

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 Ovary clear cell carcinoma	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Ovary
	NAME Chou, Wen-Ping		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S110-65395 I (PF21062)
	DATE OF BIRTH 04 September 1967		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Female		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 18 February 2021
	MEDICAL RECORD # 46754090		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 10 December 2021

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings

Loss of Heterozygosity score - Cannot Be Determined

Microsatellite status - Cannot Be Determined ^α

Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

PIK3CA H1047R

ARID1A R693*

PPP2R1A R183W

TET2 E1151*

2 Disease relevant genes with no reportable alterations: **BRCA1, BRCA2**

† See About the Test in appendix for details.

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with potential clinical benefit approved in another tumor type: Everolimus (p. 8), Temozolomide (p. 8)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 9)
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **TET2** E1151* (p. 7)

BIOMARKER FINDINGS

Loss of Heterozygosity score - Cannot Be Determined

Microsatellite status - Cannot Be Determined

Tumor Mutational Burden - Cannot Be Determined

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
PIK3CA - H1047R	none	Everolimus
10 Trials see p. 11		Temsirolimus
ARID1A - R693*	none	none
8 Trials see p. 9		

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

TET2 - E1151* p. 7

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

PPP2R1A - R183W p. 6 **TET2** - E1151* p. 7

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.

ORDERED TEST # ORD-1255383-01

BIOMARKER FINDINGS

BIOMARKER

Loss of Heterozygosity score

RESULT

Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of emerging clinical data in ovarian cancer, elevated genomic LOH may be associated with greater sensitivity to PARP inhibitors^{1,2}. In platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma, rucaparib elicited significantly longer median PFS (7.2 vs. 5.0 months, HR=0.51) and improved ORR (33.3% vs. 9.6%, p=0.0003) for patients with LOH score ≥ 16%. In the maintenance setting in platinum-sensitive, BRCA1/2 wild-type patients, rucaparib was superior to placebo in both the LOH score ≥ 16% (median PFS, 9.7 vs. 5.4 months; HR=0.44) and LOH score < 16% (median PFS, 6.7 vs. 5.4 months; HR=0.58) cohorts¹. Similar results have been reported for maintenance treatment with niraparib in ovarian cancer³ when using a different measure of HRD that includes genomic

LOH^{4,5}. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer⁶⁻⁸. However, as the LOH score for this sample could not be confidently determined, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

In a study of more than 4,000 ovarian, Fallopian tube, or peritoneal cancer samples, genomic LOH score ≥ 16% was identified in 24.2% of BRCA1/2 wild-type cases, deleterious BRCA1/2 mutation was identified in an additional 17.2% of cases, and the remaining 58.7% of cases had LOH score < 16% and were BRCA1/2 wild-type⁹. Among the histological subtypes, LOH score ≥ 16% or BRCA1/2 mutation was reported in 42.4% of serous carcinomas, 37.6% of endometrioid carcinomas, 23.5% of carcinosarcomas, 20.6% of neuroendocrine carcinomas, 13.6% of clear cell carcinomas, and 8.1% of mucinous carcinomas; in BRCA1/2 wild-type samples, the median LOH score was significantly higher in serous as compared with non-serous cases⁹. In ovarian carcinoma, the median LOH score is significantly higher for BRCA1/2-mutated cases than BRCA1/2 wild-type cases (22.2% vs. 9.8%)⁹, and mutation or methylation of BRCA1, BRCA2, or RAD51C has

been reported to be enriched in cases with increased genomic LOH^{6,10}. One study reported no association between LOH and either tumor stage or grade in ovarian serous carcinoma¹¹. In patients with high-grade serous ovarian carcinoma, the frequency of LOH has been reported to increase significantly with age¹².

FINDING SUMMARY

The loss of heterozygosity (LOH) score is a profile of the percentage of the tumor genome that is under focal loss of one allele²; focal LOH events accumulate as genomic "scars" as a result of incorrect DNA double-strand break repair when the homologous recombination pathway is deficient (HRD)^{6,10,13-14}. HRD and consequent genomic LOH occur as a result of genetic or epigenetic inactivation of one or more of the homologous recombination pathway proteins, including BRCA1, BRCA2, RAD51C, ATM, PALB2, and BRIP1¹³⁻¹⁶. Elevated genomic LOH has been associated with sensitivity to the PARP inhibitor rucaparib in BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma in both the treatment² and maintenance¹ settings. However, the LOH score in this sample could not be determined with confidence.

