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Date of request: August 10, 2017
NCCN Guidelines Panel: Colon Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Colon Cancer Guidelines Panel review the enclosed data, which supports the use of comprehensive genomic profiling (CGP) of a tumor specimen as part of the standard of care management of patients with metastatic colon cancer. CGP assays include FoundationOne®, our currently available assay, and FoundationOne *CDx*™, currently under parallel and expedited review by FDA and CMS with anticipated approval later this year. We hope that the data accompanying this letter will encourage the NCCN Colon Cancer Panel to consider including in its guidelines a recommendation favoring CGP as the methodology for assessing molecular biomarkers to guide therapy and prognostic risk estimate. The use of multiplex assays, and molecular testing methods that are able to detect mutations in specimens with at least 5% mutant allele frequency, is supported by the recent jointly published guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology [1].

Specific Changes: We request that the Panel consider amending the Principles of Pathologic Review section of NCCN Guidelines Version 2.2017 for Colon Cancer pages COL-4 and COL-A-(4) to indicate that CGP is a preferred testing methodology, allowing multiplex testing of key genomic alterations in ~10 days using a single assay. CGP allows the molecular diagnostic evaluation of a patient with metastatic colon cancer to identify predictive genomic alterations, including *KRAS* and *NRAS* alterations (across all exons), as a guide for the use of EGFR-targeted therapies; as well as tumor mutational burden (TMB), microsatellite instability (MSI), and mismatch repair gene alterations (*MLH1*, *MLH2*, *MLH6*, *PMS2*) to guide therapy using immune modulating agents such as pembrolizumab. The evaluation of TMB will identify an additional fraction of patients with MS-stable but TMB-high tumors who are also likely to benefit from immune modulation therapies. Further, CGP may identify targets for therapy using either agents approved for other indications (e.g.-testing for *HER2* amplification and non-amplification mutations), 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. When performed in a single assay, CGP will also identify prognostic genomic alterations such as *BRAF* mutations.

FDA Clearance: FoundationOne is a laboratory developed test (LDT) currently available for clinical use. FoundationOne *CDx™* is currently under parallel and expedited review by FDA and CMS with anticipated FDA approval the second half of 2017. Unlike conventional bridging studies for a single biomarker in one tumor type, achieving a broad approval involved submitting an analysis across all four classes of genomic alterations (base substitutions, indels, copy number variations and rearrangements) for a dataset comprising more than 6,000 samples. Validation and concordance was demonstrated for more than 36 distinct tumor types and a variety of specimen types (e.g., tumor resections, core biopsies, fine needle aspirates, etc.). The FoundationOne *CDx*™ assay will thus serve as both a single test to identify patients whose tumors contain alterations associated with FDA-approved therapies and as a molecular screen to facilitate access to clinical trials, permitting more rapid testing overall for novel therapies and reducing the time and cost of drug development. This anticipated FDA approved product includes variant calling across 324 genes, genomic signatures for MSI and TMB as well as clinical claims in the intended use for diseases in which current companion diagnostics exist, including breast cancer, NSCLC, melanoma, colorectal and ovarian cancers. As such, in parallel, we plan to submit analogous requests to respective NCCN disease panels for these additional cancers beyond colon. It is anticipated that this FDA approval across solid tumors will be accompanied by a CMS NCD (National Coverage Determination).

Rationale for Preferring Comprehensive Genomic Profiling: *RAS* mutations are associated with resistance to EGFR targeted therapy in up to 50% of patients with metastatic colorectal cancer (CRC) [2]. Hyper-mutated tumors associated with MSI and/or Lynch Syndrome, occur in approximately 15% of patients with CRC, and 4% of patients with advanced tumors [3,4]. These findings lead to a change in standard of care therapy. An estimated >20% of CRCs are MS-stable but have elevated TMB, suggesting that MSI status only captures a subset patients likely to respond to immunotherapies [5]. Recent data in melanoma, lung and bladder cancers suggest that TMB is an important predictive biomarker of response to

immunotherapies, and responses to checkpoint inhibitors have been reported in MS-stable TMB-high CRC with *POLE* mutations [6,7].

Detection of certain genomic alterations using CGP may lead to consideration of experimental therapy either using agents already approved for other indications or as part of clinical trials. A recent study suggests that as many as 1 in 3 CRC patients with tumors that are *RAS*/*RAF* wild-type (WT) harbor a genomic alteration that could mediate resistance to EGFR therapeutic antibodies [8]. These alterations include *EGFR* extracellular domain mutations, *HER2*, *MET*, and *FLT3* amplification, *PIK3CA* and *MEK1* mutations, and *PTEN* inactivating alterations, all of which have been reported in multiple retrospective studies and case reports of patients with primary or acquired resistance and/or shorter overall survival to cetuximab or panitumumab, and would be detected with the assays described above [9–12]. 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% of CRC cases, and in 7% of CRC cases that are *RAS/RAF* WT [8]. Patients with tumors harboring *HER2* amplification have been shown to demonstrate resistance to EGFR antibody therapy [9,13]. 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 [14]. 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 [15]. *HER2* short variant mutations are also found in 2% of CRC, and these patients are also predicted to respond to HER2-targeted therapies [16]; these alterations are detectable by CGP but would not be detected using FISH or IHC testing [8].

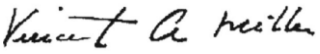
Kinase fusions of *ALK*, *RET*, *NTRKs*, *FGFRs,* and *BRAF,* which have been identified as clinically relevant predictors of response to matched targeted therapies in other tumor types including NSCLC, have been identified in a rare subset of CRCs using CGP [8] and durable responses to matched therapies targeting *ALK* or *NTRK1* have been reported [17–20].

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].

Unresectable metastatic colon cancer remains an incurable disease, and investigational therapies to develop improved treatments are a high priority. Numerous promising therapeutic approaches are based upon genomic understanding of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (NCI-MATCH) and ASCO (TAPUR). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in clinical trials, multiplex CGP assays, such as FoundationOne® and FoundationOne *CDx*™, can potentially match > 80% of patients with colon cancer to targeted therapies in clinical trials based on detected alterations, including: *KRAS*, *NRAS*, *HRAS* mutations and amplifications, *BRAF* V600 and non-V600 mutations, *HER2, EGFR, MET,* and *FLT3* amplification and mutations, *MEK1*, *PIK3CA*, *PTEN*, and *AKT* mutations and copy number changes, DNA repair pathway alterations affecting *BRCA1/2*, *POLE*, *POLD1*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and fusion of *ALK*, *ROS1*, *NTRK, BRAF, RAF1, FGFR,* and *RET.* Foundation Medicine has joined both the NCI-MATCH and ASCO TAPUR studies as an approved testing platform, and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities. Taken together, these data indicate that CGP is an essential addition to clinical care of patients with this often deadly malignancy.

Thank you for your review of this submission.

Sincerely,



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