Submitted by: Vincent A. Miller, MD
Company: Foundation Medicine, Inc.
Address: 150 Second Street, Cambridge, MA 02141
Phone: 617-418-2259
Email: vmiller@foundationmedicine.com
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NCCN Guidelines Panel: Colon Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Colon Cancer Guidelines Panel consider the requested updates and enclosed references, pertaining to the evaluation and management of patients with colon cancer.

Specific Changes and Rationale: We respectfully request that the Panel consider amending the Principles of Pathologic Review (COL-B 5 pg 5) section of NCCN Guidelines Version 2.2018 for Colon Cancer to indicate that testing for KRAS, NRAS, BRAF, and Microsatellite instability (MSI)/MMR status might be most efficiently performed by a single validated comprehensive genomic profiling (CGP) assay (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels) in order to conserve tissue and to obtain as much information as possible to inform the use of currently available biomarker driven therapies and define/refine clinical trial options. We also request evaluation of tumor mutational burden (TMB) be added as a recommendation in addition to MSI or mismatch repair (MMR) testing, to identify additional patients who are likely to benefit from immunotherapies.

If tissue is unavailable, we request that the Principles of Pathologic Review section of the guidelines be updated to suggest genomic testing via a validated, blood-based liquid biopsy, such as FoundationACT, to identify genomic alterations that may inform the patient's treatment, including the option to enroll in genomically matched clinical trials. An expanded version of the FoundationACT assay recently received a breakthrough device designation from the U.S. Food and Drug administration. This assay will include >70 genes including *KRAS*, *NRAS*, *BRAF*, and *ERBB2*, as well as MSI and blood TMB[1]. The FoundationACT assay has been reported to detect evidence of ctDNA in 82% of blood-based circulating tumor DNA (ctDNA) samples from patients with metastatic gastrointestinal tumors (72% colorectal carcinoma [CRC]), and reportable genomic alterations in 89% of these samples. Among 25 temporally-matched blood and tissue samples included in this study, 86% of alterations detected in tissue were also detected in ctDNA[2].

CGP allows the molecular diagnostic evaluation of a single sample from a patient with metastatic colon cancer to identify predictive genomic alterations, including *RAS* and *BRAF* alterations (across all exons), as a guide for the use of EGFR-targeted therapies; as well as TMB, MSI, and mismatch repair gene alterations (*MLH1*, *MLH2*, *MLH6*, *PMS2*) to guide use of immune checkpoint inhibitors.

Data in multiple solid tumor types suggest that TMB is an important predictive biomarker of response to immunotherapies, and responses to checkpoint inhibitors have been reported in in both MSI-high/TMB-high and MS-stable/TMB-high tumors[3–5]. In one study the evaluation of TMB identified >99% of CRC patients with MSI-high tumors. However, assessing TMB simultaneously with MSI status can identify an additional population of patients with MS-stable but TMB-high tumors who are also likely to benefit from check point inhibitors. This is predicted to lead to a 54% increase in the target population of metastatic CRC patients who may respond to immune checkpoint inhibitors[6].

Further, CGP may identify targets for therapy using either agents approved for other indications (eg. testing for *HER2* amplification and non-amplification mutations and *NTRK* fusions), as well as additional rare driver alterations that may inform the patient's treatment, including predicted lack of response to anti-EGFR therapies, or the option to enroll in a genomically matched clinical trial.

One in 3 CRC patients with tumors that are *RAS*/*RAF* wild-type (WT) harbor a genomic alteration (*EGFR* extracellular domain mutations, *HER2*, *MET*, and *FLT3* amplification, *PIK3CA* and *MEK1* mutations, and *PTEN* inactivating alterations) that could mediate resistance to EGFR therapeutic antibodies [7–12]. Detection of one or more of these alterations may lead to the identification of an appropriate genomically matched clinical trial, as several prospective trials in solid tumors, including CRC, are currently utilizing CGP for enrollment.

HER2 (*ERBB2*) amplification has been reported in 3% and 7% of all CRC and RAS/RAF wild-type CRC. respectively[12]. In the Phase 2 HERACLES trial of patients with HER2-positive *KRAS* WT CRC, 30% (8/27) had an overall response, 44% (12/27) had stable disease, and median PFS was 21 months following treatment with a combination of the HER2 inhibitors lapatinib and trastuzumab [13]. In the ongoing MyPathway trial of patients with HER2 amplified/overexpressed CRC treated with pertuzumab and trastuzumab 12/32 patients assessed had a partial response and 3/32 had stable disease >4 months [14]. *HER2* short variant mutations are also found in 2% of CRC, and these patients are also predicted to respond to HER2-targeted therapies [15]; these alterations are detectable by CGP but would not be detected using FISH or IHC testing [12].

Kinase fusions of *ALK*, *RET*, *NTRKs*, *FGFRs,* and *BRAF,* which have been identified as clinically relevant predictors of response to matched targeted therapies in other tumor types including NSCLC, have been identified in a rare subset of CRCs using CGP [12]. CRC patients with tumors harboring these alterations have reported lack of response to anti-EGFR therapies, but durable responses to matched therapies targeting *ALK* or *NTRK1* [16–20].

BRAF V600E mutations predict lack of response to EGFR antibodies and confer poor prognosis in CRC. However, 22% of *BRAF* mutations in CRC are non-V600, and are not typically covered by hotspot tests. These mutations predict excellent prognosis relative to cases with *BRAF* V600E or WT *BRAF*, suggesting that patients with tumors harboring non-V600 mutations may achieve benefit from less intensive therapies [21]. Clinical trials exploring effective combination therapies to effectively target BRAF V600E in CRC are also ongoing [22].

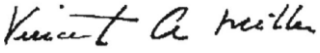
Inflammatory Bowel Disease (IBD) increases the risk of colitis-associated cancers including CRC. CGP may reveal targetable genomic alterations rarely or never seen in “sporadic” CRC (eg, IDH1 R132)[23].

An inherited genetic mutation may be the driving factor in the development of approximately 5% of CRCs[24]. Evaluation for MMR protein expression and MSI status may be suggestive of inheritance of Lynch Syndrome or a variant, but will not identify other potential inherited drivers, such as APC alterations. CGP testing of somatic tumor specimens may identify potential germline mutations including those in the MMR pathway, APC or MUTYH, for example, and these patients and their families could then potentially be referred for germline testing.

Taken together these data suggest that routine broad-based CGP of patients with colon cancer via a single assay is the most efficient and through approach to identify both common genomic alterations and genomic signatures, such as TMB and MSI, to identify patients for genomics-matched clinical trials and approved therapies.

Thank you for your review of this submission.

Sincerely,



Vincent A. Miller, M.D.
Chief Medical Officer
Foundation Medicine

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