

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 Skin melanoma
NAME Tsai, Hsiu Hsiung
DATE OF BIRTH 06 April 1941
SEX Male
MEDICAL RECORD # 33214436

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Lung
SPECIMEN ID S111-44872B (PF23024)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 02 November 2022
SPECIMEN RECEIVED 14 March 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

KRAS Q61R

MTAP loss

CCND3 amplification - equivocal[†]

CDKN2A/B CDKN2B loss, CDKN2A loss

CRKL amplification

MAPK1 amplification - equivocal[†]

VEGFA amplification - equivocal[†]

3 Disease relevant genes with no reportable alterations: **BRAF, KIT, NRAS**

[†] 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

Microsatellite status - MS-Stable

Tumor Mutational Burden - 4 Muts/Mb

GENOMIC FINDINGS

KRAS - Q61R

10 Trials see p. [8](#)

MTAP - loss

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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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.

CCND3 - amplification - equivocal.....	p. 5	MAPK1 - amplification - equivocal.....	p. 7
CDKN2A/B - CDKN2B loss, CDKN2A loss.....	p. 6	VEGFA - amplification - equivocal.....	p. 7
CRKL - amplification.....	p. 6		

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

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

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BIOMARKER 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 has been detected in 16-32% of cutaneous melanomas in several small datasets, with the majority exhibiting MSI-low⁶. A higher frequency of MSI (low and high) has been reported in metastatic tumors (20-77%) compared to primary tumors (2-30%)⁷. No association between MSI status and clinicopathological features of patients with melanoma was reported in one study⁸.

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 tumor⁹. 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 PMS2⁹⁻¹¹. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹²⁻¹⁴. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{9,11,13-14}.

BIOMARKER

Tumor Mutational Burden

RESULT

4 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-L1¹⁵⁻¹⁷, anti-PD-1 therapies¹⁵⁻¹⁸, and combination nivolumab and ipilimumab¹⁹⁻²⁴. In multiple studies of immune checkpoint inhibitors in melanoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-1 or anti-PD-L1 treatments^{18,25-26}. Increased TMB has been associated with longer PFS and OS for patients with melanoma treated with nivolumab, with studies reporting increased benefit for patients with a mutational load above 162 missense mutations per tumor (~equivalency >8 Muts/Mb

as measured by this assay)²⁷. Increased TMB (~equivalency >10.8 Muts/Mb as measured by this assay) has also been associated with longer PFS and OS for patients with melanoma treated with combination nivolumab and ipilimumab²⁷. Improved PFS and OS of patients with melanoma treated with ipilimumab has been observed across all TMB levels²⁸.

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that various melanoma subtypes harbored median TMBs between 6.3 and 14.4 Muts/Mb, and 25% to 40% of cases had elevated TMBs of greater than 20 Muts/Mb²⁹. Malignant melanoma has been reported to have a high prevalence of somatic mutations compared with other tumor types³⁰, with desmoplastic melanoma ranking among the highest of melanoma subtypes (median TMB of 62 Muts/Mb)³¹. Higher mutational load has been reported in NF1-mutant melanoma samples compared with BRAF-mutant, NRAS-mutant, or BRAF/NRAS/NF1 wild-type samples²⁵. In 1 study, elevated TMB correlated with PD-L1 positive status and increased OS in tissue specimens from patients with Stage 3 melanoma³². In another study, elevated

tissue TMB (>20 Muts/Mb) was associated with longer PFS and OS in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy as compared with patients with lower TMB²⁵. Increased TMB has also been associated with histologic stage and cumulative sun exposure³³.

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 melanoma³⁴⁻³⁵ and cigarette smoke in lung cancer³⁶⁻³⁷, treatment with temozolomide-based chemotherapy in glioma³⁸⁻³⁹, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁴⁰⁻⁴⁴, and microsatellite instability (MSI)^{40,43-44}. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1 or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents^{15-16,18,25,45-48}.

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ORDERED TEST # ORD-1585457-01

GENOMIC FINDINGS

GENE

KRAS

ALTERATION

Q61R

TRANSCRIPT ID

NM_004985.3

CODING SEQUENCE EFFECT

182A>G

VARIANT CHROMOSOMAL POSITION

chr12:25380276

VARIANT ALLELE FREQUENCY (% VAF)

72.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁴⁹⁻⁵⁴. While clinical responses have been reported for patients with KRAS-mutated ovarian⁵⁵⁻⁵⁸, cervical small cell neuroendocrine⁵⁹, or uterine cancer⁵⁷ treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC⁶⁰⁻⁶³, pancreatic cancer⁶⁴⁻⁶⁶, and NSCLC^{61,67-68}. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with

KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer⁶⁹. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer⁷⁰⁻⁷² and KRAS-mutated endometrioid adenocarcinoma⁷³. 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 myeloma⁷⁴. 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 study⁷⁵⁻⁷⁶. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors⁷⁷⁻⁷⁸. 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 mutations⁷⁹. 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 cancer⁸⁰. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors⁸¹⁻⁸². 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 mutations⁸³⁻⁸⁴.

