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NCCN Guidelines Panel: Melanoma

Castle Biosciences Inc. would like to thank the NCCN Panel for updating guidance on gene expression profiling (GEP) in the 2020 guideline versions. While we appreciate the fact that the panel recognizes that GEP can be an adjunct to staging, the evidence supporting GEP is stronger than represented in the guidelines. We respectfully request that the following recent publications regarding the DecisionDx-Melanoma test (31-GEP) are considered when updating language to better reflect the available evidence: two recent meta-analyses,[1-2] multiple prospective clinical validity studies,[3-7] and prospective and retrospective clinical utility[8-10] studies. Suggested changes are included after the Rationale and Literature Summary.

Rationale and Literature Summary:

Clinical Validation – The 31-GEP test has been validated by 5 prospective studies (including 3 academic, non-industry-sponsored),[3-7] 2 systematic review and meta-analyses each including >1400 patients[1-2] and multiple retrospective studies[11-12]. Each study has consistently shown the 31-GEP test to have added impact on prognostication in combination with AJCC staging and SLNB across different patient groups with early-stage melanoma.

Summary of findings on 31-GEP	Study design	Class 1 vs Class 2 outcome	Ref
GEP adds prognostic information to current staging factors to increase identification of high-risk patients, including those diagnosed with early stage disease (n=322)	**Prospective**	3-y RFS: 97% vs 77%; 3-y DMFS: 97% vs 77%; 3-y OS: 99% vs 92%	3
Academic-sponsored: GEP Class 2 patients were 22 times more likely to develop metastasis; authors offer GEP to all melanoma patients (n=256)	**Prospective**	3-y RFS*: 98.1% vs 74.4%. 3-y OS: 99.3% vs 85.8%; Sensitivity: 77%; NPV: 99%	4
Academic-sponsored: GEP Class 2 results were significant, independent predictor of metastasis in context of clinicopathologic features used in staging; GEP Class 2 results accurately identified 74% of SLNB-negative patients that experienced recurrence (n=159)	**Prospective**	3-y RFS: 97% vs 47%; 3-y DMFS: 99% vs 64%	5
Academic-sponsored: GEP identified recurrence risk in stage IB-II patients, including those with low-risk AJCC stage (n=86)	**Prospective**	Rate of recurrence: 0% vs 21%; Sensitivity: 100%	6
Large study: GEP identified T1-T2 melanoma at low risk for SLNB positivity (n=1421)	**Prospective**	SLN positivity: 2.8% vs 16.4 %**	7
Meta-analysis: GEP consistently and accurately predicts recurrence or distant metastasis across AJCC stages I-III across multiple studies and augments the ability to identify high-risk patients (n=1479)	**Meta-analysis**	5-y RFS: 91.4% vs 43.6%** 5-y DMFS: 94.1% vs 55.5%**	1
GEP identified patients likely to recur within traditionally low-risk patients (SLNB-negative, Stage I-IIA, ≤1mm tumor) (n=690). Study reporting on combined previous 3 cohorts.	Retrospective	RFS: 90% vs 37%**; DMFS: 94% vs 50%**; Melanoma OS: 99% vs 75%**	11
GEP improved identification of high-risk melanomas when combined with AJCC prediction in stage I-II patients (n=205), indicating the test provides additional prognostic information to traditional staging	Retrospective	**AJCC low-risk**: 5-y RFS 95% vs 62%; 5-y DMFS 96% vs 76%; 5-y OS 96% vs 71% **AJCC high-risk**: 5-y RFS 75% vs 17%; 5y DMFS 92% vs 39%; 5-y OS 83% vs 44%	12

*Reported as disease-free survival
**Class 1A vs. Class 2B.

