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Response to “Comparison of Gene Expression Profiling and Chromosome 3 Analysis by Fluorescent in situ Hybridization and Multiplex Ligation Probe Amplification in Fine-Needle Aspiration Biopsy Specimens of Uveal Melanoma”

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We read with interest the article by Klufas et al. [1] comparing gene expression profiling (GEP) and FISH/MLPA for chromosome 3 in a small cohort of uveal melanoma patients. The results from this single-center study confirm the presence of discordance between GEP and chromosome 3 testing, which has been reported previously [2]. However, the authors erroneously suggest that DNA testing (FISH or MLPA) is “more sensitive at detecting high risk for metastasis patients” [1].

We wholeheartedly agree with the accompanying editorial, in which the authors state: “any technical advantage of each test can only be speculated because prognostic superiority of either test (GEP or MLPA) cannot be ascertained by this study as the prognostic prediction was not correlated with patient survival” [3].

The GEP signature was designed with the goal of identifying patients at high risk for metastasis and not to identify chromosome 3 copy number changes, so these tests are measuring different, albeit related, biological properties. The GEP test measures expression of 12 discriminating genes on 7 chromosomes, including chromosome 3. Therefore, Class 1 and 2 GEPs are not surrogates for disomy and monosomy 3, respectively, and thus, some discordance between 2 tests measuring different endpoints is to be expected. The 15–16% discordance found between chromosome 3 and GEP assessment is consistent with reports by the Collaborative Ocular Oncology Group (COOG) [2] and others. To date, the COOG report is the only study that has reported survival data for discordant cases and showed that GEP was a more accurate predictor of clinical outcomes [2].

The authors refer to GEP as an “inherently inaccurate test” [1] without providing any support for this assertion. The prognostic value of this test has been demonstrated in several single- and multi-center studies with consistent accuracy in identifying the great majority of patients who develop metastasis as Class 2. Here and previously [4], the authors criticize GEP for producing a result in non-uveal melanoma tissue; however, GEP is not a diagnostic test and should not be used as such. It is important to clarify misinterpretations of GEP, particularly as the authors have previously

suggested a superior accuracy of chromosome testing over GEP despite the absence of clinical outcomes to support such claims [5].

An important issue raised by the authors is technical reliability, as biopsy specimens are a precious resource. Although in this retrospective cohort of 49 tumors tested with both methods the authors report 94% technical success for MLPA, the overall technical success of the commercial MLPA test has not been reported, and higher failure rates for chromosomal tests have been reported previously. Importantly, GEP technical success was originally shown to be 97% [2] and remains so after >5,500 patients tested [6].

In summary, it is inappropriate for the authors to claim superiority of chromosomal testing and to suggest that GEP is incorrect in predicting a good prognosis for Class 1/monosomy 3 tumors given the lack of metastasis and additional long-term outcomes in their study and the consistent evidence of the accuracy of the GEP test in the literature [7–10].

Disclosure Statement

K.M.P. and F.A.M. are employees and option holders of Castle Biosciences, Inc., the provider of DecisionDx-UM GEP.

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