FREQUENCY & PROGNOSIS

KRAS mutations have been reported in up to 2% of cutaneous melanoma samples, but have not been found in uveal melanoma cases (cBioPortal, COSMIC, Feb 2023)⁸⁵⁻⁸⁷. One study reported KRAS mutations in 4/71 (6%) mucosal melanoma samples⁸⁸. The RAS pathway is a significant driver in melanoma tumorigenesis, although mutations in BRAF and NRAS are more frequently observed than KRAS mutations⁸⁹. In melanoma, high KRAS expression has been reported to be associated with metastasis and with reduced median OS compared with low KRAS expression⁹⁰. Mutations in KRAS have also been associated with worse median OS for patients with melanoma brain metastases⁹¹.

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^{50,92}. 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^{50,93-115}.

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GENOMIC FINDINGS

GENE

MTAP

ALTERATION

loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A¹¹⁶⁻¹¹⁷ or PRMT5 inhibition¹¹⁷⁻¹¹⁹. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss¹²⁰. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors¹²¹, dual PRMT1 and PRMT5 inhibitors¹²²⁻¹²⁴, and PRMT5 inhibitors that selectively bind the PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193¹²⁵. In preclinical models, MTAP inactivation showed

increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA¹²⁶⁻¹³⁶. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and SD for 24% (13/55) of patients¹³⁷. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed¹³⁸.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers¹³⁹⁻¹⁴⁰; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma¹⁴¹, gastrointestinal stromal tumors¹⁴², mantle cell lymphoma (MCL)¹⁴³, melanoma¹⁴⁴⁻¹⁴⁵, gastric cancer¹⁴⁶, myxofibrosarcoma¹⁴⁷, nasopharyngeal carcinoma¹⁴⁸, ovarian carcinoma¹³⁹ and non-small cell lung cancer¹⁴⁹. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia¹⁵⁰ or in astrocytoma¹⁵¹. However, MTAP has also been reported to be

overexpressed in colorectal cancer (CRC) samples¹⁵², and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM¹⁵³. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma¹⁵⁴⁻¹⁵⁵, esophageal cancer¹⁵⁶⁻¹⁵⁷, osteosarcoma¹⁵⁸, and CRC¹⁵⁹.

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity¹⁶⁰⁻¹⁶¹. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment^{141,162-163}, thereby reducing intracellular arginine methylation¹¹⁷⁻¹¹⁹ and altering cell signaling¹⁶³⁻¹⁶⁴. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE

CCND3

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of preclinical studies, amplification or activation of CCND3 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib¹⁶⁵ and

palbociclib¹⁶⁶⁻¹⁶⁸; however, 1 preclinical study implicated CCND3 overexpression as a potential mechanism of resistance to palbociclib¹⁶⁹.

FREQUENCY & PROGNOSIS

In the TCGA datasets, CCND3 amplification has been reported in 4% of cutaneous melanoma and 6.3% (5/80) of uveal melanoma cases (cBioPortal, Oct 2022)⁸⁶⁻⁸⁷. A study reported cyclin D3 expression has been reported in 96% of primary melanomas, 97% of metastatic melanomas, and 20% of superficial tumors, and association between high cyclin D3 expression and early relapse and

decreased overall survival in patients with superficial melanoma tumors¹⁷⁰.

FINDING SUMMARY

CCND3 encodes cyclin D3, a G1/S-specific cell cycle regulator. Cyclin D3 interacts with and regulates the cyclin-dependent kinases CDK4 and CDK6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle¹⁷¹. CCND3 amplification has been associated with increased cyclin D3 expression¹⁷².