BIOMARKER

Microsatellite status

RESULT

Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)¹⁷⁻¹⁸ may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab¹⁹⁻²⁴ and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab²⁵⁻²⁷. As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is

unclear.

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples²⁸⁻²⁹, including 3.8% (1/26) of ovarian endometrioid adenocarcinomas³⁰, and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)³¹. No association of MSI-H with stage or survival was found in patients with ovarian cancer^{28,32}.

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 tumor³³. 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 PMS2³³⁻³⁵. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes³³, which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)³⁶. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers³⁶⁻³⁸ and has an estimated prevalence in the general population ranging from 1:600 to 1:2000³⁹⁻⁴¹. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

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Electronically signed by Tyler Janovitz, MD, PhD | 23 December 2021
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ORDERED TEST # ORD-1255383-01

BIOMARKER FINDINGS

BIOMARKER

Tumor Mutational Burden

RESULT

Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1⁴²⁻⁴⁴, anti-PD-1 therapies⁴²⁻⁴⁵, and combination nivolumab and ipilimumab⁴⁶⁻⁵¹. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors^{42-45,52}. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors⁴². Analyses across several solid tumor types reported that patients with higher TMB (defined as $\geq 16-20$

Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy⁵³ or those with lower TMB treated with PD-1 or PD-L1-targeting agents⁴³. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for 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^{45,52}. Together, these studies suggest that patients with TMB ≥ 10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

Ovarian clear cell carcinoma harbors a median TMB of 2.7 mutations per megabase (mut/Mb), and 1.7% of cases have high TMB (> 20 mut/Mb)⁵⁴. In a study of high grade serous ovarian cancer, homologous recombination (HR)-deficient tumors, which comprised $\sim 50\%$ of all samples,

harbored a higher neoantigen load compared to HR-proficient tumors; higher neoantigen load was associated with longer OS but not disease free survival⁵⁵.

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 melanoma⁵⁶⁻⁵⁷ and cigarette smoke in lung cancer^{23,58}, treatment with temozolomide-based chemotherapy in glioma⁵⁹⁻⁶⁰, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁶¹⁻⁶⁵, and microsatellite instability (MSI)^{61,64-65}. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types^{43-45,52}. However, the TMB level in this sample could not be determined with confidence.

ORDERED TEST # ORD-1255383-01

GENOMIC FINDINGS

GENE

PIK3CA

ALTERATION

H1047R

TRANSCRIPT ID

NM_006218

CODING SEQUENCE EFFECT

3140A>G

VARIANT ALLELE FREQUENCY (% VAF)

5.0%

study⁷⁹. A separate Phase 1b study of taselisib in combination with the CDK4/6 inhibitor palbociclib for patients with PIK3CA-mutated solid tumors reported an ORR of 0% (n=12) and a DCR of 17% (2/12)⁸⁰. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control (3 PRs, 8 SDs)⁸¹. The PI3K inhibitor alpelisib demonstrated an ORR of 6.0% (8/134) and a DCR of 58% (78/134) in a study for patients with PIK3CA-mutated solid tumors⁸². However, the PI3K inhibitor copanlisib exhibited limited efficacy in PIK3CA-mutated tumors⁸³⁻⁸⁴.

ovarian clear cell carcinomas reported an association of coexistent alterations in ARID1A and PIK3CA with poor prognosis⁸⁸. There are differing reports on the impact of PIK3CA alteration on prognosis in patients with ovarian carcinoma; PIK3CA mutation or overexpression was associated with favorable survival in patients with ovarian clear cell carcinoma⁸⁹⁻⁹⁰, whereas PIK3CA amplification has been associated with higher grade ovarian tumors⁹¹⁻⁹³ and with shorter survival in patients with ovarian cancer in general⁹⁴⁻⁹⁷.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K⁶⁶⁻⁶⁸, AKT⁶⁹⁻⁷⁰, or mTOR⁷¹⁻⁷⁸. In the Phase 2 MATCH trial for patients with PIK3CA-mutated solid tumors, 28% (18/65) of patients experienced PFS lasting at least 6 months after treatment with taselisib; however, no ORs were observed in this

