

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 Pancreas ductal adenocarcinoma	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Pancreas
	NAME Yeh, Yu Min		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S111-71438G (PF22147)
	DATE OF BIRTH 15 August 1974		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Male		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 05 October 2022
	MEDICAL RECORD # 48978138		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 20 December 2022

Biomarker Findings

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.

ATM Q298*, R457*

KRAS Q61H

CDKN2A/B p16INK4a splice site 458-2A>G, CDKN2A rearrangement intron 1

MAP2K4 R110*

SMAD4 T59fs*12

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

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. [8](#))
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: **ATM** R457* (p. [4](#))

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 0 Muts/Mb

GENOMIC FINDINGS

ATM - Q298*, R457*

10 Trials [see p. 8](#)

KRAS - Q61H

3 Trials [see p. 10](#)

THERAPY AND CLINICAL TRIAL IMPLICATIONS

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

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

ATM - R457* [p. 4](#)

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

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.

CDKN2A/B - p16INK4a splice site 458-2A>G,	MAP2K4 - R110* p. 6
CDKN2A rearrangement intron 1 p. 6	SMAD4 - T59fs*12 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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ORDERED TEST # ORD-1529340-01

BIOMARKER FINDINGS

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 inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. In a retrospective

analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, $p=0.001$)⁵.

FREQUENCY & PROGNOSIS

MSI is rare in pancreatic carcinoma, reported in less than 1% of samples ($n \geq 1,000$)⁶⁻¹⁰. The prognostic significance of MSI in pancreatic cancer is unknown (PubMed, Aug 2022).

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 tumor¹¹. 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 PMS2¹¹⁻¹³. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹⁴⁻¹⁶. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{11,13,15-16}.

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-L1¹⁷⁻¹⁹, anti-PD-1 therapies¹⁷⁻²⁰, and combination nivolumab and ipilimumab²¹⁻²⁶. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors^{17-20,27-31}. 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 types²⁷; similar findings were observed in the KEYNOTE 028 and 012 trials²⁰. 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)³¹. 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 samples³². 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/Mb³⁰. Similarly, 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 chemotherapy³³ or those with lower TMB treated with PD-1 or PD-L1-targeting agents¹⁸.

FREQUENCY & PROGNOSIS

Pancreatic carcinomas, including ductal and acinar subtypes, have been reported to harbor a median TMB of 2-3 mutations per megabase (mut/megab), and 0-2% of cases have high TMB (> 20 muts/

Mb)³⁴; TMB has not been assessed in pancreatic mucinous neoplasms (PubMed, Oct 2022). A study of patients with pancreatic ductal adenocarcinoma harboring mismatch repair gene mutations reported improved prognosis for patients with high TMB measured in tissue samples (defined as > 50 mutations; survival 69-314 months) compared to those with lower TMB (average of 5.7 mutations; 10-42 months)³⁵.

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 melanoma³⁶⁻³⁷ and cigarette smoke in lung cancer³⁸⁻³⁹, treatment with temozolomide-based chemotherapy in glioma⁴⁰⁻⁴¹, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁴²⁻⁴⁶, and microsatellite instability (MSI)^{42,45-46}. 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^{18-19,27}.

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ORDERED TEST # ORD-1529340-01

GENOMIC FINDINGS

GENE

ATM

ALTERATION

Q298*, R457*

TRANSCRIPT ID

NM_000051.3, NM_000051.3

CODING SEQUENCE EFFECT

892C>T, 1369C>T

VARIANT CHROMOSOMAL POSITION

chr11:108115744, chr11:108121561

VARIANT ALLELE FREQUENCY (% VAF)

13.5%, 48.0%

responses (ORs) were experienced by 50% (4/8) of patients with loss of ATM expression, compared with 14% (3/21) patients with intact ATM⁶⁰. Studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors⁶¹⁻⁶³ and hematologic malignancies^{61,64} also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity⁶⁵.

