Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Breast Cancer Guidelines Panel review the enclosed data supporting updates to the Guidelines and include comprehensive genomic profiling (CGP) assays such as FoundationOne®, our currently available assay, and FoundationOne CDx™, currently under parallel and expedited review by FDA and CMS with anticipated approval later this year, in the work-up of patients with Stage IV or recurrent breast cancer. 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., 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 and expedite 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 signature analysis for MSI (microsatellite instability) and TMB (tumor mutational burden), 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 the respective NCCN disease panels for these additional cancers beyond breast. It is anticipated that this FDA approval across solid tumors will be accompanied by a simultaneous CMS NCD (National Coverage Determination).

Specific Changes: This request is to include CGP, via a single assay (as opposed to sequential testing of single biomarkers), in the initial evaluation of a patient with recurrent or Stage IV breast cancer (BINV 17) to identify genomic alterations in PIK3CA, ERBB2 (HER2), ESR1, BRCA1/2, AKT1, and genes regulating the cell cycle, as well as other driver alterations that may inform the patient’s treatment, including the option to enroll in genomically matched clinical trials (BINV 21-23). CGP can also detect high MSI (MSI-H), and identify patients who are eligible to receive pembrolizumab based on its FDA approval for treatment of MSI-H solid tumors. Tissue biopsy at first recurrence/metastatic disease to evaluate ER/PR and HER2 status is standard of care [1] and is recommended by the NCCN® Guidelines (BINV-17), and provides an opportunity to obtain tissue for CGP. We also request CGP be included in the “Principles of HER2 testing” (BINV-A) as a method to identify ERBB2 short variant mutations that are not assessed by routine HER2 testing methods. The FoundationOne® and FoundationOne CDx™ assays also detect ERBB2 amplification with 98.6% accuracy compared to FISH [2]; in those cases where HER2 status by standard IHC/FISH testing is equivocal [3], CGP may provide a separate assay to inform on HER2 status.

FDA Clearance: FoundationOne® is a laboratory developed test (LDT) currently available for clinical use to inform the patient’s treatment options. FoundationOne CDx™ is currently under parallel and expedited review by FDA and CMS with anticipated FDA approval in the second half of 2017.

Rationale: ERBB2 (HER2) amplification testing is a routine part of the breast cancer work-up; however, other types of targetable ERBB2 alterations that are not detected by standard-of-care FISH or IHC tests occur in up to 3% of breast cancers, including diverse activating ERBB2 short variant mutations that occur in 2% of cases that lack ERBB2 amplification [4]. ERBB2 short variant mutations are enriched in invasive lobular breast cancer where they are detected up to 18% of cases [5, 6]. The efficacy of HER2 inhibition in patients with ERBB2-mutated, but not amplified, breast cancer, was evaluated in a Phase 2 trial of neratinib alone or in combination with fulvestrant and best response rates of 33.3% (95% CI: 15.6%-55.3%) were reported for patients with estrogen receptor-negative [ER(-)] breast cancer and 58.3% (95% CI: 23.4%-83.3%) for patients with ER-positive [ER+] breast cancer [7]. Responses to HER2 monoclonal
antibodies or tyrosine kinase inhibitors have also been described in case reports for patients with ERBB2 sequence mutations [8–11].

Genomic alterations in the PI3K/AKT/MTOR pathway are common in breast cancer. PIK3CA, PTEN and AKT1 alterations are observed in 35%, 5%, and 2.4% of cases, respectively, and may be predictive biomarkers for therapies targeting this pathway [12]. In a Phase 3 trial for hormone receptor-positive/HER2-negative breast cancer, patients with PIK3CA mutation had improved progression free survival (PFS; 7.0 vs 3.2 months) and overall response rate (ORR) when treated with the PI3K inhibitor buparlisib plus fulvestrant compared to placebo plus fulvestrant; patients wild-type for PIK3CA did not benefit from buparlisib [13]. Several phase 1/2 trials in patients with ER+ or triple negative breast cancer (TNBC) have shown that tumors with PIK3CA, PTEN or AKT1 genomic alterations may preferentially respond to AKT inhibitors [14–16]. In a Phase 2 trial of the AKT inhibitor ipatasertib plus paclitaxel for metastatic TNBC, in comparison to unselected patients, the pre-defined subgroup with PIK3CA, AKT1, or PTEN genomic alterations derived the greatest benefit from ipatasertib plus paclitaxel compared to placebo plus paclitaxel (PFS, 9.0 vs 4.9 months) [15]. In a Phase 1 trial of the AKT inhibitor AZD5363 for patients with AKT1 E17K mutation, best ORRs were 30% and 33% for ER+ breast cancer and TNBC, respectively [16].

The FoundationOne® and FoundationOne CDx™ assays can detect alterations in BRCA1/2, which are mutated in approximately 10% of all breast tumors [17], and may be predictive of responses to PARP inhibitors such as olaparib [18].

ESR1 mutations result in estrogen-independent ER activation and are detected in 25%-39% of patients with metastatic ER+ breast cancer who have progressed on endocrine therapy [19]. Analyses of Phase 2 and 3 trials for patients with ER+ breast cancer suggest that patients whose tumors harbored ESR1 mutations may not derive clinical benefit from aromatase inhibitors such as exemestane in comparison to fulvestrant-containing treatment regimens [19–21].

FGFR1 amplification is detected in 13% of breast cancer cases [12] and preliminary data from a Phase 1/2a study of the multikinase inhibitor lucitanib demonstrated partial responses in 4/8 (50%) patients with FGFR1-amplified breast cancer [22]. Patients with tumors harboring alterations in EGF or ERBB2, each mutated at frequencies of 1-2% in breast cancer, have experienced antitumor responses to matched targeted therapies [23, 24]. Although MSI-H status is relatively rare in breast cancer, MSI-H is significantly associated with overall survival in numerous tumor types treated with pembrolizumab or nivolumab [25, 26]; pembrolizumab is FDA-approved for solid tumors with MSI-H status. Routine broad-based testing of patients with breast cancer using CGP may be a rational approach to identify both common genomic alterations and rare alterations such as MSI-H.

Metastatic disease is incurable and patients require opportunities for enrollment into clinical trials. Numerous promising therapeutic approaches are based upon a 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 therapeutic clinical trials, CGP assays, such as FoundationOne® and FoundationOne CDx™, can potentially match more than 80% of patients with breast cancer to targeted therapies in clinical trials based on detected alterations, including the following: ERBB2 amplification and mutations; inactivating alterations in BRCA1/2, ATM, PALB2, PTEN, NF1/2 or TSC1/2; activating mutations in PIK3CA and AKT1; FGFR1/2/3 amplification, mutations and fusions; activating mutations and fusions affecting EGF and BRAF; NTRK1 and RET fusions; amplification of CCND1/2/3 or CDK4/6. 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 the clinical care of patients with this often deadly malignancy.

Thank you for your review of this submission.

Sincerely,

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


