ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Breast carcinoma (NOS)

DATE OF BIRTH 20 March 1974
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Hospital Regional Lambayeque
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 319645
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Breast
SPECIMEN ID H21-3840
SPECIMEN TYPE Block
DATE OF COLLECTION 03 April 2019
SPECIMEN RECEIVED 16 February 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

FGFR2 amplification
PTEN deletion exon 8
TP53 splice site 375+1G>A

4 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2, ERBB2, PIK3CA***

4 Therapies with Clinical Benefit
0 Therapies with Lack of Response
20 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***PTEN* - deletion exon 8**	none	Everolimus 2A
10 Trials *see p. 10*		Temsirolimus
***FGFR2* - amplification**	none	Erdafitinib
10 Trials *see p. 8*		Pazopanib

☐ *NCCN category*

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI is extremely rare in breast cancer, reported in 0-1% of cases across studies[6-11]. The incidence of MSI is increased in triple-negative breast cancer[9-11] and in tumors with homologous recombination defects, such as mutations in BRCA1/2[9,11]. Notably, in Lynch syndrome–related breast cancer, MSI has been reported in 51-85% of cases[12-17]. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence[18].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[19]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[19-21]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[22-24]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[19,21,23-24].

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-33]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[25-28,34]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[25]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[35] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[26]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[28,34]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Breast carcinoma harbors a median TMB of 3.8 muts/Mb, and 3.1% of cases have high TMB (>20 muts/Mb)[36]. A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors[37]. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 Muts/Mb for luminal A tumors, 1.38 Muts/Mb for luminal B tumors, 2.05 Muts/Mb for HER2-enriched tumors, and 1.68 Muts/Mb for basal-like tumors[38]. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors[37,39-40]. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma[37,39-40]. In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors[37]. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb[40]. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (>mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data[41].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[42-43] and cigarette smoke in lung cancer[44-45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[48-52], and microsatellite instability (MSI)[48,51-52]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[26-27,34].

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GENE
FGFR2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

FGFR2 activating mutations, amplification, or fusions may confer sensitivity to FGFR-targeting kinase inhibitors such as erdafitinib[53], pemigatinib[54-55], E7090[56], pazopanib[57-58], ponatinib[59], AZD4547[60-62], derazantinib[61-62], Debio-1347[63], infigratinib[64], and futibatinib[65]. In the context of FGFR2 amplification, clinical benefit has been reported for patients with breast cancer treated with erdafitinib[66] and infigratinib[64]. In a Phase 2 study of the FGFR inhibitor AZD4547, responses were reported in 33% (3/9) of patients with FGFR2-amplified gastroesophageal cancer; in this study, higher-level amplification correlated with higher likelihood of response to FGFR inhibitors[60]. However, a randomized Phase 2 study of AZD4547 compared with paclitaxel for the treatment of patients with advanced stomach adenocarcinoma harboring FGFR2 amplification or polysomy reported no significant increase in median PFS, median OS, or ORR[61].

FREQUENCY & PROGNOSIS

FGFR2 amplification has been reported in breast cancer at frequencies ranging from 1-12%[67-70]. FGFR2 protein expression has been reported in 13% of triple-negative breast cancer cases[70] and in ~60% of invasive ductal carcinomas[71]. In a study of 125 patients with invasive ductal carcinoma, high-level FGFR2 protein expression was associated with decreased overall and disease-free survival[71] and a meta-analysis of over 11,000 patients with breast cancer showed a significant association between FGFR2/3 expression and reduced overall survival[72]. In contrast, a study of triple-negative breast cancer showed no correlation between FGFR2 amplification or overexpression with survival[70].

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[73-74]. FGFR2 amplification has been reported in a variety of cancer types[75] and has been shown to correlate with increased mRNA and protein expression[60,76]. Higher level, clonal FGFR2 amplification has been reported to correlate with higher response rates to FGFR inhibitors[60,77].

