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 03 March 1966
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 14-12829 (H21-243)
SPECIMEN TYPE Block
DATE OF COLLECTION 07 March 2014
SPECIMEN RECEIVED 24 January 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 5 Muts/Mb

Genomic Findings

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

BRCA1 E111fs*3
MYC amplification - equivocal†
RAD21 amplification - equivocal†
TP53 I255F

† See About the Test in appendix for details.

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

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 5 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)
***BRCA1* -** E111fs*3	Olaparib	1	Niraparib
10 Trials *see p. 10*	Talazoparib	1	Rucaparib
***MYC* -** amplification - equivocal	none		none
7 Trials *see p. 12*			

1 *NCCN category*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic data and were detected at an allele frequency of >10%. See appendix for details.

***BRCA1* -** E111fs*3 ..... p. 4

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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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.

RAD21 - amplification - equivocal ..... p. 5

TP53 - I255F ..... p. 6

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
5 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
BRCA1

ALTERATION
E111fs*3

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
329_330insA

VARIANT ALLELE FREQUENCY (% VAF)
25.8%

POTENTIAL TREATMENT STRATEGIES

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[53-70] or to ATR inhibitors[71-72]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[54,59,62,69-70] and for patients with platinum-resistant or -refractory disease[53,58,65,68]. In a Phase 1 monotherapy trial of the WEE1 inhibitor adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression[73]. The PARP inhibitors talazoparib and olaparib have shown significant clinical efficacy for patients with HER2-negative advanced breast cancer and a germline BRCA mutation in Phase 3 studies[56,74]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and either platinum-refractory peritoneal or ovarian carcinoma experienced a PR or prolonged SD[75]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[71]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[76]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[77]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[78], ovarian carcinoma[79], and TNBC[80] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[81-90].

FREQUENCY & PROGNOSIS

In the Breast Invasive Carcinoma TCGA datasets, BRCA1 mutations have been reported in 2-4% of cases[38,91]. A study of patients with sporadic breast cancer identified BRCA1 mutation in 9.3% (4/43) of cases[92]. BRCA1 mutations account for approximately 4.6-7% of breast cancer cases in patients with a family history of breast cancer[93-94]. A study reported decreased nuclear BRCA1 protein expression in breast carcinoma samples (n=22), as compared to normal breast tissue[95]. For BRCA1 and BRCA2 mutation carriers, the risk of developing breast cancer by age 70 has been found to be approximately 57-65% and 39-49%, respectively, and a lifetime risk of up to 90% has also been reported[96-98].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[99]. Alterations such as seen here may disrupt BRCA1 function or expression[100-102].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the BRCA1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2020)[103]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[104-105], and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[106]. Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%[107]. The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population[106,108-113]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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GENE
MYC

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no available therapies that directly target MYC. However, preclinical data indicate that MYC overexpression may predict sensitivity to investigational agents targeting CDK1[114-115], CDK2[116], Aurora kinase A[117-124], Aurora kinase B[125-128], glutaminase[129-132], or BET bromodomain-containing proteins[133-136], as well as agents targeting both HDAC and PI3K[137-139]. A Phase 2 study reported a PFS benefit associated with a combination of the Aurora A kinase inhibitor alisertib and paclitaxel as second-line therapy for patients with MYC-overexpressed small cell lung cancer but not for patients without MYC overexpression[140]. A patient with MYC-amplified invasive ductal breast carcinoma experienced a PR to an Aurora kinase inhibitor[141]. The glutaminase inhibitor CB-839, in combination with either everolimus or cabozantinib, has demonstrated encouraging efficacy in Phase 1 and 2 studies enrolling patients with pretreated advanced renal cell carcinoma[142-143] . MYC amplification has also been suggested to predict response to chemotherapy in patients with breast cancer in some studies[144-145]. Preclinical evidence suggests that colon cancer cells with MYC amplification may be more sensitive to 5-fluorouracil and paclitaxel[146-147].

