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NCCN Guidelines Panel: Melanoma (Uveal Melanoma)

We appreciate the NCCN's rigorous criteria for assigning evidence categories to guideline recommendations, as it is essential that clinical decision-making be based on the highest level of peer-reviewed science available. We also appreciate that the current version of the NCCN Guidelines for Uveal Melanoma (v1.2019) includes the DecisionDx-UM test as one of the multiple biomarkers to aid in follow up and imaging decisions (UM-4). However, we'd like to point out that within these biomarkers, no distinction is made on the level of evidence supporting their use or whether they are independent of each other. Specifically, Gene Expression Profiling (GEP) using the DecisionDx-UM test is the most validated biomarker of risk for uveal melanoma (UM) patients, achieving a Category 1 level of evidence, which is not reflected in the guideline. We are concerned that this could lead to confusion for providers, as histologic features could be judged to substitute for molecular risk assessment, when histology has been shown to not provide independent prognostic value when compared directly to molecular features in both univariate and multivariate analysis.

In addition, we note that the NCCN Biomarkers Compendium has mistakenly omitted the use of GEP in their Uveal Melanoma section.

Specific Changes Requested:

1. We request that the NCCN Uveal Melanoma Panel assign an evidence Category 1 to the recommendation for GEP testing in the Follow Up section of the guidelines for uveal melanoma (UM-4).
2. We request that the NCCN Biomarkers Compendium be updated to reflect the inclusion of GEP as a biomarker to guide follow up and systemic imaging in the uveal melanoma guidelines (v1.2019).

FDA status: Not applicable to this submission.

Rationale: DecisionDx-UM is the only prognostic test for UM that has undergone prospective validation, as required to achieve a category 1A level of evidence according to the system outlined by the NCCN's task force for evaluating the clinical utility of tumor markers in oncology[1].

DecisionDx-UM is a genomic test that classifies patients diagnosed with Uveal Melanoma (UM) as low (Class 1A), intermediate (Class 1B), or high risk (Class 2) for metastasis based on the RNA expression of 15 genes in the primary tumor tissue. The DecisionDx-UM Class result has been included in the UM guidelines since its first iteration (v1.2018) as a method for risk stratification that may be used to inform frequency of follow-up, including systemic imaging and blood tests, and determine possible eligibility for clinical trials. However, it is important to distinguish that the DecisionDx-UM Class result is the only risk factor that has consistently been shown to be both independent of and superior to all of the other methods of prognostication listed in the guidelines, and is the only test to have undergone prospective validation.

The NCCN's task force for evaluating the clinical utility of tumor markers in oncology outlines a comprehensive system for evaluating evidence in support of clinical biomarker tests[1]. As the DecisionDx-UM test has been prospectively validated, with the marker as the primary objective of the study[2], it achieves a Category 1A level of evidence as outlined by this system. Furthermore, multiple independent

prospective studies have confirmed the test's clinical validity, and thus the DecisionDx-UM has not only achieved but surpassed the threshold needed for meeting Category 1A evidence according to the system adopted by NCCN (Table 1).

Table 1. DecisionDx-UM meets NCCN criteria for highest level of evidence for a molecular test

Level of Evidence IA: Prospective, marker primary objective; well powered or meta-analysis[1]		Onken 2012[2] Correa and Augburger 2014[3], 2016[4] Plasseraud 2016[5], Aaberg 2020[6]
Clinical Trial	Prospective clinical trial designed to address tumor marker	✓
Patients and patient data	Prospectively enrolled, treated, and followed in prospective, randomized control trial	✓
Specimen collection, processing, and archival	Specimens collected, processed and assayed for specific marker in real time	✓
Statistical design and analysis	Study powered to address tumor marker question	✓
Validation	Result unlikely to be play of chance; although preferred, validation not required	✓

[1]Febbo et al., 2011

Clinical validity:
(Prospective studies in bold)
- [2]**Onken et al., 2012. *Ophthalmology***
- Gill and Char., 2012. *Can J Ophthalmol.*
- Chappell et al., 2012. *Am J Opthalmol.*
- [3]**Correa and Augsburger et al., 2014. *Graefes Arch Clin Exp Ophth***
- [4]**Correa and Augsburger et al., 2016. *Am J Ophthalmol.***
- Decatur et al., 2016. *JAMA Ophthalmol.*
- Walter et al., 2016. *JAMA Ophthalmol.*
- [5]**Plasseraud et al., 2016. *J. Oncol.***
- Demirci et al., 2018. *Am J Ophthalmol.*
- Cai et al., 2018. *Am J Ophthalmol.*
- [6]**Aaberg et al., 2020. *Ocul Oncol Pathol.* (in press)**

Given that physicians in the U.S. and across the world follow NCCN recommendations, it is important that the NCCN UM Panel incorporates the different levels of evidence that exist for each of the biomarkers that inform follow up and surveillance decisions for UM patients. As presented above, the DecisionDx-UM test is supported by a much higher level of published evidence than other methods of prognostication, which lack the same level of validation and prognostic accuracy and thus cannot serve as substitutes for this test. We therefore respectfully urge the panel to assign an evidence Category 1 to the recommendation for gene expression profiling with DecisionDx-UM. In addition, for this same reason, this test should not be omitted from the Biomarkers Compendium.

Should you have any questions about this test, or its body of scientific evidence and associated publications, please feel free to contact me directly.

Sincerely,

Jay Braxton

Jay Braxton, PharmD

References:

1. Febbo, P. G. et al. NCCN Task Force report: Evaluating the Clinical Utility of Tumor Markers in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2011; 9 Suppl 5:S1-32; quiz S33.
2. Onken, M. D. et al. Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. Ophthalmology. 2012; 119(8):1596–603.
3. Correa, Z. M. & Augsburger, J. J. Sufficiency of FNAB aspirates of posterior uveal melanoma for cytologic versus GEP classification in 159 patients, and relative prognostic significance of these classifications. Graefes Arch Clin Exp Ophthalmol. 2014; 252(1):131–135.
4. Corrêa, Z. M. & Augsburger, J. J. Independent Prognostic Significance of Gene Expression Profile Class and Largest Basal Diameter of Posterior Uveal Melanomas. Am J Ophthalmol. 2016; 162:20-27e1.
5. Plasseraud, K. M. et al. Clinical Performance and Management Outcomes with the DecisionDx-UM Gene Expression Profile Test in a Prospective Multicenter Study. J Oncol. 2016; 2016:5325762.
6. Aaberg, T.M., et al. Gene Expression Profiling in Uveal Melanoma: Five-Year Prospective Outcomes and Meta-Analysis. Ocul Oncol Pathol. 2020; In press.