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NCCN Guidelines Panel: Melanoma

On behalf of Castle Biosciences Inc., I respectfully request that the NCCN Melanoma Panel 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).

Based on a wide body of published evidence (18 peer-reviewed publications to date) supporting DecisionDx-Melanoma as a much needed accurate, independent and clinically useful biomarker for determining metastatic risk, we suggest the following changes to *NCCN Clinical Practice Guidelines in Oncology - Cutaneous Melanoma*:

- Footnote d, pages ME-1 to ME-3: "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."

- Principles of Molecular Testing, Prognostic Testing, page ME-C 1: "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."

Rationale: NCCN guidelines recommend differential management of patients according to melanoma specific survival (MSS) risk stratification based on AJCC staging. Patients with Stages IA-IIA NED are recommended to be followed in a less aggressive manner compared to patients with Stage IIB-IV NED melanoma. The guidelines also recognize that risk of metastasis should influence decisions on SLN biopsy (SLNB) and follow up schedule. However, risk stratification based solely on pathological and clinical staging misses many patients with biologically aggressive disease. Those patients are not offered the benefit of enhanced surveillance for early detection of metastatic disease and represent a substantial number of patients who die from melanoma[1-4]. Additionally, SLNB eligibility criteria based on clinical factors has resulted in a SLN positivity rate of only 16% for patients with intermediate thickness tumors, and approximately 5% for patients with thin (≤1 mm) tumors[1,5].

DecisionDx-Melanoma is supported by eighteen peer-reviewed scientific publications reporting analytical/clinical validation and clinical utility studies[6-23]. Clinical validation was performed in three multicenter, prospectively designed archival tissue studies including 690 patients, and four prospective, independent studies totaling 788 patients[1-8]. Therefore, the test's clinical validity and independence from other prognostic features has been demonstrated in retrospective and prospective cohorts with average- to low- risk melanoma[6-13]. DecisionDx-Melanoma accuracy for identifying patients with a low risk of a positive SLNB has also been demonstrated in a prospectively tested cohort of 1,421 patients[14]. Retrospective and prospective studies have shown the clinical decision impact, informing management decisions in 47-53% of patients who are tested[15-20]. The risk-guided adjustments to patient follow-up and surveillance reported by these studies are consistent with the NCCN recommendations that are based on a patient's risk of recurrence.

NCCN guidelines currently state that it is unclear whether the DecisionDx-Melanoma test provides clinically actionable information when used in addition to, or comparison with, other clinicopathologic variables (ME-C). First, no other clinical factors aside from thickness, ulceration and node status have been shown to consistently provide independent prognostic information in multivariate models for inclusion in AJCC staging. Second, DecisionDx-Melanoma has consistently been shown to add independent prognostic information in multivariate models that included thickness, ulceration and SLN status[6-13,21]. Further, we believe it is unreasonable for the NCCN guidelines to require existing or future GEP platforms to be evaluated against models that are currently in development, not publicly available and not clinically validated as stated in ME-C . We urge the panel to recognize that risk can be identified in different ways (through clinicopathologic or molecular factors), and that once a patient has been stratified into a low or high-risk group by one approach it can be further refined if another approach provides statistically independent prognostic information, as has been demonstrated for DecisionDx-Melanoma. A patient who is high-risk based on a validated molecular classifier deserves to be managed in the same fashion as a patient identified as high-risk based on clinicopathologic factors.

The guidelines state that, "Newer prognostic molecular techniques should not replace standard staging procedures". We wholeheartedly agree with this statement. Our studies have shown that the combination of SLN status and molecular Class provides the best accuracy for identifying patient at high risk of metastatic recurrence and death[3-4]. However, there is recognition among the medical community, including NCCN panel members, of a need for better selection of patients for surgical staging, given that the vast majority of patients (80-95%) have a negative SLN and do not derive benefit from a SLNB procedure[1,5,24-25]. A recent study has shown that the test can identify a population of patients that has a very low risk of a positive SLN (i.e. below the 5% threshold specified by NCCN guidelines)[14]. By identifying patients unlikely to have a positive node who are below the threshold already in clinical use, the test can reduce the number of unnecessary surgical procedures, improve the yield of the SLNB procedure and better direct resources to those patients who need them most.

Thus, the peer-reviewed, published evidence demonstrates that patients at high risk for recurrence can be identified by molecular testing in addition to clinicopathologic staging[6-23]. This evidence has given confidence to physicians at ~60% of the NCCN panel member institutions to order the test and to 2,986 clinicians throughout the U.S. in 2018 for using the 31-GEP test in the management of over 12,450 patients. We request that the NCCN panel members jointly evaluate the available data and adjust current recommendations to recognize that i) DecisionDx-Melanoma identifies a molecular signature of primary melanoma tumors that is independently associated with disease recurrence and death, and ii) patients identified as high risk by the test deserve to be managed in the same fashion as patients identified as high-risk based on clinical factors.

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).

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

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9. Gastman BR et al. J Am Acad Dermatol 80, 149-157 e4 (2019)
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11. Greenhaw, BN et al. Dermatol Surg 44, 1494-1500 (2018)
12. Keller J et al. Cancer Med 8, 2205-2212 (2019)
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14. Vetto JT et al. Future Oncol 15, 1207-1217 (2019)
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16. Farberg et al. J Drugs Dermatol 16, 428-431 (2017)
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21. Gastman BR et al. Head Neck (2019)
22. Ferris LK et al. J Am Acad Dermatol 76, 818-825 e3 (2017)
23. Cook RW et al. Diagn Pathol 13, 13 (2018)
24. Egger ME et al. J Am Coll Surg 228(4):466-472 (2019)
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