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 \textit{BRAF}, \textit{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,\textsuperscript{1} and The Cancer Genome Atlas Network recently classified four subtypes of melanoma by genotype: \textit{BRAF}, \textit{RAS}, \textit{NF1}, and Triple-WT.\textsuperscript{2} Activating mutations in \textit{BRAF} (\textit{BRAF-V600}) are found in approximately half of all advanced melanomas,\textsuperscript{3} and patients with unresectable or metastatic melanoma with \textit{BRAF} V600E or V600K mutations can be treated with combination \textit{BRAF} and MEK inhibitors (dabrafenib/trametinib). The Melanoma NCCN Guidelines v 2.2018 recommend testing for \textit{BRAF} V600E or V600K using FDA-approved tests, namely polymerase chain reaction (PCR)-based tests.\textsuperscript{4} \textit{BRAF} V600 mutations can also be detected by using next-generation sequencing (NGS)-based tests,\textsuperscript{5,6} and an NGS-based \textit{BRAF} V600E or V600K diagnostic test has recently gained FDA approval.\textsuperscript{7} Ma et al. recently analyzed 117 cancer patients with \textit{BRAF} mutations using commercially available PCR-based tests as well as NGS-based tests and found that 47\% of \textit{BRAF} mutations were missed by commercial kits and were only detectable by NGS.\textsuperscript{8} Recent data suggest that non-V600 \textit{BRAF} mutations are relatively common in melanoma when NGS-based tests are employed for detection.\textsuperscript{9} Notably, there are multiple reports of clinical responses to \textit{BRAF} inhibitors in patients with non-V600 \textit{BRAF} mutations.\textsuperscript{10,12}

Additional gene mutations are relatively common in advanced melanoma, including \textit{NRAS}, \textit{TP53}, \textit{KIT}, \textit{PDGFRA2}, Tert promoter, and others.\textsuperscript{13} Mutant \textit{NRAS} is found in 15-20\% of patients with advanced melanoma, and recent clinical data suggest that \textit{NRAS}-mutated melanoma may be sensitive to MEK inhibitors.\textsuperscript{14,15} Recent data also suggest that \textit{TP53} mutations in advanced melanoma may be prognostic for longer overall survival.\textsuperscript{16} 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.\textsuperscript{17} 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 \textit{CDKN2A} or additional genes that may contain melanoma-predisposing mutations in certain patients (Guideline section ME-9).\textsuperscript{4}

Proposed Changes

\textbf{Current Excerpt 1: Footnote\textsuperscript{6} of Figures ME-8, 9, 10, 11, and 14: Melanoma Workup}

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

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

\textbf{Current Excerpt 2: Bullet point of Figures ME-9 and 10: Common Follow-up Recommendations for All Patients}
“Consider referral to a genetics counselor for p16/CDKN2A mutation testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family. Testing for other genes that can harbor melanoma-predisposing mutations (eg. CDK4, TERT, MITF, and BAP1) may be warranted.”

Proposed Change: “Consider referral to a genetics counselor for NGS-based germline testing panels of p16/CDKN2A mutation testing in the presence of 3 or more invasive melanomas, or a mix of invasive melanomas, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family. Testing for other genes germline mutations that can harbor melanoma-predisposing mutations (eg. CDK4, TERT, MITF, and BAP1) may be warranted.”

The following articles are submitted in support of consideration of NGS-based testing in the context of genetic testing of BRAF, CDKN2A, and additional genes in melanoma. We would like to acknowledge the contributions of NCCN panel members, who are also co-authors or co-contributors in some of these publications.


Sincerely,

Thank you for your consideration,

Amy Mueller MD
Medical Director, Oncology
Illumina