

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 high grade serous carcinoma	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Ovary
	NAME Liu Su, Hung Chou		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S110-67208 M
	DATE OF BIRTH 20 August 1951		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Female		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 20 August 2021
	MEDICAL RECORD # 32708477/PF23054		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 15 May 2023

Biomarker Findings

Homologous Recombination status - HRD Not Detected

Loss of Heterozygosity score - 5.6%

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings

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

AKT2 amplification

CDK4 amplification - equivocal[†]

TP53 H168R

ERBB3 amplification - equivocal[†]

GATA6 amplification

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

[†] See About the Test in appendix for details.

Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. [8](#))

BIOMARKER FINDINGS

Homologous Recombination status - HRD Not Detected

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GENOMIC FINDINGS

AKT2 - amplification

10 Trials [see p. 8](#)

CDK4 - amplification - equivocal

10 Trials [see p. 10](#)

THERAPY AND CLINICAL TRIAL IMPLICATIONS

HRD Not Detected defined as absence of deleterious **BRCA1/2** alteration and LOH score < 16% or Cannot Be Determined (Coleman et al., 2017; 28916367).

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

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)

none

none

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

none

none

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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
TP53 - H168R	none	none
2 Trials see p. 12		

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.

ERBB3 - amplification - equivocal..... p. 7 **GATA6** - amplification..... 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.

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BIOMARKER FINDINGS

BIOMARKER

Loss of Heterozygosity score

RESULT
5.6%

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 inhibitors¹⁻². 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 $\geq 16\%$ ². In the maintenance setting in platinum-sensitive, BRCA1/2 wild-type patients, rucaparib was superior to placebo in both the LOH score $\geq 16\%$ (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 LOH⁴⁻⁵. Increased LOH has also been associated with improved sensitivity to platinum-containing chemotherapy regimens in patients with ovarian or breast cancer⁶⁻⁸.

FREQUENCY & PROGNOSIS

In a study of more than 4,000 ovarian, Fallopian tube, or peritoneal cancer samples, genomic LOH score $\geq 16\%$ 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 $\geq 16\%$ 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. This sample harbors a genomic LOH score below levels that have been associated with improved rates of clinical benefit from treatment with the PARP inhibitor rucaparib in patients with platinum-sensitive, BRCA1/2 wild-type ovarian, peritoneal, or Fallopian tube carcinoma². However, patients with lower genomic LOH have also responded to rucaparib, and this type of LOH score does not preclude benefit from PARP inhibitors¹⁻².

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors¹⁷⁻¹⁹, including approved therapies nivolumab and pembrolizumab²⁰. 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)²¹.

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been reported in 1.6-19.7% of ovarian cancer samples²²⁻²³, including 3.8% (1/26) of ovarian endometrioid adenocarcinomas²⁴, and 10.0% (3/30) of ovarian clear cell carcinomas (CCOCs)²⁵. No association of MSI-H with stage or survival was found in patients with ovarian cancer^{22,26}.

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 tumor²⁷. 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 PMS2²⁷⁻²⁹. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers³⁰⁻³². MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{27,29,31-32}.

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BIOMARKER FINDINGS

BIOMARKER

Tumor Mutational Burden

RESULT

0 Muts/Mb

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-L1³³⁻³⁵, anti-PD-1 therapies³³⁻³⁶, and combination nivolumab and ipilimumab³⁷⁻⁴². In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors^{33-36,43-47}. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥ 10 Muts/Mb (as measured by this assay) compared with those with TMB < 10 Muts/Mb in a large cohort that included multiple tumor types⁴³; similar findings were observed in the KEYNOTE 028 and 012 trials³⁶. At the same TMB cutpoint, retrospective analysis of

patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores < 10 Muts/Mb (HR=0.68)⁴⁷. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples⁴⁸. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and < 16 Muts/Mb⁴⁶. Similarly, 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 chemotherapy⁴⁹ or those with lower TMB treated with PD-1 or PD-L1-targeting agents³⁴.

FREQUENCY & PROGNOSIS

Ovarian carcinomas, including peritoneal and Fallopian tube carcinomas, harbor a median TMB of 2.7-3.6 mutations per megabase (Muts/Mb) depending upon subtype, and up to 2.1% of cases

have high TMB (> 20 Muts/Mb)⁵⁰. In a study of high grade serous ovarian cancer, homologous recombination (HR)-deficient tumors, which comprised ~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 survival⁵¹.

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 melanoma⁵²⁻⁵³ and cigarette smoke in lung cancer⁵⁴⁻⁵⁵, treatment with temozolomide-based chemotherapy in glioma⁵⁶⁻⁵⁷, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁵⁸⁻⁶², and microsatellite instability (MSI)^{58,61-62}. 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^{34-35,43}.