FREQUENCY & PROGNOSIS
In the TCGA dataset, MYC amplification was observed in 15% of breast invasive carcinoma cases[38]. MYC amplification has been associated with an aggressive phenotype, early onset, and poor prognosis in patients with breast cancer, although the data have been conflicting[144,148-150].

FINDING SUMMARY
MYC (c-MYC) encodes a transcription factor that regulates many genes related to cell cycle regulation and cell growth. It is an oncogene and may be activated in as many as 20% of cancers[151]. MYC dysregulation (amplification, overexpression, translocation) has been identified in a number of different cancer types[152]. MYC amplification has been significantly linked with increased mRNA and protein levels and results in the dysregulation of a large number of target genes[151,153-154].

GENE
RAD21

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no therapies to target alterations in this gene.

FREQUENCY & PROGNOSIS
RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers[155]. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes[156-157], including sporadic Grade 3 but not Grade 1 cancers[156], as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers[156]. Furthermore, SNPs in or near RAD21 have been linked with risk of breast cancer development[158-159]. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer[160] and in colorectal cancer (CRC), especially in KRAS-mutant CRC[161]. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer[162]. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression[163]. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic[164]. Downregulation of RAD21 expression resulted in sensitization of cultured breast[157,165] and CRC[161] cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

FINDING SUMMARY
RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex[166-169]. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging[170], but also leads to an increase in deletions, insertions, and other rearrangements[171]. High RAD21 expression has also been associated with increased genomic instability[156]. Cohesin complex also organizes chromatin domains and regulates gene expression[172-173]. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression[174]. RAD21 amplification has been correlated with increased expression in breast[156-157,175] and endometrial[160] cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

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GENE
TP53

ALTERATION
I255F

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
763A>T

VARIANT ALLELE FREQUENCY (% VAF)
26.3%

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[176-179], or p53 gene therapy and immunotherapeutics such as SGT-53[180-184] and ALT-801[185]. 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[186]. 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[187]. 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[188]. 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[189]. 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[190]. 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[191]. 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[184]. 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[192]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[193-195]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[196]. 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[197-198]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[199-200]. 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[38,201-205]. TP53 mutations that are located within the region encoding the DNA binding domain are associated with poor prognosis in patients with breast cancer[203,206-207]. 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[208-210]. 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[211-216]. 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[211-212]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[217]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[215,218-219]. 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[220]. Alterations such as seen here may disrupt TP53 function or expression[221-225].

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[226-228], including sarcomas[229-230]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[231] to 1:20,000[230]. 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[232]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Olaparib

Assay findings association

BRCA1
E111fs*3

AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in ovarian cancer[63-67] as well as strong clinical evidence in multiple other cancer types[53-55,63,66,70,233] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

A Phase 3 study of olaparib monotherapy for patients with germline BRCA1/2 (gBRCA1/2) mutated HER2-negative metastatic breast cancer reported a significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (59.9% vs. 28.8%) compared to standard chemotherapy[56]. Phase 2 studies of olaparib monotherapy for patients with BRCA-mutated advanced breast cancer reported median PFS of 3.7 to 5.7 months and high clinical benefit rates (60%–85%)[53,55,66] . The Phase 2 MEDIOLA trial of olaparib with durvalumab for patients with gBRCA1/2-mutated metastatic breast cancer reported an ORR of 63.3% and a median PFS of 8.2 months[234]. A Phase 1 trial of olaparib with the PI3K inhibitor buparlisib reported an ORR of 33.3% (4/12) for patients with gBRCA1/2-mutated breast cancer[235]. A Phase 1 trial of olaparib plus carboplatin for patients with gBRCA1/2-mutated breast cancer reported an ORR of 87.5% (7/8)[236]. Patients with HER2-negative metastatic breast cancer and germline BRCA mutation achieved significantly longer median PFS (7.0 vs. 4.2 months, HR=0.58) and a higher ORR (59.9% vs. 28.8%) on olaparib compared with standard chemotherapy (capecitabine, eribulin, or vinorelbine) in a Phase 3 study[56]. Phase 1 trials of olaparib plus chemotherapy for patients with triple-negative breast cancer (TNBC) reported ORRs of 37% to 38%[237-238] . A small Phase 1 trial reported a 20% ORR (1/5) for patients with breast cancer and wild-type germline BRCA status following combination treatment with olaparib and buparlisib[235]. A Phase 2 study comparing durvalumab in combination with olaparib and paclitaxel (DOP) to chemotherapy alone reported pathologic complete response (pCR) for 37% versus 22% of patients with HER2-negative breast cancer, 47% versus 27% of patients with TNBC, and 28% versus 14% of patients with HR-positive HER2-negative breast cancer[239].