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GENE
PTEN

ALTERATION
deletion exon 8

POTENTIAL TREATMENT STRATEGIES

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[78-82] such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)[83-85], and PI3K-beta-selective inhibitors are in clinical trials for PTEN-deficient tumors. However, the NCI-MATCH Phase 2 study observed limited activity of the PI3K-betaselective inhibitor GSK2636771 as monotherapy in PTEN-deficient cancers, with a median PFS of 1.8 months. The best outcomes were 1 PR (1/22, prostate cancer), SD (7/22) for patients with PTEN deletion/mutation, and SD (9/34) for patients with PTEN protein loss[86]. Clinical data in breast[87-88] and prostate cancer[89-90] suggest that PTEN alterations may predict sensitivity to pan-AKT inhibitors such as ipatasertib or capivasertib. Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR=0.44) or capivasertib (9.3 vs. 3.7 months, HR=0.30) to paclitaxel, compared with paclitaxel and placebo, for patients with metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations[91]. However, data from the Phase 2 LOTUS trial reported an improved PFS for patients with PIK3CA/AKT1/PTEN-altered triple negative breast cancer treated with ipatasertib plus paclitaxel compared to paclitaxel alone (9.0 vs 4.9 months)[92]; however, the Phase 3 IPATunity130 trial did not report a significant PFS improvement for first-line ipatasertib in combination with paclitaxel relative to paclitaxel alone (7.4 vs 6.1 months)[93]. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[94-98], and clinical benefit has been observed for patients with PTEN-altered breast cancer[99], ovarian cancer[100], endometrial cancer[98], and other tumor types[101] treated with PARP inhibitors. However, several studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[97,102-103]. Limited clinical evidence in glioblastoma[104], leiomyosarcoma[105], NSCLC[106], and melanoma[107] suggests that PTEN alterations may predict a lack of response to anti-PD-1 therapy. In an analysis of 39 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression[107]. In a retrospective analysis of 66 patients with glioblastoma, tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations[104]. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss[105]. A patient with NSCLC whose tumor harbored a PTEN alteration exhibited a lack of response to nivolumab and pembrolizumab[106]. Clinical and preclinical evidence suggests that PTEN loss or mutation may predict resistance to PI3K inhibitors[108-110], and to CDK inhibitors such as palbociclib, ribociclib, and abemaciclib[108,111].

FREQUENCY & PROGNOSIS

In the TCGA dataset, PTEN mutation has been reported in 4% of breast invasive carcinomas, while putative homozygous deletion of PTEN has been reported in 2% of cases[38]. PTEN mutation has also been observed in 5.3% (1/19) of metaplastic breast cancers[112] and 2% of invasive lobular carcinoma tumors analyzed[113]. PTEN mutations are associated more frequently with triple-negative breast cancer than with HER2- or hormone-positive breast cancer[114-115]. Loss or reduction of PTEN expression has been observed in 28% of invasive ductal breast carcinomas and has been correlated with metastasis and poor patient prognosis, including decreased 2-year disease-free survival[116-118].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[80]. Alterations such as seen here may disrupt PTEN function or expression[119-159].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[160-161]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[160,162]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[160]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

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GENE
TP53

ALTERATION
splice site 375+1G>A

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
375+1G>A

VARIANT ALLELE FREQUENCY (% VAF)
32.0%

POTENTIAL TREATMENT STRATEGIES

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[163-166], or p53 gene therapy and immunotherapeutics such as SGT-53[167-171] and ALT-801[172]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[173]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[174]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[175]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[176]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[177]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[178]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[171]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[179]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[180-181]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[182-183]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in breast cancer; mutations in this gene have been identified in 27-37% of breast carcinoma samples[38,184-188]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[186,189-190]. TP53 mutation is also implicated in breast cancer susceptibility, as TP53 mutation carriers have an 18-60 fold increased risk for early onset breast cancer[191-193].

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[194-199]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[194-195]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[200]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[198,201-202]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[203]. Alterations such as seen here may disrupt TP53 function or expression[204-208].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[209-211], including sarcomas[212-213]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[214] to 1:20,000[213]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[215]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Erdafitinib

Assay findings association

FGFR2
amplification

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence for FGFR2 fusions[53,216-217] , limited evidence for FGFR2 mutations[217-218] and limited evidence for FGFR2 amplification[66], and preclinical data[219-220] , FGFR2 activating alterations may confer sensitivity to erdafitinib.

SUPPORTING DATA

Clinical data on the efficacy of erdafitinib for the treatment of breast cancer are limited (PubMed, Feb 2021).