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GENOMIC FINDINGS

GENE

AKT2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or activation of AKT2 may promote AKT-mTOR pathway activation and may predict sensitivity to inhibitors of the AKT and downstream mTOR pathways. Clinical benefit has been achieved in 1 patient with AKT2 amplification

treated with an mTOR inhibitor⁶³. In preclinical studies, the AKT inhibitor MK-2206 showed evidence of enhancing anti-tumor activity of other chemotherapeutic agents in lung and ovarian tumor cells⁶⁴.

FREQUENCY & PROGNOSIS

AKT2 amplification has been reported frequently in ovarian⁶⁵⁻⁶⁷ and Fallopian tube carcinomas⁶⁸. In the TCGA dataset, amplification of AKT2 has been found in 7% of ovarian serous carcinoma cases¹⁵. Higher AKT2 expression has been reported to be associated with longer PFS in epithelial ovarian and primary peritoneal carcinomas⁶⁹.

FINDING SUMMARY

AKT2 encodes an intracellular serine/threonine kinase that is also known as PKB-beta. AKT2 is one of three members of the AKT gene family, and activation of AKT2 has been implicated in multiple malignancies⁷⁰⁻⁷¹. AKT isoforms appear to have different roles in tumorigenesis; AKT1 appears to contribute to the initiation of tumors, whereas AKT2 promotes invasion and metastasis in breast tumors⁷². Although AKT2 amplification has been reported to associate with AKT2 overexpression^{66-67,73}, studies in various cancers suggest that AKT2 phosphorylation may have greater clinical relevance than AKT2 amplification or mRNA overexpression⁷⁴⁻⁷⁵.

GENE

CDK4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

CDK4 amplification or activation may predict sensitivity to CDK4/6 inhibitors such as abemaciclib, palbociclib, and ribociclib⁷⁶⁻⁷⁹. Clinical benefit has been reported for limited tumor types including patients with CDK4-amplified liposarcoma and sarcoma in response to treatment with abemaciclib⁸⁰, palbociclib^{76,81}, and ribociclib⁸².

FREQUENCY & PROGNOSIS

CDK4 amplification has been reported in 0.4-1.0% of high-grade ovarian serous carcinomas^{15,83-84}. Overexpression of CDK4 mRNA has been reported in 14% (7/48) of ovarian carcinomas in one study, although CDK4 amplification was not observed⁸⁵. Immunohistochemical analysis of 103 samples of ovarian tumors showed that 61% of benign tumors, 70% of borderline tumors, and 74% of malignant tumors expressed CDK4⁸⁶. Alteration in the p16-cyclin D1/CDK4-Rb pathway was found to be predictive of lower overall survival in a study of 107 patients with epithelial ovarian cancer⁸⁷. However, in a study of 103 ovarian tumors, no significant correlation was observed between CDK4 protein expression and overall survival unless p16 expression was also decreased, in which case overall survival was lower⁸⁶.

FINDING SUMMARY

CDK4 encodes the cyclin-dependent kinase 4, which regulates the cell cycle, senescence, and apoptosis⁸⁸. CDK4 and its functional homolog CDK6 are activated by D-type cyclins and promote cell cycle progression by inactivating the tumor suppressor Rb⁸⁹⁻⁹⁰. Amplification of the chromosomal region that includes CDK4 has been reported in multiple cancer types, including lung cancer, glioblastoma, and liposarcoma, and has been associated with overexpression of CDK4 protein^{76,91-97}.

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GENOMIC FINDINGS

GENE

TP53

ALTERATION

H168R

HGVS VARIANT

NM_000546.4: c.503A>G (p.H168R)

VARIANT CHROMOSOMAL POSITION

chr17:7578427

VARIANT ALLELE FREQUENCY (% VAF)

78.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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 adavosertib⁹⁸⁻¹⁰¹ or p53 gene therapy such as SGT53¹⁰²⁻¹⁰⁶. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype¹⁰⁷. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer¹⁰⁸. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer¹⁰⁹. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone¹¹⁰. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib

combined with paclitaxel¹¹¹. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations¹¹². The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring¹¹³. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage¹⁰⁶. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR¹¹⁴. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)¹¹⁵.

FREQUENCY & PROGNOSIS

TP53 alterations have been reported in 29-80% of ovarian tumors, with a higher incidence in high-grade pelvic (primary ovarian, tubal, or peritoneal) serous carcinoma, with incidence of 91-97%^{15,116-122}. Aberrant p53 expression has been associated with higher ovarian serous carcinoma grade (89-90% of high-grade vs. 6.6-9% of low-grade vs. 0% of benign)¹²³⁻¹²⁵. TP53 mutations have been reported to be more frequent in advanced stage (63%, 55/87) and higher grade (65%, 42/64) than earlier stage (31%, 14/45) and lower grade (41%, 7/17) ovarian carcinomas¹²¹. Meta-analysis has suggested that TP53 expression was associated with poorer survival in ovarian epithelial cancers, although the effect was modest and considerable variability was

observed between studies¹²⁶.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers¹²⁷. Alterations such as seen here may disrupt TP53 function or expression¹²⁸⁻¹³².