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 1-4%, and ATM loss in 0-5%, of pancreatic adenocarcinomas⁶⁶⁻⁶⁸. Expression of the ATM protein has been observed in 67.7% of pancreatic tumors, where it was correlated with p53 expression⁶⁹. Published data investigating the prognostic implications of ATM alterations in pancreatic cancer are limited (PubMed, Oct 2022). Some familial mutations in ATM have been suggested to increase the risk of developing pancreatic cancer⁷⁰⁻⁷¹. One study found that presence of a germline ATM pathogenic variant was significantly associated with frequency of pancreatic ductal adenocarcinoma (HR=7.73)⁷².

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response⁷³. Loss of functional ATM promotes tumorigenesis⁷⁴. Alterations such as seen here may disrupt ATM function or expression⁷⁵⁻⁷⁷.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the ATM variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with ataxia-telangiectasia syndrome (ClinVar, Sep 2022)⁷⁸. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer⁷⁹. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome⁸⁰. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer^{73,80}. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide⁸⁰. In the appropriate clinical context, germline testing of ATM 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 expansion⁸¹⁻⁸⁶. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH^{85,87-88}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors⁴⁷⁻⁴⁸. Clinical responses have been reported for patients with ATM-mutated prostate cancer treated with PARP inhibitors⁴⁹⁻⁵¹ and PARP inhibitors have shown limited clinical benefit for patients with other ATM-mutated solid tumors including pancreatic cancer⁵²⁻⁵³, colorectal cancer⁵⁴, papillary renal cell carcinoma⁵⁵, ovarian cancer⁵⁶, small cell bowel cancer⁵³, and biliary tract cancer⁵⁷. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib⁵⁸ and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344⁵⁹ harbored ATM inactivation or protein loss. In a Phase 2 study of a combination of the ATR inhibitor ceralasertib and durvalumab for patients with advanced gastric cancer, objective

ORDERED TEST # ORD-1529340-01

GENOMIC FINDINGS

GENE

KRAS

ALTERATION

Q61H

TRANSCRIPT ID

NM_004985.3

CODING SEQUENCE EFFECT

183A>T

VARIANT CHROMOSOMAL POSITION

chr12:25380275

VARIANT ALLELE FREQUENCY (% VAF)

15.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁸⁹⁻⁹⁴. For patients with pancreatic cancer, MEK inhibitor combinations are under investigation. A Phase 2 study of trametinib with pembrolizumab versus gemcitabine after stereotactic body radiotherapy (SBRT) reported increased median OS (mOS, 14.9 months vs. 12.8 months, HR=0.69) benefit for patients with KRAS-mutated, PD-L1 positive disease⁹⁵. Combination MEK/autophagy inhibitors are also under investigation based on preclinical evidence of increased autophagy downstream of KRAS-mutated pancreatic tumors⁹⁶⁻⁹⁷. A heavily pretreated patient with pancreatic cancer treated with trametinib plus hydroxychloroquine

experienced a PR⁹⁶. A Phase 2 study of the reoviral agent pelareorep with gemcitabine for patients with pancreatic cancer reported 1 PR, 23 SDs, and 5 PDs for 34 patients with a favorable median OS of 10.2 months⁹⁸. A Phase 1b study of second-line pelareorep with pembrolizumab and chemotherapy reported 1 PR of 17.4 months and a DCR of 30% (3/10)⁹⁹; an earlier study reported no benefit from pelareorep in combination with paclitaxel/carboplatin¹⁰⁰. Trials combining MEK inhibitors with other targeted therapies, such as EGFR inhibitors¹⁰¹ or PI3K-AKT pathway inhibitors¹⁰²⁻¹⁰³, reported no PRs and frequent adverse events for patients with KRAS-mutated pancreatic cancer. Clinical trials combining various MEK inhibitors with gemcitabine reported no additional benefit compared to gemcitabine alone irrespective of KRAS mutation status¹⁰⁴⁻¹⁰⁷, despite promising results in earlier trials of MEK inhibitor monotherapies¹⁰⁸⁻¹¹³. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NSCLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma¹¹⁴. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study¹¹⁵⁻¹¹⁶. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors¹¹⁷⁻¹¹⁸. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with

NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations¹¹⁹. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer¹²⁰. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors¹²¹⁻¹²². Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations¹²³⁻¹²⁴.

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 91-95% of pancreatic ductal adenocarcinoma cases^{67,125}, with the majority of mutations found at codon 12¹²⁶⁻¹²⁹. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma¹²⁷.