FREQUENCY & PROGNOSIS

PIK3CA mutation frequency is variable among different subtypes of ovarian cancer. Mutations were detected in 33% of clear cell carcinomas and in 12% of advanced epithelial ovarian carcinomas; however, PIK3CA mutations were detected in 3% of high-grade serous ovarian cancers and in fewer than 1% of tumors in the TCGA Ovarian Serous Cystadenocarcinoma dataset^{15,85-87}. A study of

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival⁹⁸⁻⁹⁹. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic¹⁰⁰⁻¹²⁰.

ORDERED TEST # ORD-1255383-01

GENOMIC FINDINGS

GENE

ARID1A

ALTERATION

R693*

TRANSCRIPT ID

NM_006015

CODING SEQUENCE EFFECT

2077C>T

VARIANT ALLELE FREQUENCY (% VAF)

5.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib¹²¹. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib

combined with olaparib¹²². One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan¹²³. In a Phase 1 trial, a patient with metastatic colorectal cancer harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months¹²⁴. On the basis of limited preclinical evidence from studies in ovarian cancer, ARID1A inactivation may predict sensitivity to EZH2 inhibitors¹²⁵⁻¹²⁶, which are under investigation in clinical trials. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway¹²⁷⁻¹²⁹. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy¹³⁰. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma¹³¹⁻¹³² and to 5-fluorouracil in colorectal cancer cell lines¹³³.

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported

in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2021)¹³⁴⁻¹⁴². ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas^{130,130,143-145}, CRC^{130,146-148}, and gastric cancer^{130,149-153}. Several studies have reported no correlation between ARID1A loss and clinicopathological parameters in ovarian clear cell or endometrioid carcinomas or other endometrial cancers¹⁵⁴⁻¹⁵⁷, whereas others suggest that ARID1A loss is a negative prognostic factor^{132,158}.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor^{138,152,159-165}. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss^{138,150,160-161,166}, whereas ARID1A missense mutations are mostly uncharacterized.

GENE

PPP2R1A

ALTERATION

R183W

TRANSCRIPT ID

NM_014225

CODING SEQUENCE EFFECT

547C>T

VARIANT ALLELE FREQUENCY (% VAF)

3.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to directly address genomic alterations in PPP2R1A. Activation of PP2A with forskolin or the

sphingosine analogue FTY720 has been shown to be beneficial in the context of CML and ALL¹⁶⁷, and is being investigated in solid tumors of the lung, breast, and colon¹⁶⁸⁻¹⁷⁰. In addition, other agents have been shown to upregulate PP2A activity in the context of various tumors¹⁷¹. However, the efficacy of these compounds in the context of PPP2R1A mutations has not yet been evaluated (PubMed, 2021).

FREQUENCY & PROGNOSIS

PPP2R1A mutations have been reported in several subtypes of ovarian and uterine carcinoma, most frequently in uterine serous carcinoma (up to 26%) (COSMIC, cBioPortal, 2021)¹³⁴⁻¹³⁶. In addition, concurrent mutations in PPP2R1A, PIK3CA, and TP53 have been reported in cases of uterine serous carcinoma, and were also found in associated serous endometrial intraepithelial carcinomas,

suggesting the alterations arose early in the pre-invasive stage of the disease¹⁷². PPP2R1A mutations have been reported in 9/42 carcinosarcoma samples analyzed¹⁷³.

FINDING SUMMARY

PPP2R1A encodes a regulatory subunit of protein phosphatase 2 (PP2A), which is involved in regulation of the cell cycle transition from mitosis to interphase¹⁷⁴. A spatially constrained pattern of somatic missense alterations in PPP2R1A, clustered around codons 179, 182, and 256, has been documented^{172-173,175-177}. Although the functional consequences of these PPP2R1A alterations have not been clearly characterized, they are presumed to disrupt binding of the PP2A regulatory and catalytic subunits, dysregulating normal PP2A function and cell cycle progression¹⁷⁶.