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 cancers¹³³⁻¹³⁵, including sarcomas¹³⁶⁻¹³⁷. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹³⁸ to 1:20,000¹³⁷. 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 30¹³⁹. In the appropriate clinical context, germline testing of TP53 is recommended.

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 expansion¹⁴⁰⁻¹⁴⁵. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹⁴⁰⁻¹⁴¹. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease¹⁴⁶. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{144,147-148}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENOMIC FINDINGS

GENE

ERBB3

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling¹⁴⁹⁻¹⁵². Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Clinical

and preclinical data support sensitivity of ERBB3 activating mutations to various anti-ERBB2 agents^{151,153-157}, but data are generally limited for ERBB3 amplification. Biomarker analyses of several Phase 3 trials have not identified an association of ERBB3 expression levels with benefit from trastuzumab-, pertuzumab-, or T-DM1-containing regimens in HER2-positive breast cancer¹⁵⁸⁻¹⁶¹, T-DM1 in HER2-positive gastric and gastroesophageal junction (GEJ) cancer¹⁶², pertuzumab combined with chemotherapy in ovarian cancer¹⁶³, or afatinib in HNSCC¹⁶⁴. Similarly, ERBB3 expression levels were not associated with PFS or OS from lapatinib plus capecitabine in a Phase 2 study of gastric/GEJ cancer¹⁶⁵ or in retrospective studies of HER2-positive breast cancer¹⁶⁶⁻¹⁶⁸.

FREQUENCY & PROGNOSIS

In the Ovarian Serous Cystadenocarcinoma TCGA dataset, ERBB3 amplification and mutation were detected in 4% and <1% of cases, respectively¹⁵. In the literature, overexpression of ERBB3 protein has been detected in 53-76% of ovarian carcinomas¹⁶⁹⁻¹⁷⁰. ERBB3 protein overexpression in ovarian cancer has been correlated with poor prognosis¹⁷⁰⁻¹⁷².

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family¹⁷³. One study has demonstrated a weak but significant association between ERBB3 gene amplification and ERBB3 protein expression in breast cancer tissue¹⁷⁴.

GENE

GATA6

ALTERATION

amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in GATA6. Patients with GATA6-high pancreatic tumors exhibited better clinical outcomes following treatment with adjuvant chemotherapy ($p=0.003$) or first-line folfirinox ($HR=1.90$, $p=0.025$) treatment compared

with low GATA6 expressing tumors, while no difference was observed for patients treated with gemcitabine¹⁷⁵⁻¹⁷⁶.

FREQUENCY & PROGNOSIS

Amplification of the GATA6 locus, 18q11.2, has been reported with highest incidences in esophageal adenocarcinomas (21%, 18/85) and pancreaticobiliary carcinomas (19%, 7/37)¹⁷⁷⁻¹⁷⁸, and at lower rates in small intestine cancer (5.5%)¹⁷⁹, urothelial bladder carcinoma (3.9%), lung adenocarcinoma (1.7%), and ovarian carcinoma (1.8%)^{15,180-181}. While low GATA6 expression correlated with poor prognosis for patients with non-small cell lung cancer (NSCLC)¹⁸², gastric cancer¹⁸³, bladder cancer¹⁸⁴, or esophageal

adenocarcinomas without neoadjuvant treatment¹⁸⁵, high GATA6 expression has been associated with poor outcome for patients with colon cancer¹⁸⁶, breast cancer¹⁸⁷, ovarian cancer¹⁸⁸, cholangiocarcinoma¹⁸⁹, and NSCLC following EGFR-TKI treatment¹⁹⁰.

FINDING SUMMARY

GATA6 encodes a zinc finger transcription factor, which is involved in the development of several tissues and is expressed in proliferating cells throughout the intestinal tract¹⁹¹. GATA6 has been described as both a tumor suppressor and an oncogene, which may be dependent on the tumor type.

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Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1629801-01

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.clinicaltrials.gov). Or, visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
AKT2
ALTERATION

amplification

RATIONALE

AKT2 amplification or mutation may lead to AKT-mTOR pathway activation and may predict sensitivity to inhibitors of this pathway.