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation^{90,130}. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, and K117N have been characterized as activating and oncogenic^{90,131-153}.

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ORDERED TEST # ORD-1529340-01

GENOMIC FINDINGS

GENE
CDKN2A/B

ALTERATION

p16INK4a splice site 458-2A>G, CDKN2A rearrangement
intron 1

TRANSCRIPT ID

NM_000077.4

CODING SEQUENCE EFFECT

458-2A>G

VARIANT CHROMOSOMAL POSITION

chr9:21968243

VARIANT ALLELE FREQUENCY (% VAF)

13.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib¹⁵⁴⁻¹⁵⁷. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib¹⁵⁸ and palbociclib treatment¹⁵⁹⁻¹⁶⁰. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents¹⁶¹⁻¹⁶⁷; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors¹⁶⁸⁻¹⁶⁹, the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

CDKN2A/B loss has been reported in 36% of pancreatic ductal carcinomas⁶⁷. CDKN2A loss has been reported in 25-100% of pancreatic ductal adenocarcinomas analyzed, with a portion of those due to gene deletion^{127,170-172}. A study of multiple pancreatic cancer subtypes reported no CDKN2A mutations (0/6 samples) and loss of heterozygosity in only one of four samples of pancreatic acinar carcinomas, compared to mutation or loss of heterozygosity in 38% and 67% of pancreatic ductal carcinomas, respectively¹⁷³. Promoter methylation affecting p16INK4a and p14ARF has been reported in 43% (16/37) and 20.6% (7/34), respectively, of pancreatic fluid specimens of patients with pancreatic carcinoma¹⁷⁴. The loss or decrease of p16INK4a expression levels in pancreatic ductal adenocarcinoma has been reported in 32-80% of samples analyzed and one study reported concurrent loss of p16INK4a and p14ARF protein expression in 68% (19/28) of cases^{170,175-176}. p16INK4a expression has been associated with improved overall survival in pancreatic adenocarcinoma patients in univariate and multivariate analysis¹⁷⁷. Furthermore, CDKN2A alterations (deletion or mutation) in the presence of concomitant KRAS mutation may correlate with shorter survival in patients with pancreatic ductal adenocarcinoma¹⁷⁵.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b¹⁷⁸⁻¹⁷⁹. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the

Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control¹⁸⁰⁻¹⁸¹. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition¹⁸²⁻¹⁸³. One or more alterations observed here are predicted to result in p16INK4a loss of function¹⁸⁴⁻²⁰⁵. One or more alterations observed here are predicted to have wildtype p16INK4a function^{184,189-194,196,198-200,202,204,206}. One or more alterations seen here are predicted to result in p14ARF loss of function^{188,205,207-209}. One or more alterations seen here are predicted to have wildtype p14ARF function¹⁸⁷⁻¹⁸⁸.

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer²¹⁰. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma²¹¹⁻²¹². CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases²¹³⁻²¹⁵. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors²¹⁶⁻²¹⁸. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MAP2K4

ALTERATION

R110*

TRANSCRIPT ID

NM_003010.2

CODING SEQUENCE EFFECT

328C>T

VARIANT CHROMOSOMAL POSITION

chr17:11984782

VARIANT ALLELE FREQUENCY (% VAF)

15.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to target MAP2K4 loss or inactivation. However, a preclinical study reported that inactivation of MAP2K4 may confer sensitivity to MEK inhibitors²¹⁹.

FREQUENCY & PROGNOSIS

MAP2K4 mutation and homozygous deletion have been observed in 1-3% and 2-6% of pancreatic adenocarcinoma cases, respectively^{67,125,220}. In one study, loss of MKK4 protein showed a trend toward association with shorter survival of

patients with pancreatic cancer (p = 0.09)²²¹.

FINDING SUMMARY

MAP2K4 encodes the protein kinase MKK4, a member of a MAPK signaling cascade that leads to apoptosis in response to cellular stress²²². MAP2K4 has been proposed to act as a tumor suppressor in several cancer types, including pancreatic cancer, but has also been suggested to act as an oncogene in certain situations²²²⁻²²⁸. Alterations such as seen here may disrupt MAP2K4 function or expression^{223-224,229-230}.