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GENOMIC FINDINGS

GENE

CDKN2A/B

ALTERATION

CDKN2B loss, CDKN2A loss

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 palbociclib¹⁷³⁻¹⁷⁶. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib¹⁷⁷ and palbociclib treatment¹⁷⁸⁻¹⁷⁹. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents¹⁸⁰⁻¹⁸⁶; it is not known whether CDK4/6 inhibitors would be beneficial in this case. The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib^{183-184,187-188}, direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited¹⁸⁹⁻¹⁹⁰. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors¹⁹¹⁻¹⁹², the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Concomitant loss of p16INK4a and p14ARF in melanoma is common, although loss of activity of either may also occur as a result of transcript-specific mutations or hypermethylation¹⁹³⁻¹⁹⁹. Homozygous deletion of CDKN2A and/or CDKN2B has been reported in 14-29% of melanoma cases (cBioPortal, Oct 2022)^{86-87,200-202}. Various correlations between CDKN2A alterations and tumor histology or patient prognosis in melanoma have been reported in the literature, with some studies reporting CDKN2A deletion to be associated with adverse prognosis and other studies reporting no association between CDKN2A deletion and prognosis^{200-201,203-204}. Studies suggest that deletion of CDKN2A is an early event in melanoma tumorigenesis, and loss of p16INK4a has been associated with increased DNA damage in human benign melanocytic tumors and has been suggested to contribute to tumorigenesis by promoting the proliferation of cells with genetic damage²⁰⁵⁻²⁰⁶. CDKN2A alterations affecting p16INK4a, p14ARF, or both have been strongly associated (up to a 76% risk) with familial melanoma²⁰⁷⁻²¹⁷.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b²¹⁸⁻²¹⁹. 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 control²²⁰⁻²²¹. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition²²²⁻²²³. One or more alterations observed here are predicted to result in p16INK4a loss of function²²⁴⁻²⁴⁵. One or more alterations seen here are predicted to result in p14ARF loss of function^{228,245-248}. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b²⁴⁹.

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 cancer²⁵⁰. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma²⁵¹⁻²⁵². CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases²⁵³⁻²⁵⁵. 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 tumors²⁵⁶⁻²⁵⁸. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE

CRKL

ALTERATION

amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that directly target CRKL²⁵⁹⁻²⁶⁰. Preclinical studies report that some cancer cell lines with CRKL amplification are sensitive to tyrosine kinase inhibitor (TKI) dasatinib²⁵⁹⁻²⁶¹. However, a patient with CRKL-amplified pancreatic cancer did not respond to

dasatinib²⁶². CRKL amplification has been shown to be a mechanism of acquired resistance to EGFR TKIs^{260,263}.

FREQUENCY & PROGNOSIS

CRKL amplification has been identified in various solid tumor types, including uterine carcinosarcoma (7%), pancreatic ductal adenocarcinoma (5.5%)²⁶⁴, lung squamous cell carcinoma (4.5%)²⁶⁵, sarcoma (4%), ovarian serous cystadenocarcinoma (3%), bladder urothelial carcinoma (3%)²⁶⁶, and melanoma (2%) (cBioPortal, 2023)⁸⁶⁻⁸⁷. Increased CRKL expression has been reported in many tumor types, including lung²⁶⁷⁻²⁶⁸, breast²⁶⁹⁻²⁷⁰, ovarian²⁷⁰⁻²⁷¹, pancreatic²⁷², skin²⁷⁰, colon^{270,273}, hepatocellular²⁷⁴, and gastric cancers²⁵⁹.

CRKL overexpression has been shown to significantly correlate with reduced OS for patients with NSCLC or hepatocellular carcinoma^{268,274} and with tumor size and metastasis for patients with breast cancer²⁶⁹.

FINDING SUMMARY

CRKL encodes an adaptor protein that has been shown to mediate growth, motility, and adhesion in solid tumor cells²⁷⁵. Studies in non-small cell lung cancer (NSCLC) and pancreatic cancer cells have linked CRKL amplification and overexpression with increased cell proliferation and with tumorigenesis^{260,267-268,272}.

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GENOMIC FINDINGS

GENE

MAPK1

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs that directly target ERK2, although ERK1/2 inhibitors are in clinical trials. In preclinical studies, ERK1/2 inhibitors have been shown to inhibit the activities of ERK2 mutations²⁷⁶⁻²⁷⁸ or restore sensitivity to the EGFR inhibitor WZ4002 in a WZ4002-resistant cell line harboring MAPK1 amplification²⁷⁹.

FREQUENCY & PROGNOSIS

MAPK1 amplification has been reported with the highest incidence in sarcoma (4%), lung squamous cell carcinoma (3%), ovarian serous cystadenocarcinoma (2%), bladder urothelial carcinoma (2%), esophageal squamous cell carcinoma (2%), and testicular germ cell cancer (2%); MAPK1 amplification has been reported in fewer than 1% of hematologic malignancies (cBioPortal, 2023)⁸⁶⁻⁸⁷. In the scientific literature, MAPK1 amplification has been observed in 7% (5/68) of Type 2 ovarian carcinomas²⁸⁰, 18% (4/22) of laryngeal squamous cell carcinomas²⁸¹, and 9% (3/34) of angiosarcoma²⁸². MAPK1 amplification is associated with significantly shorter PFS in patients with ovarian cancer²⁸⁰. Further, higher levels of ERK2 or phosphorylated ERK2 expression is a predictor of poor prognosis of acute

myelogenous leukemia²⁸³ or angioimmunoblastic T-cell lymphoma²⁸⁴.