Erdafitinib has been primarily studied for the treatment of FGFR-altered urothelial carcinoma. A Phase 2 study evaluating erdafitinib for the treatment of patients with metastatic or unresectable urothelial carcinoma (mUC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an ORR of 40% (40/99, 3 CR), and a DCR of 80% (79/99)[221]. A Phase 1 trial of erdafitinib reported clinical responses in for patients with various FGFR2- or FGFR3-altered solid tumors[53,218,222-223] , including cholangiocarcinoma (27% ORR, 3/11), NSCLC (5% ORR, 1/21), breast (9% ORR, 3/34), and ovarian (9% ORR, 1/11), while other cancers including endometrial carcinoma and glioblastoma showed a low ORR (2%, 1/58)[66]. Following progression on multiple other lines of therapy, a patient with metastatic FGFR2-fusion-positive NSCLC treated with erdafitinib exhibited an 11-month PR[222].

Everolimus

Assay findings association

PTEN
deletion exon 8

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

PTEN inactivation may predict benefit from mTOR inhibitors, such as everolimus, based on clinical data in various tumor types. For patients with prostate cancer, PTEN loss correlated with response to single-agent everolimus[224]. Retrospective clinical data suggest that patients with advanced breast cancer and PTEN inactivation, particularly in the context of HER2-positive disease, may benefit from everolimus combined with targeted therapy and/or chemotherapy[225-227] .

SUPPORTING DATA

In an exploratory cohort of the BOLERO-2 Phase 3 study, the addition of everolimus to exemestane in the first line for hormone receptor-positive (HR+), HER2-negative (HER2-) breast cancer improve the median PFS compared to exemestane alone (11.5 vs. 4.1 months, HR = 0.39)[228]. Everolimus combined with exemestane as second-line therapy in the same setting also improved the median PFS compared with exemestane in BOLERO-2 (7.8 vs. 3.2 months, HR = 0.45)[229-231] , and modestly improved the median PFS compared with everolimus alone in BOLERO-6 (8.4 vs. 6.8 months, HR = 0.74)[232]. Patients with HR+, HER2- breast cancer also benefited from everolimus combined with other antiestrogen therapies, including letrozole, tamoxifen, and anastrozole[226,233-234] . For patients with HR+, HER- breast cancer who progressed on antiestrogen therapies, addition of everolimus to the most recent endocrine therapy showed efficacy with 8% ORR and median PFS of 6.6 months[235]. For patients with HER2+ breast cancer, everolimus combined with trastuzumab plus paclitaxel did not significantly improve median PFS in the full study population (15.0 months with everolimus vs. 14.5 months with placebo), but increased PFS in the HR-negative subpopulation (20.3 vs. 13.1 months)[236]. For patients with trastuzumab-resistant HER2+ breast cancer, the addition of everolimus to trastuzumab plus vinorelbine prolonged median PFS (7.0 vs. 5.8 months)[237]. Patients with metastatic triple-negative breast cancer treated with everolimus plus carboplatin achieved a clinical benefit rate of 36% (9/25)[238]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[239], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[240].

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Pazopanib

Assay findings association

FGFR2
amplification

AREAS OF THERAPEUTIC USE

Pazopanib is a tyrosine kinase inhibitor that targets VEGFRs, PDGFRs, FGFRs, KIT, ITK, LCK, and c-FMS. It is FDA approved for the treatment of advanced renal cell carcinoma and soft tissue sarcomas that have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

FGFR2 amplification may predict sensitivity to pazopanib. In a Phase 2 study of pazopanib plus capecitabine and oxaliplatin for the treatment of patients with advanced gastric cancer, 6/7 patients with FGFR2 protein expression exhibited a PR, and PFS was significantly improved in patients with FGFR2 expression than in those without (8.5 vs. 5.6 months, p=0.050)[241].

SUPPORTING DATA

A Phase 2 clinical trial of pazopanib in breast cancer reported 55% disease stabilization[242]. A Phase 2 study of heavily pretreated post-menopausal hormone receptor positive (HR+) breast cancer treated with a combination of pazopanib and nonsteroidal aromatase inhibitor reported 7% partial responses (PRs; 2/28) and 18% stable diseases (SDs; 5/28), with 7 patients having progression-free survival (PFS) greater than 6 months[243]. Phase 2 clinical trials of pazopanib with lapatinib in patients with HER2-positive breast cancer reported that the combination was associated with higher response rate than lapatinib alone but did not bring about an increase in PFS[244-245] . A multicenter single-arm Phase 2 study evaluating pazopanib combined with paclitaxel as neoadjuvant following doxorubicin/cyclophosphamide reported complete responses in 9% (6/67) and 38% (10/26) of patients with HR+ and triple-negative locally advanced breast cancer cases, respectively; however, a high level of toxicity led to discontinuation of pazopanib in 61% of patients[246].