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GENOMIC FINDINGS

GENE

SMAD4

ALTERATION

T59fs*12

TRANSCRIPT ID

NM_005359.5

CODING SEQUENCE EFFECT

173_174insTTTA

VARIANT CHROMOSOMAL POSITION

chr18:48573589

VARIANT ALLELE FREQUENCY (% VAF)

14.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SMAD4. Preclinical studies in colorectal cancer have reported associations of SMAD4 inactivation or loss with sensitivity to inhibitors of Aurora kinase A²³¹ and the Wnt/beta-catenin pathway²³².

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with

improved responses to chemotherapeutic agents in patients with pancreatic cancer²³³⁻²³⁵ and non-small cell lung cancer (NSCLC)²³⁶. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy²³⁷ and adjuvant chemoradiotherapy²³⁸.

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)⁶⁷, pancreatic acinar cell carcinoma (26%)²³⁹, cholangiocarcinoma (25%)²⁴⁰, small intestine cancer (20%)²⁴¹, appendiceal adenocarcinoma (14-20% mutation; 57% deletion)²⁴²⁻²⁴³, colorectal adenocarcinoma (CRC; 14%)⁴⁵, esophageal adenocarcinoma (14%)²⁴⁴, and stomach adenocarcinoma (13%)²⁴⁵. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)²⁴⁶ and intraductal papillary mucinous neoplasms (IPMN)²⁴⁷; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs²⁴⁸. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma²⁴⁹. Reduced SMAD4 expression

has been associated with worse prognosis in various cancer types, including CRC²⁵⁰⁻²⁵², appendiceal mucinous neoplasm²⁵³, gastric adenocarcinoma²⁵⁴⁻²⁵⁵, esophageal adenocarcinoma²⁵⁶, esophageal squamous cell carcinoma²⁵⁷, breast cancer²⁵⁸, and prostate cancer²⁵⁹.

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling²⁶⁰⁻²⁶¹. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating²⁶²⁻²⁷⁵.

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome²⁷⁶⁻²⁷⁸, which is associated with an increased risk of gastrointestinal cancers²⁷⁹. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65²⁸⁰. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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ORDERED TEST # ORD-1529340-01

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
ATM
ALTERATION
Q298*, R457*

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or

DNA-PKcs inhibitors.

NCT04644068
PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Guangzhou (China), Seoul (Korea, Republic of), Chongqing (China), Chengdu (China), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Lublin (Poland), Warszawa (Poland)

NCT04425876
PHASE 1

A Study of Fluzoparib in Combination With mFOLFIRINOX in Patients With Resectable Pancreatic Cancer

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT04123366
PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895
PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Beer-Sheva (Israel), Istanbul (Turkey)

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), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

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ORDERED TEST # ORD-1529340-01

CLINICAL TRIALS
NCT05035745
PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

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)

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)

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

LOCATIONS: Hawaii, Washington, Oregon, California

NCT04497116
PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

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ORDERED TEST # ORD-1529340-01

CLINICAL TRIALS
GENE
KRAS
ALTERATION
Q61H
RATIONALE

Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant pancreatic cancer. Emerging data suggest patients with KRAS-mutant pancreatic cancer may be sensitive to

combination MEK/autophagy inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

NCT03825289
PHASE 1

Trametinib and Hydroxychloroquine in Treating Patients With Pancreatic Cancer

TARGETS
MEK
LOCATIONS: Utah

NCT04892017
PHASE 1/2

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

TARGETS
ULK1, ULK2, MEK
LOCATIONS: Massachusetts, Texas, Pennsylvania

NCT04132505
PHASE 1

Binimetinib and Hydroxychloroquine in Treating Patients With KRAS Mutant Metastatic Pancreatic Cancer

TARGETS
MEK
LOCATIONS: Texas

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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.

SETD2
I1974V

TSC2
P666L

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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	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFI1A	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	TGFBP2
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**	TPR2SS2

*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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ORDERED TEST # ORD-1529340-01

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, Ciplstraat 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. 2022. 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.
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. 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.
 4. 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.

5. 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.
6. 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.
7. 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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ORDERED TEST # ORD-1529340-01

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) 7.4.0

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The median exon coverage for this sample is 871x

ORDERED TEST # ORD-1529340-01

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