ORDERED TEST # ORD-1255383-01

GENOMIC FINDINGS
GENE
TET2
ALTERATION

E1151*

TRANSCRIPT ID

NM_017628

CODING SEQUENCE EFFECT

3451G>T

VARIANT ALLELE FREQUENCY (% VAF)

49.5%

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2021)¹³⁵⁻¹³⁶. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2021).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation¹⁷⁸⁻¹⁷⁹. Alterations such as seen here may disrupt TET2 function or expression¹⁸⁰⁻¹⁸⁴.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

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 expansion¹⁸⁵⁻¹⁹⁰. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹⁸⁵⁻¹⁸⁶. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease¹⁹¹. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{189,192-193}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1255383-01

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Everolimus

Assay findings association
PIK3CA
H1047R

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

On the basis of clinical evidence⁷¹⁻⁷⁸, PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors^{75-78,194-198}.

SUPPORTING DATA

A Phase 1 clinical trial of everolimus in combination with bevacizumab and panitumumab in patients with advanced

solid tumors reported long-term disease control in three patients with ovarian cancer¹⁹⁹. In a Phase 1 clinical trial of everolimus in combination with chemotherapy regimens in patients with solid tumors, complete responses were experienced by 2/27 patients, including one patient with primary peritoneal carcinoma and one patient with pancreatic cancer, and partial responses were experienced by 3 additional patients²⁰⁰. However, a Phase 2 trial of 150 patients with primary peritoneal cancer, epithelial ovarian cancer, or Fallopian tube cancer reported that the addition of everolimus to bevacizumab did not significantly increase overall patient survival, and may have contributed to reduced therapy tolerability²⁰¹. A case study of a patient with platinum-resistant recurrent ovarian clear cell carcinoma reported achievement of stable disease in response to everolimus monotherapy²⁰². 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 tumors²⁰³, 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 months²⁰⁴.

Temsirolimus

Assay findings association
PIK3CA
H1047R

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

On the basis of clinical evidence⁷¹⁻⁷⁸, PIK3CA activating mutations may predict sensitivity to mTOR inhibitors such as everolimus and temsirolimus. Studies have reported modest activity of these therapies as single agents (ORRs of 0-4%), but improved activity has been observed when they are combined with other agents such as bevacizumab and doxorubicin (ORRs of 25-44%), for patients with PIK3CA-mutated solid tumors^{75-78,194-198}.

SUPPORTING DATA

Phase 2 studies have reported limited efficacy for single-agent temsirolimus in genomically unselected recurrent or platinum-refractory ovarian cancer; 24% (13/54) of patients experienced progression-free survival (PFS) for 6 months or more²⁰⁵⁻²⁰⁶. A Phase 2 study of temsirolimus

in ovarian clear cell carcinoma (OCCC) reported responses in 14% (3/22) of patients treated with single-agent temsirolimus; in addition, 5% (1/21) complete response (CR), 10% (2/21) partial response (PR), and 29% (6/21) stable disease (SD) lasting more than 3 months were reported in patients treated with temsirolimus in combination with trabectedin²⁰⁷. Treatment of OCCC with temsirolimus in combination with carboplatin and paclitaxel followed by temsirolimus consolidation therapy elicited an ORR of 63% (19/30), median PFS of 12 months, and median overall survival of 25 months²⁰⁸. A Phase 1 trial of temsirolimus combined with liposomal doxorubicin and bevacizumab in patients with breast and gynecological malignancies reported 1% (1/74) CR, 19% (14/74) PR, and 18% (13/74) SD rates⁷⁸. A Phase 1 study of temsirolimus in combination with bevacizumab reported that 62% (8/13) of patients with ovarian or primary peritoneal serous carcinoma achieved SD for more than 6 months²⁰⁹. Combination therapy with paclitaxel, bevacizumab, and temsirolimus in advanced solid tumors achieved 1 PR lasting 6 months and 1 SD lasting 18 months for ovarian cancer²¹⁰.

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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Electronically signed by Tyler Janovitz, MD, PhD | 23 December 2021
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1255383-01

CLINICAL TRIALS

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](https://www.foundationmedicine.com/genomic-testing#support-services). Or visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
ARID1A
RATIONALE
 ARID1A loss or inactivation may predict sensitivity to ATR inhibitors. On the basis of

preclinical evidence, ARID1A loss or inactivation may predict sensitivity to EZH2 inhibitors.

