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NCCN Guidelines Panel: MPN

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Myeloproliferative Neoplasms Panel consider the requested updates pertaining to the evaluation and management of patients with MPN.

Requested Updates and Rationale: Update the algorithm on MPN-1 to clarify that multigene NGS panels include larger panels (>50 genes) and comprehensive genomic profiling (CGP) as follows: "Molecular testing (blood) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with ET and MF) and JAK2 exon 12 mutations (for patients with PV) or molecular testing using multigene NGS panel (> 50 genes or comprehensive genomic profiling) that includes JAK2, CALR, and MPL"

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 MPN, 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 overall samples had biologically relevant alterations identified beyond those included in the guidelines. In addition, 64% of triple negative (JAK2/CALR/MPL negative) samples for known or suspected MPN had at least one other biologically relevant alteration. Alterations in genes independently associated with inferior survival that may inform treatment planning (including transplant) were identified in genes including ASXL1 (22% of MPN samples), SRSF2 (10%), EZH2 (4%), TP53 (4%), and IDH1/2 (2%). These findings support the clinical utility of a CGP test approach to inform treatment planning, including clinical trial options[5].
- 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

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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.