Clinical Utility – 1 prospective and 2 retrospective studies including a total of 494 patients (all prospectively tested) showed the impact of the 31-GEP test in treatment and management decisions.[8-10] Recently, an expert consensus panel convened by the National Society of Cutaneous Medicine provided 14 evidence-based recommendations on 31-GEP testing in an appropriate use criteria statement.[13]

Summary of findings on 31-GEP	Study design	Class 1 change in decision	Class 2 change in decision	Ref
6 institutions: GEP directly influenced clinical management of patients; implemented changes reflected the predicted recurrence risk (n=156)	Retrospective	37%	77%	8
16 institutions: GEP was used to guide risk-appropriate patient management and was a significant factor for treatment changes, including directing more frequent and intense surveillance to Class 2 patients (n=247)	Prospective	36%	85%	9
Single center (OHSU): GEP results significantly associated with management of stage I-II patients after SLNB. For node negative patients, Class 2 results led to more aggressive follow up and management (n=91)	Retrospective	53%		10

Suggested Changes: Based on the evidence presented above, please consider the following suggested changes:

- **ME-1, ME-2, ME-3 Footnote d**: "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~~."
- **ME-C1, 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~~ test~~s~~ 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 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)~~."

FDA Status: DecisionDx Melanoma is performed in the central laboratory of Castle Biosciences that is regulated under the Clinical Laboratory Improvement Amendments (CLIA). FDA clearance is not required.

Respectfully submitted,

Castle Biosciences

References:

1. 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. doi.org/10.1016/j.jaad.2020.03.053
2. Litchman GH, Prado G, Teplitz RW & Rigel DS. A systematic review and meta-analysis of gene expression profiling for primary cutaneous melanoma prognosis. *SKIN J Cutaneous Med* 2020;4:221-37.
3. Hsueh EC, DeBloom JR, Lee J, et al. Interim analysis of survival in a prospective, multi-center registry cohort of cutaneous melanoma tested with a prognostic 31-gene expression profile test. *J Hematol Oncol* 2017;10(152):1-8.
4. Greenhaw BN, Zitelli JA, Brodland DG. Estimation of prognosis in invasive cutaneous melanoma: An independent study of the accuracy of a gene expression profile test. *Dermatol Surg* 2018;44:1494-1500. doi: 10.1097/DSS.0000000000001588
5. Keller J, Schwartz TL, Lizalek JM, et al. Prospective validation of the prognostic 31-gene expression profiling test in primary cutaneous melanoma. *Cancer Med* 2019;8:2205-12.
6. Podlipnik S, Carrera C, Boada A, et al. Early outcome of a 31-gene expression profile test in 86 AJCC stage Ib-II melanoma patients. A prospective multicenter cohort study. *J Eur Acad Dermatol Venereol* 2019;33:857-62.
7. Vetto JT, Hsueh EC, Gastman BR, et al. Guidance of sentinel lymph node biopsy decisions in patients with T1-T2 melanoma using gene expression profiling. *Future Oncol* 2019;15:1207-17.
8. Berger AC, Davidson RS, Poitras JK, et al. Clinical impact of a 31-gene expression profile test for cutaneous melanoma in 156 prospectively and consecutively tested patients. *Curr Med Res Opin* 2016;32:1599-1604.
9. Dillon LD, Gadzia JE, Davidson RS, et al. Prospective, multicenter clinical impact evaluation of a 31-gene expression profile test for management of melanoma patients. *SKIN J Cutaneous Med* 2018;2:111-21.
10. Schuitevoerder D, Heath M, Cook RW, et al. Impact of gene expression profiling on decision-making in clinically node negative melanoma patients after surgical staging. *J Drugs Dermatol* 2018;17:196-9.
11. Gastman BR, Gerami P, Kurley SJ, et al. Identification of patients at risk for metastasis using a prognostic 31-gene expression profile in subpopulations of melanoma patients with favorable outcomes by standard criteria. *J Am Acad Dermatol* 2019. 80:149-157. doi:10.1016/j.jaad.2018.07.028.
12. Ferris LK, Farberg AS, Middlebrook B, et al. Identification of high-risk cutaneous melanoma tumors is improved when combining the online American Joint Committee on Cancer Individualized Melanoma Patient Outcome Prediction Tool with a 31-gene expression profile-based classification. *J Am Acad Dermatol* 2017;76;818-25.e3.
13. Berman B, Ceilley R, Cockerell C, et al. Appropriate use criteria for the integration of diagnostic and prognostic gene expression profile assays into the management of cutaneous malignant melanoma: an expert panel consensus-based modified Delphi process assessment. *SKIN J Cutaneous Med* 2019;3:291-306.