Temsirolimus

Assay findings association

PTEN
deletion exon 8

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

PTEN inactivation may predict benefit from mTOR inhibitors, such as temsirolimus, based on clinical data in various tumor types. Out of 10 patients with metaplastic breast cancer and PTEN alterations, 2 cases responded to temsirolimus or everolimus plus doxorubicin and bevacizumab[247-248] . Temsirolimus achieved SD for 6/7 patients with PTEN-deficient cervical carcinoma[249]. Clinical studies in renal cell carcinoma[250-251] , glioblastoma[252-253] , or endometrial cancer[254-257] did not observe a correlation of PTEN deficiency with response to temsirolimus, although several patients with those tumor types and PTEN loss have benefited from mTOR inhibitors.

SUPPORTING DATA

A Phase 1 trial examining the combination of temsirolimus, liposomal doxorubicin, and bevacizumab in 74 patients with breast and gynecological malignancies reported that 37.9% of patients experienced either a CR (1.4%), PR (18.9%), or SD (17.6%); among 25 patients with PIK3CA mutation or PTEN loss, 52% experienced a CR, PR (36%), or SD (16%)[258]. Another Phase 1 trial including patients with several types of cancer reported a 42% incidence of complete or partial responses in patients with metastatic breast cancer[259]. However, a Phase 2 study of temsirolimus in pretreated patients with metastatic breast cancer reported minimal clinical activity and no association with PTEN protein or PIK3CA mutation status[260]. A Phase 3 placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer was terminated at the second interim since the addition of temsirolimus to letrozole did not improve PFS as a first-line therapy[261]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[248].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
FGFR2

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR2.

ALTERATION
amplification

NCT04083976

PHASE 2

A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations

TARGETS
FGFRs

LOCATIONS: San Salvador De Jujuy (Argentina), Cordoba (Argentina), Ijuí (Brazil), Ciudad Autónoma de Buenos Aires (Argentina), Buenos Aires (Argentina), Capital Federal (Argentina), Ciudad Autonoma de Buenos Aires (Argentina), Barretos (Brazil), La Plata Lpl Lpl (Argentina), Curitiba (Brazil)

NCT04042116

PHASE 1/2

A Study to Evaluate Lucitanib in Combination With Nivolumab in Patients With a Solid Tumor

TARGETS
FGFRs, VEGFRs, PD-1

LOCATIONS: Florida, North Carolina, Tennessee, Oklahoma, Ohio, Pennsylvania, New York, Massachusetts, Colorado, California

NCT03797326

PHASE 2

Efficacy and Safety of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) in Previously Treated Participants With Select Solid Tumors (MK-7902-005/E7080-G000-224/LEAP-005)

TARGETS
PD-1, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Florida, Tennessee, New Jersey, New York, Toronto (Canada), Wisconsin, South Dakota, Quebec (Canada), Winnipeg (Canada), California

NCT04024436

PHASE 2

A Study of TAS-120 in Patients With Metastatic Breast Cancer

TARGETS
FGFRs, ER

LOCATIONS: Florida, Texas, Tennessee, Missouri

NCT03992131

PHASE 1/2

A Study to Evaluate Rucaparib in Combination With Other Anticancer Agents in Patients With a Solid Tumor (SEASTAR)

TARGETS
PARP, FGFRs, VEGFRs, TOP1

LOCATIONS: Texas, Tennessee, Massachusetts

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NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, KIT, PDGFRA, RET, VEGFRs, PD-1

LOCATIONS: Texas, Missouri, Ohio, New York, New Jersey, Michigan, Hamilton (Canada), Toronto (Canada), Ottawa (Canada), California

NCT04233567

PHASE 2

Infigratinib for the Treatment of Advanced or Metastatic Solid Tumors in Patients With FGFR Gene Mutations

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Ohio

NCT02691767

PHASE NULL

Study to Evaluate the Safety and Efficacy of Pazopanib, in Subject With Refractory Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