FINDING SUMMARY

MAPK1, also known as ERK2, encodes a mitogen-activated protein kinase family member that is involved in the transduction of proliferation and differentiation signals. MAPK1 amplification is associated with increased MAPK1 gene expression²⁷⁹. MAPK1 amplification was detected in one patient with non-small cell lung cancer who exhibited resistance to erlotinib²⁷⁹. Preclinical evidence suggests that amplification of MAPK1 may reduce sensitivity to the third-generation EGFR inhibitor WZ4002 as well as to cytotoxic chemotherapy²⁷⁹.

GENE

VEGFA

ALTERATION

amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The approved VEGFA-targeted agents bevacizumab and ziv-aflibercept have demonstrated efficacy in multiple tumor types; however, expression or amplification of VEGFA has not been established as a reliable biomarker of response to these therapies²⁸⁵⁻³¹⁶. Preclinical hepatocellular carcinoma (HCC) models with VEGFA

amplification showed increased sensitivity to sorafenib, and a small retrospective study reported significantly increased OS for 7 patients with VEGFA-amplified HCC treated with sorafenib³¹⁷. However, a prospective biomarker study showed that VEGFA amplification detected by circulating cell-free DNA was not significantly associated with DCR, time to progression, or median OS for patients with HCC treated with first-line sorafenib³¹⁸. It is currently not known if VEGFA amplification predicts response to other inhibitors targeting VEGFRs.

FREQUENCY & PROGNOSIS

In the TCGA dataset, VEGFA amplification and mutation were observed in 3% and 2% of cutaneous melanoma cases, respectively³¹⁹. VEGFA

concentration has been reported as elevated in melanoma³²⁰ and uveal melanoma cases³²¹⁻³²² and has been correlated with increased tumor size and metastasis³²¹⁻³²³.

FINDING SUMMARY

VEGFA (vascular endothelial growth factor A) encodes a ligand that promotes angiogenesis through the receptor tyrosine kinases VEGFR1 and VEGFR2³²⁴. VEGFA promotes tumor growth by activating both autocrine VEGFR signaling in tumor cells and paracrine signaling to fibroblasts and immune cells in the tumor microenvironment³²⁴. VEGFA has been reported to be amplified in cancer⁸⁷, and is associated with response to sorafenib³¹⁷.

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ORDERED TEST # ORD-1585457-01

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
KRAS
ALTERATION
Q61R

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited

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

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)

NCT04985604
PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT03284502
PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs, NRAS

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

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)

NCT03175432
PHASE 2

Study of BEvacizumab in Combination With ATezolizumab in Patients With Untreated Melanoma Brain Metastases

TARGETS
VEGFA, PD-L1, MEK

LOCATIONS: Texas

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CLINICAL TRIALS
NCT03905148
PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), California, Texas

NCT02645149
PHASE 2

Molecular Profiling and Matched Targeted Therapy for Patients With Metastatic Melanoma

TARGETS
ROS1, ALK, MEK, CDK6, CDK4

LOCATIONS: Wollstonecraft (Australia)

NCT05159245
PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Kuopio (Finland), Helsinki (Finland), Tampere (Finland), Turku (Finland)

NCT04817956
PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

NCT04551521
PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

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

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CLINICAL TRIALS
GENE
MTAP
ALTERATION

loss

RATIONALE

MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05094336
PHASE 1/2

AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Tainan (Taiwan), Hong Kong (Hong Kong), Nagoya-shi (Japan), Chuo-ku (Japan), Kashiwa-shi (Japan), Camperdown (Australia), Halle (Saale) (Germany), Salzburg (Austria), Wuerzburg (Germany), Ulm (Germany)

NCT05275478
PHASE 1/2

Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Lyon (France), Villejuif (France), Missouri, Massachusetts, Tennessee, Texas, Virginia

NCT05245500
PHASE 1/2

Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion

TARGETS
PRMT5-MTA

LOCATIONS: Colorado, Arizona, Minnesota, Massachusetts, New York, Tennessee, Texas, Florida

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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.

ASXL1

R625Q

BCOR

P152L

CCND2

amplification

CDK6

R305S

CDKN1B

amplification

EP300

amplification

ERBB4

E276G

FGF23

amplification

FGF6

amplification

FGFR2

V463D

GNAS

A280T

KDM5A

amplification

KRAS

amplification

MKNK1

R35Q

MST1R

K881N

NF1

M1162V

PARP2

A522V

PIK3C2G

amplification

POLE

A2142T

PTPRO

amplification

RAD52

amplification

RET

Q681E

TEK

loss

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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	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	PDCC1 (PD-1)	PDCC1LG2 (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, 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. 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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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 $\geq 16\%$ 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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ORDERED TEST # ORD-1585457-01

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
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

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) 7.6.0

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The median exon coverage for this sample is 813x

ORDERED TEST # ORD-1585457-01

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APPENDIX

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