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Talazoparib

Assay findings association

BRCA1
E111fs*3

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data in breast cancer[74,240-241] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[242-245] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

In the Phase 3 EMBRACA trial, patients with HER2-negative advanced breast cancer and germline BRCA mutations achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (63% vs. 27%), and improved quality of life on talazoparib compared with standard chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)[74,241] . Clinical benefit from talazoparib was observed for patients with either triple-negative or hormone receptor-positive (HR+) breast cancer, and for those with CNS metastases[74]. Final OS analysis showed that talazoparib did not significantly improve OS compared with chemotherapy (median OS [mOS] 19.3 vs. 19.5 months, HR=0.85) but did significantly delay definitive clinically meaningful deterioration in global health status/quality of life[246]. Retrospective genomic analysis showed that MYC amplification was associated with significantly shorter mOS for patients with triple-negative cancer treated with talazoparib, but not for those treated with chemotherapy; in contrast, for patients with HR+ cancer, MYC amplification was associated with shorter mOS for the chemotherapy treatment group, but not for the talazoparib treatment group[247]. The efficacy of single-agent talazoparib for the treatment of BRCA-mutated advanced breast cancer was also demonstrated in earlier-phase studies, which reported ORRs of 21%-50%[240,243]. As neoadjuvant treatment for BRCA-mutated HER2-negative breast cancer, talazoparib led to a pathologic complete response (pCR) for 53% (10/19) of patients[248]. In the Phase 2 I-SPY2 trial, talazoparib with synergy-dosed irinotecan (TI) for patients with early stage, high-risk HER2-negative breast cancer reported fewer Grade 3/4 adverse events compared with the chemotherapy control arm (paclitaxel with doxorubicin and cyclophosphamide [AC]), although a similar pCR rate was observed[249]. Notably, 6/10 patients with germline BRCA mutations achieved a pCR with TI treatment[249]. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, those with HER2-negative advanced breast cancer experienced an ORR of 31% (4/13 PRs), with responses observed for 3 patients with germline PALB2 mutations and for 1 patient with germline CHEK2 and FANCA mutations as well as somatic PTEN mutation; 3 additional patients with germline PALB2 or somatic ATR or PTEN alterations had SD ≥6 months[250].

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Niraparib

Assay findings association

BRCA1
E111fs*3

AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in ovarian and breast cancers[57-58,251] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

In a Phase 1 study of niraparib treatment for patients with solid tumors, 2/4 patients with breast cancer and BRCA1/2 mutations experienced a PR[58]. An open label study combining PD-1 inhibitor pembrolizumab with niraparib for patients with TNBC reported an ORR of 21% and DCR of 49%; ORR and DCR for patients with BRCA alterations were 47% and 80%, respectively, with 2 CRs, 5 PRs, 5 SDs and mPFS of 8.3 months[252].

Rucaparib

Assay findings association

BRCA1
E111fs*3

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence in ovarian cancer[59-60,187] , as well as clinical data in other cancer types[60,253-254] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and BRCA1/2 mutations, no objective responses were reported in breast cancer patients[60]. However, 39% (9/23) of evaluable patients with breast cancer achieved stable disease lasting 12 weeks or more[60]. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 1 patient with breast cancer and a BRCA mutation given the recommended Phase 2 dose reported an objective response[253].