NCT03239015
PHASE 2

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

TARGETS

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

LOCATIONS: Shanghai (China)

NCT04803318
PHASE 2

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

TARGETS

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

LOCATIONS: Guangzhou (China)

NCT05125523
PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS

mTOR

LOCATIONS: Tianjin (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)

NCT04551521
PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS

PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

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ORDERED TEST # ORD-1629801-01

CLINICAL TRIALS
NCT03297606
PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS

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

LOCATIONS: Vancouver (Canada), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT05036226
PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS

DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT03673787
PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS

AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT05276973
PHASE 1

Testing the Addition of Ipatasertib to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) for Stage III or IV Epithelial Ovarian Cancer

TARGETS

AKTs

LOCATIONS: Wisconsin, Oklahoma, Ohio, Rhode Island, Virginia, Georgia

NCT01582191
PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS

mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

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CLINICAL TRIALS

GENE

CDK4

RATIONALE

CDK4 amplification may predict sensitivity to CDK4/6 inhibitors.

ALTERATION

amplification - equivocal

NCT04282031
PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS

CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

NCT04553133
PHASE 1/2

PF-07104091 as a Single Agent and in Combination Therapy

TARGETS

CDK6, Aromatase, CDK4, CDK2

LOCATIONS: Shanghai (China), Koto (Japan), Kashiwa (Japan), Iowa, Michigan, Massachusetts, Kentucky, New York

NCT03239015
PHASE 2

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

TARGETS

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

LOCATIONS: Shanghai (China)

NCT04557449
PHASE 1

Study to Test the Safety and Tolerability of PF-07220060 in Participants With Advance Solid Tumors

TARGETS

CDK4, Aromatase, ER

LOCATIONS: Wuhan (China), Zhengzhou (China), Xi'an (China), Beijing (China), Nove Zamky (Slovakia), Bratislava (Slovakia), Praha 2 (Czechia), Edinburgh (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

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

CDK4, CDK6, FLT3, VEGFRs, CSF1R, KIT, RET, mTOR, ERBB2, MEK, BRAF, PARP, PD-1, CTLA-4, PD-L1, TRKB, ALK, TRKC, ROS1, TRKA, FGFRs

LOCATIONS: Hawaii, Washington, Oregon, California

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CLINICAL TRIALS

NCT05262400

PHASE 1/2

A Study to Learn About the Study Medicine (Called PF-07220060 in Combination With PF-07104091) In Participants With Breast Cancer and Solid Tumors

TARGETS
CDK2, Aromatase, CDK4, ER

LOCATIONS: Prague (Czechia), Washington, California, Michigan, Massachusetts, Texas, Merida (Mexico)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

LOCATIONS: Vancouver (Canada), Kelowna (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

LOCATIONS: Washington, Oregon, Idaho, Montana

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Illinois, Massachusetts, Arkansas, New York, Virginia, Texas, Florida

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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ORDERED TEST # ORD-1629801-01

CLINICAL TRIALS
GENE
TP53
ALTERATION
H168R
RATIONALE

TP53 loss of function alterations may predict sensitivity to WEE1 inhibitors. TP53 missense mutations may predict sensitivity to therapies that reactivate mutant p53.

NCT04516447
PHASE 1

A Study of ZN-c3 in Patients With Platinum-Resistant Ovarian Cancer

TARGETS
WEE1
LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Sunshine Coast (Australia), South Brisbane (Australia), Melbourne (Australia), Belgrade (Serbia), Tuzla (Bosnia and Herzegovina), Banja Luka (Bosnia and Herzegovina), Colorado

NCT03968653
PHASE 1

Study of Oral Debio 0123 in Combination With Carboplatin in Participants With Advanced Solid Tumors

TARGETS
WEE1
LOCATIONS: Groningen (Netherlands), Nijmegen (Netherlands), Leiden (Netherlands), Barcelona (Spain)

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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.

BCORL1

NM_021946.4: c.2615T>G
(p.V872G)
chrX:129149363

ERBB2

amplification[†]
EWSR1

rearrangement

TERT

NM_198253.2: c.-145C>T
chr5:1295249

[†] An ERBB2 amplification of copy number 4 was detected. While this result is considered a variant of unknown significance across tumor types, in a clinical concordance study of breast cancer samples with an FDA-approved FISH test, 70% (7 out of 10 samples) with copy number 4 were positive with an average ratio of 2.3, and 30% (3 out of 10) samples were negative by the FISH test.

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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 or WTX)	
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	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	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
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	GID4 (C17orf39)	GNA11	GNA13	GNAS	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFA1	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	MRE11 (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	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	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
PRKN (PARK2)	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	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFB2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	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**	TPRSS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS


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

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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 PRINCIPLE

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. 2023. 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 fraction-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

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APPENDIX

About FoundationOne®CDx

- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- 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.
 - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16 will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
 - 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.

- 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.
- 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.
- 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

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APPENDIX
About FoundationOne®CDx

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 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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.8.0

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