On behalf of Illumina, I respectfully request the NCCN Melanoma guideline panel to review the enclosed to support the consideration of next-generation (NGS)-based testing in germline and somatic mutation analysis of melanoma.

**Specific Requested Changes:**

We propose that consideration of NGS-based testing be considered in the context of genetic testing of **BRAF**, **CDKN2A**, and additional genes as suggested in the Melanoma NCCN Guidelines v 2.2018.

**FDA Clearance:**

The recommendation to use a multigene testing technique is not associated with any specific FDA-cleared product/s.

**Rationale:**

Melanoma is characterized by a high degree of genomic instability,¹ and The Cancer Genome Atlas Network recently classified four subtypes of melanoma by genotype: **BRAF**, **RAS**, **NF1**, and Triple-WT.² Activating mutations in **BRAF** (**BRAF**-V600) are found in approximately half of all advanced melanomas,³ and patients with unresectable or metastatic melanoma with **BRAF** V600E or V600K mutations can be treated with combination **BRAF** and **MEK** inhibitors (dabrafenib/trametinib). The Melanoma NCCN Guidelines v 2.2018 recommend testing for **BRAF** V600E or V600K using FDA-approved tests, namely polymerase chain reaction (PCR)-based tests.⁴ **BRAF** V600 mutations can also be detected by using next-generation sequencing (NGS)-based tests,⁵,⁶ and an NGS-based **BRAF** V600E or V600K diagnostic test has recently gained FDA approval.⁷ Ma et al. recently analyzed 117 cancer patients with **BRAF** mutations using commercially available PCR-based tests as well as NGS-based tests and found that 47% of **BRAF** mutations were missed by commercial kits and were only detectable by NGS.⁸ Recent data suggest that non-V600 **BRAF** mutations are relatively common in melanoma when NGS-based tests are employed for detection.⁹ Notably, there are multiple reports of clinical responses to **BRAF** inhibitors in patients with non-V600 **BRAF** mutations.¹⁰,¹¹

Additional gene mutations are relatively common in advanced melanoma, including **NRAS**, **TP53**, **KIT**, **PDGFRA2**, Tert promoter, and others.¹² Mutant **NRAS** is found in 15-20% of patients with advanced melanoma, and recent clinical data suggest that **NRAS**-mutated melanoma may be sensitive to **MEK** inhibitors.¹³,¹⁴ Recent data also suggest that **TP53** mutations in advanced melanoma may be prognostic for longer overall survival.¹⁵ Taken together, these data highlight the superiority of broader NGS-based genetic tests for advanced melanoma. In a recent NGS-based analysis of metastatic melanoma patients, Carlson et al. demonstrated that 29% of melanoma samples contained a genetic alteration that could be targeted by an FDA-approved therapy.¹⁶ NGS-based tests have the added advantage of accommodating somatic and germline testing in the same test, and the Melanoma NCCN Guidelines v 2.2018 call for mutation testing of **CDKN2A** or additional genes that may contain melanoma-predisposing mutations in certain patients (Guideline section ME-9).⁴

**Proposed Changes**

**Current Excerpt 1: Footnote**⁴ of Figures ME-8, 9, 10, 11, and 14: Melanoma Workup

“Obtain tissue to ascertain alterations in **BRAF**, and in the appropriate clinical setting, **KIT** from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy.”

**Proposed Change:** “Obtain tissue for **NGS-based testing** to ascertain alterations in **BRAF**, and in the appropriate clinical setting, **KIT** from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy

**Current Excerpt 2: Bullet point of Figures ME-9 and 10: Common Follow-up Recommendations for All Patients**
Thank you for your consideration,

Sincerely,

Amy Mueller MD
Medical Director, Oncology
Illumina