NCT02450136

PHASE NULL

Single-arm Study to Evaluate the Safety and Efficacy of Pazopanib, in Subjects With FGFR2 Amplification, FGFR2 Mutation Refractory Solid Tumors

TARGETS
FGFR1, FGFR2, FGFR3, KIT, VEGFRs

LOCATIONS: Seoul (Korea, Republic of)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

LOCATIONS: Kashiwa (Japan), Chuo-Ku (Japan)

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GENE
PTEN

ALTERATION
deletion exon 8

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04305496

PHASE 3

Capivasertib+Fulvestrant vs Placebo+Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic HR+/HER2– Breast Cancer

TARGETS
ER, AKTs

LOCATIONS: Lima (Peru), Arequipa (Peru), La Rioja (Argentina), Rosario (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Viedma (Argentina), Florida, Georgia, Tennessee

NCT04191135

PHASE 2/3

Study of Olaparib Plus Pembrolizumab Versus Chemotherapy Plus Pembrolizumab After Induction With First-Line Chemotherapy Plus Pembrolizumab in Triple Negative Breast Cancer (TNBC) (MK-7339-009/KEYLYNK-009)

TARGETS
PD-1, PARP

LOCATIONS: Cali (Colombia), Medellin (Colombia), La Serena (Chile), Monteria (Colombia), Vina del Mar (Chile), Santiago (Chile), Barranquilla (Colombia), Temuco (Chile), Florida, Texas

NCT03997123

PHASE 3

Capivasertib+Paclitaxel as First Line Treatment for Patients With Locally Advanced or Metastatic TNBC

TARGETS
AKTs

LOCATIONS: Rosario (Argentina), Londrina (Brazil), Goiania (Brazil), São José do Rio Preto (Brazil), Mar del Plata (Argentina), Caba (Argentina), Ciudad Autonoma De Buenos Aire (Argentina), Ciudad Autónoma de Bs. As. (Argentina), Barretos (Brazil), La Plata (Argentina)

NCT04060862

PHASE 3

A Study of Ipatasertib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Hormone Receptor Positive and HER2 Negative Locally Advanced Unresectable or Metastatic Breast Cancer

TARGETS
AKTs, CDK4, CDK6, ER

LOCATIONS: Porto Alegre (Brazil), Georgia, New Jersey, Hamilton (Canada), Calgary (Canada), Barcelona (Spain), Manchester (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Malvern (Australia)

NCT03598257

PHASE 2

Radiation Therapy With or Without Olaparib in Treating Patients With Inflammatory Breast Cancer

TARGETS
PARP

LOCATIONS: San Juan (Puerto Rico), Florida, Louisiana, Georgia, Texas, South Carolina

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Florida, Louisiana, Texas

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NCT02498613

PHASE 2

A Phase 2 Study of Cediranib in Combination With Olaparib in Advanced Solid Tumors

TARGETS
PARP, VEGFRs

LOCATIONS: Florida, Texas, Tennessee, Virginia, Connecticut, Massachusetts, Toronto (Canada), California

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Texas, Connecticut, Newcastle upon Tyne (United Kingdom)

NCT03939897

PHASE 1/2

Testing the Addition of Copanlisib to Usual Treatment (Fulvestrant and Abemaciclib) in Metastatic Breast Cancer - Dose-Finding Study

TARGETS
PI3K, CDK4, CDK6, ER

LOCATIONS: Alabama, Kentucky, Missouri, Ohio, New York, California

NCT03280563

PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Hormone Receptor (HR)-Positive Human Epidermal Growth Factor Receptor 2 (HER2)-Negative Breast Cancer

TARGETS
PD-L1, ER, HDAC, AKTs, CDK4, CDK6

LOCATIONS: North Carolina, Tennessee, Maryland, Pennsylvania, New York, Illinois, California

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NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

AXIN1
R298Q

CIC
P1551A

CTNNB1
E477Q

EPHB1
E65K

FANCC
I290V

FH
F225S

KMT2A (MLL)
A53V

LTK
I662T

MAF
L380M

MAP3K1
L78P

MERTK
E712D

NSD3 (WHSC1L1)
A1293V

RET
Q70R

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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics

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of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31

INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters with no conflicts), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *BAP1, BRCA1, BRCA2, BRIP1, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

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The median exon coverage for this sample is 937x

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531