Chief Medical Officer
Castle Biosciences, Inc.
820 S. Friendswood Drive, Suite 201
Friendswood, TX 77546
Tel: (832) 974.1562 / Email: fmonzon@castlebiosciences.com
Date of request: 6/24/2016
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 2.2016 ME-1 to ME-3, footnote c notes, "*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)".* ME-7 footnote cc states, "*follow up schedule is influenced by the risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles/dysplastic nevi and patient physician concern*". We suggest the following changes:

1. ME-7 footnote cc "*follow up schedule is influenced by risk of recurrence (which may be determined by clinical and pathologic measures along with gene expression profiling), prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles/dysplastic nevi and patient physician concern*".
2. ME-1 to ME-3 footnote c "*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*".

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: While patients with early stage melanoma (i.e. AJCC Stage I and II) are regarded as good-prognosis based on population-based risk estimates, ultimately the vast majority of melanoma-related deaths occur in this population [7-8]. In the MSLT-1 clinical trial, 41 deaths were observed in the intermediate thickness SLN positive group compared to 83 deaths for the SLN negative group [7]. Thus, two-thirds of patients who eventually die from melanoma are considered to be at lower risk for metastatic disease and death by current staging criteria.

The DecisionDx-Melanoma test is a 31-gene expression profile (GEP) that assesses intrinsic tumor biology of cutaneous melanoma to determine a patient's risk for metastasis [5]. The test classifies patients into low risk (Class 1), or high risk (Class 2), for developing metastasis within five years of diagnosis, and identifies over 70% of SLNB negative patients who will develop recurrence and are at an increased risk of death. Analytical and clinical validation was performed in three multicenter, archival tissue studies that have demonstrated that the test performs with high accuracy [1-3].

The first study described the development of the test and performance characteristics in a 104 patient validation cohort [1]. The second study evaluated performance in patients eligible for a sentinel lymph node

biopsy (SLNB) and GEP class was shown to be an independent predictor of DMFS and overall survival (OS) in multivariate analysis including SLNB ($p<0.005$)[2]. The third study evaluated performance with a new independent cohort of 334 patients. Performance statistics for RFS, DMFS and MSS compared favorably to SLN status and addition of molecular class helped improve sensitivity and specificity [3]. Of 83 SLNB negative cases, 13 had a distant metastatic event and the test identified 77% (10) of these patients as high-risk Class 2 [3]. Multivariate analysis in all three studies has shown that the test accurately predicts risk for recurrence free survival (RFS), distant metastasis free survival (DMFS) and melanoma specific survival (MSS) in stage I-II patients, independent of the standard staging clinicopathologic factors. Negative Predictive Value (NPV) for MSS in Stage I-II patients was 99% [3].

In addition to the three multi-center archival tissue studies, two prospective, independent single center studies have recently confirmed the prognostic accuracy of the DecisionDx-Melanoma test. In a prospective cohort of 159 consecutive melanoma patients undergoing SLNB at a Surgical Oncology center were tested at time of initial evaluation (median follow up = 18m). Breslow thickness, ulceration, SLNB positivity and DFS were significantly associated with GEP classification ($P= 0.008$, <0.0001, <0.0001, 0.01, <0.0001 respectively) [4]. Two of 117 Class 1 (1.7%) and 16 of 42 Class 2 (38%) patients recurred, while 10 of 139 (6.7%) SLNB negative and 8 of 20 (40%) SLNB positive patients recurred. In the second independent study with 257 patients in a Dermatology practice (median follow up = 23m), the test correctly identified 67% of the metastatic patients as high risk with an odds ratio of 22 for metastases for Class 2 patients and an NPV of 98% for Class 1 patients [5].

Clinical decision impact has been evaluated in a retrospective study, which included 156 cutaneous melanoma patients from six institutions who were consecutively tested from May 2013 to December 2015 [6]. Documented post-test changes in management were observed in 53% of patients, with the majority (94%) of follow-up changes concordant with the risk indicated by the test result ($p<0.0001$): increased intensity of surveillance for Class 2 and decreased for Class 1 patients. Seventy-seven percent of Class 2 patients underwent management changes compared to 37% of Class 1 patients ($p<0.0001$, Fisher's exact) [6].

In summary, the DecisionDx-Melanoma test has shown consistent prognostic value in three consecutive multicenter clinical validation studies and two independent single center prospective studies, all of which demonstrated the ability of the test to stratify Stage I and II cutaneous melanoma patients as low or high risk beyond current clinical/pathological staging criteria. The high rate of decision change shown in Berger et al [6], likely reflects how the information about tumor biology provided by the DecisionDx-Melanoma test is clinically meaningful to physicians and patients, allowing low-risk patients to be managed with less costly, low-intensity surveillance, and focus intensive surveillance in a small subset of high-risk patients.

The following cited articles are submitted in support of this proposed change:

1. Gerami P, et al. Clin Cancer Res 2015;21(1):175-183.
2. Gerami P, et al. J Amer Acad Derm 2015;72(5):780-785 e783.
3. Zager J, et al. J Clin Oncol, 2016. 34(suppl; abstr 9581).
4. Hsueh E, et al. J Clin Oncol, 2016. 34(suppl; abstr 9565).
5. Greenhaw BD, et al. ACMS 2016: Orlando, FL.
6. Berger AC, et al. Curr Med Res Opin, 2016, Jun 3:1-6. [Epub ahead of print]

Other references cited:

7. Morton DL, et al. N Engl J Med 2014;370(7): 599-609
8. Shaikh WR, et al. J Natl Cancer Inst 2016;108(1).