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NCCN Guidelines Panel: AML

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Acute Myeloid Leukemia Panel consider the requested updates pertaining to the evaluation and management of patients with AML.

Requested Updates and Rationale: Update footnote (a) on page EVAL1-A to state *"multiplex gene panels and next generation sequencing analysis, including panels with >50 genes and comprehensive genomic profiling, are recommended for a comprehensive prognostic assessment".* Update footnote (fff) on page AML-10 to state *"Molecular profiling (including IDH1/IDH2, FLT3 mutations) is suggested as it may assist with selection of therapy and appropriate clinical trials. Multiplex gene panels and next generation sequencing analysis, including panels with >50 genes and comprehensive genomic profiling, are recommended for a comprehensive assessment"*

Comprehensive genomic profiling utilizes next generation sequencing (NGS) technology to examine entire regions of cancer-relevant genes (in contrast to limited "hot spot" tests) for all tumor types, identifying the four main classes of genomic alterations - base substitutions, insertions or deletions, copy number alterations, gene rearrangements, and assesses patterns of mutations across related genes in established cancer pathways to report complex biomarkers such as tumor mutational burden and microsatellite instability, to inform cancer treatment decisions via a single assay[1].

CGP assays have been validated against traditional orthogonal methods for hematologic malignancies and show a high level of concordance for detecting somatic alterations, which provide tumor classification, risk assessment, prognosis, disease monitoring, and treatment optimization[2,3]. The CGP approach has proven effective in detecting all types of genomic alterations, including fusion transcripts, which increases the ability to identify clinically relevant genomic alterations with therapeutic relevance[2,3].

In addition, CGP has been shown to increase clinical trial enrollment across a wide variety of refractory cancers and hematologic malignancies by identifying biologically relevant alterations in current NCCN guidelines and beyond.

- CGP of 235 patients with hematologic malignancies, including AML, identified that most patients had complex and unique molecular profiles. The majority of patients (75%) had ≥1 potentially actionable alteration and while most of the patients with evaluable tumor mutational burden (TMB) had a low TMB, 12% of patients had intermediate or high TMB. The authors conclude that CGP testing provides opportunity for clinical trials in hematologic malignancies to rationally test the application of genomically targeted therapeutics or immunotherapy, particularly in relapsed/refractory patients who have either exhausted or are unable to tolerate standard chemotherapy[4].
- In a database review of clinical CGP results for 4,800 patients with hematologic malignancies, the majority of alterations identified were in genes included in current NCCN guidelines, however, 17-26% of samples had biologically relevant alterations identified beyond those included in the guidelines, suggesting clinical utility of a CGP test approach to inform treatment planning, including clinical trial options[5].
- A clinical trial assay based on FoundationOne Heme is currently being utilized to provide genomic assessment in the Leukemia and Lymphoma Society BeatAML Master Trial (NCT03013998) for newly diagnosed patients with AML age 60 or older.
- In a prospective trial of patients with a wide variety of refractory tumors at an academic institution, a CGP test strategy with a large (409) gene NGS panel increased clinical trial enrollment from 11% to 19 % compared to a smaller (46 or 50) gene NGS hotspot panel[6].
- A retrospective analysis of medical records at a community oncology practice over a three year period for patients with advanced solid and hematologic malignancies concluded that clinical trial enrollment was facilitated by CGP use in the community setting[7].

Thank you for your review of this submission.

Sincerely,

Brian Alexander, M.D.
Chief Medical Officer
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References

1. FDA Label: Foundation Medicine Inc. FoundationOne® CDx Technical Information. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S013C.pdf

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3. Ptashkin R, et al. Abstract 3409: MSK-IMPACT Heme: Validation and clinical experience of a comprehensive molecular profiling platform for hematologic malignancies. 10.1158/1538-7445.AM2019-3409 Published July 2019

4. Galanina N, Bejar R, Choi M, et al. Comprehensive Genomic Profiling Reveals Diverse but Actionable Molecular Portfolios across Hematologic Malignancies: Implications for Next Generation Clinical Trials. *Cancers (Basel)*. 2018;11(1):11. Published 2018 Dec 21.

5. Maxwell K. et al. Patient Access to Comprehensive Genomic Profiling for Hematologic Malignancies: Analysis of The Payer Coverage Landscape and Results of Testing in 4,800 Patients. Presented March 2019 NCCN Meeting (pdf attached)

6. Kopetz S., et al. Use of a Targeted Exome Next-Generation Sequencing Panel Offers Therapeutic Opportunity and Clinical Benefit in a Subset of Patients With Advanced Cancers**.** *JCO Precision Oncology*-published online March 8, 2019

7. Reitsma M, Fox J, Borre PV, et al. Effect of a Collaboration Between a Health Plan, Oncology Practice, and Comprehensive Genomic Profiling Company from the Payer Perspective. *J Manag Care Spec Pharm*. 2019;25(5):601-611.