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
BRCA1

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

ALTERATION
E111fs*3

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

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

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Florida, Texas, Georgia, Alabama, North Carolina, Virginia, Oklahoma, Pennsylvania, Indiana

NCT04171700

PHASE 2

A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes

TARGETS
PARP

LOCATIONS: Florida, Tennessee, Texas, Oklahoma, Pennsylvania, New York

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

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ORDERED TEST # ORD-1002562-01

CLINICAL TRIALS

NCT02849496

PHASE 2

Olaparib With or Without Atezolizumab in Treating Patients With Locally Advanced or Metastatic Non-HER2-Positive Breast Cancer

TARGETS
PD-L1, PARP

LOCATIONS: Florida, North Carolina, Texas, Tennessee, Maryland, Missouri, Ohio

NCT03188965

PHASE 1

First-in-human Study of ATR Inhibitor BAY1895344 in Patients With Advanced Solid Tumors and Lymphomas

TARGETS
ATR

LOCATIONS: Florida, Texas, Georgia, Virginia, Pennsylvania, New York, Ohio, Massachusetts

NCT02595931

PHASE 1

ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
ATR

LOCATIONS: Florida, North Carolina, Tennessee, Missouri, Pennsylvania, Connecticut, Massachusetts, California

NCT04041128

PHASE NULL

PARP Inhibition During Pre-surgical Window in Breast/Ovary Cancer

TARGETS
PARP

LOCATIONS: Texas

NCT02810743

PHASE 3

Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer

TARGETS
PARP

LOCATIONS: Rotterdam (Netherlands), Leiden (Netherlands), Amsterdam (Netherlands), Utrecht (Netherlands), Maastricht (Netherlands), Nijmegen (Netherlands), Enschede (Netherlands), Groningen (Netherlands)

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GENE
MYC

ALTERATION
amplification - equivocal

RATIONALE
MYC amplification may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, including Aurora kinase A and B, and of BET domain proteins, which are reported to downregulate MYC expression and MYC-dependent transcriptional programs.

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Florida, Texas, Virginia, New York, Arizona

NCT03901469

PHASE 2

A Study of ZEN003694 and Talazoparib in Patients With Triple Negative Breast Cancer

TARGETS
BRD2, BRD3, BRD4, BRDT, PARP

LOCATIONS: Texas, Tennessee, Pennsylvania, New York, Kansas, Arizona, Madrid (Spain), Barcelona (Spain), Brussels (Belgium), Leuven (Belgium)

NCT02516553

PHASE 1

BI 894999 First in Human Dose Finding Study in Advanced Malignancies

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Texas, New York, Ohio, Massachusetts, California, Madrid (Spain), Nantes (France), Barcelona (Spain), Villejuif (France), Paris (France)

NCT02419417

PHASE 1/2

Study of BMS-986158 in Subjects With Select Advanced Solid Tumors

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: South Carolina, Massachusetts, Villejuif (France), Lyon Cedex 08 (France), Melbourne (Australia)

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

NCT03654547

PHASE 1

Safety of TT-00420 Monotherapy in Patients With Advanced Solid Tumors and Triple Negative Breast Cancer

TARGETS
Aurora kinase A, Aurora kinase B

LOCATIONS: Texas

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Madrid (Spain), Bordeaux (France), Barcelona (Spain), Villejuif (France), Rozzano (MI) (Italy), Meldola (Italy), Napoli, Campania (Italy), Kashiwa (Japan)

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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.

ATRX
E1464del

FGFR4
I509V

GNAS
S54fs*5

GRM3
D873N

KMT2A (MLL)
A53V

NOTCH1
Q2361K

NT5C2
E561del

PDCD1 (PD-1)
R231Q

SDHA
I319V

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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 502x

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