ALTERATION
 R693*

NCT02264678
PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
 ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT02630199
PHASE 1

Study of AZD6738, DNA Damage Repair/Novel Anti-cancer Agent, in Combination With Paclitaxel, in Refractory Cancer

TARGETS
 ATR

LOCATIONS: Seoul (Korea, Republic of)

NCT04266912
PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
 ATR, PD-L1

LOCATIONS: Texas

NCT04104776
PHASE 1/2

A Study of CPI-0209 in Patients With Advanced Solid Tumors

TARGETS
 EZH2, TOP1

LOCATIONS: Washington, Michigan, Ohio, Massachusetts, New Jersey, Texas, Virginia, Georgia

NCT04514497
PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
 ATR, TOP1

LOCATIONS: Arizona, Oklahoma, Missouri, Connecticut, Tennessee

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Electronically signed by Tyler Janovitz, MD, PhD | 23 December 2021
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
 Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
 Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

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CLINICAL TRIALS

NCT03641547

PHASE 1

M6620 Plus Standard Treatment in Oesophageal and Other Cancer

TARGETS
 ATR

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom), Cardiff (United Kingdom)

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
 ATR

LOCATIONS: Cambridge (United Kingdom)

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: California, Missouri, Pennsylvania, Massachusetts, Connecticut, Tennessee, Florida

ORDERED TEST # ORD-1255383-01

CLINICAL TRIALS
GENE
PIK3CA
ALTERATION
H1047R

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of

this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib.

NCT04589845
PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Tainan (Taiwan), Seoul (Korea, Republic of), Beijing (China), Woolloongabba (Australia), Darlinghurst (Australia), Randwick (Australia), Melbourne (Australia), Haifa (Israel)

NCT03239015
PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB2, ERBB4, PARP, mTOR, MET, RET, ROS1, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463
PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

NCT02688881
PHASE 4

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

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

NCT04803318
PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03772561
PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

ORDERED TEST # ORD-1255383-01

CLINICAL TRIALS

NCT04801966
PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK,
PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03994796
PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Alaska, Washington

NCT04632992
PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, PD-L1,
ERBB2, ERBB3, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Montana

NCT03648489
PHASE 2

Dual mTORC Inhibition in advanCed/Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer (of Clear Cell, Endometrioid and High Grade Serous Type, and Carcinosarcoma)

TARGETS
mTORC1, mTORC2

LOCATIONS: Berlin (Germany), Dresden (Germany), Essen (Germany), Sheffield (United Kingdom), Nottingham (United Kingdom), Lancaster (United Kingdom), Barrow In Furness (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Northwood (United Kingdom)

ORDERED TEST # ORD-1255383-01

APPENDIX
Variants of Unknown Significance

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.

AXL
T112M

CSF1R
V647I

DAXX
E457del

GRM3
D374N

IDH1
I266V

MLL2
R3508Q

ORDERED TEST # ORD-1255383-01

APPENDIX
Genes Assayed in FoundationOne®CDx

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
BTB	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	ERRF1	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	FOXO2	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	KDMSA	KDMS5C	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	NFKB1A	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	SOC3
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	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPRPS2

*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)

ORDERED TEST # ORD-1255383-01

APPENDIX
About FoundationOne®CDx

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.


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 Therapies and Clinical Trials
Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, 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. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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ORDERED TEST # ORD-1255383-01

APPENDIX

About FoundationOne®CDx

- Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
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 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.
 4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
 5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine

whether the patient is a candidate for biopsy.

6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of *HER2* overexpression as 20% in breast cancer. Based on the F1CDx *HER2* CDx concordance study, approximately 10% of *HER2* amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

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), 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 *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *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.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1*, *CBL*, *DNMT3A*, *IDH2*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear

ORDERED TEST # ORD-1255383-01

APPENDIX

About FoundationOne®CDx

cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. 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
mut/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

MR Suite Version 5.2.0

The median exon coverage for this sample is 911x

ORDERED TEST # ORD-1255383-01

APPENDIX
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APPENDIX
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