

**ABOUT THE TEST** FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

<b>PATIENT</b>	<b>DISEASE</b> Unknown primary adenocarcinoma	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN SITE</b> Ovary
	<b>NAME</b> Huang, Chien Chung		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN ID</b> S112-66168H (PF23084)
	<b>DATE OF BIRTH</b> 04 January 1951		<b>ADDITIONAL RECIPIENT</b> None		<b>SPECIMEN TYPE</b> Slide Deck
	<b>SEX</b> Female		<b>MEDICAL FACILITY ID</b> 205872		<b>DATE OF COLLECTION</b> 21 March 2023
	<b>MEDICAL RECORD #</b> 17051911 PF23084		<b>PATHOLOGIST</b> Not Provided		<b>SPECIMEN RECEIVED</b> 22 June 2023

**Sample qualified for low tumor purity. Sensitivity for detecting copy-number alterations (including in *ERBB2*), other genomic alterations, and signatures may be reduced and TMB may be underreported. Refer to the appendix for limitations statements.**

### Biomarker Findings

**Microsatellite status** - Cannot Be Determined<sup>α</sup>  
**Tumor Mutational Burden** - Cannot Be Determined

### Genomic Findings

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

**SMAD4** G386D

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

### Report Highlights

- There are no highlights associated with this patient's genomic findings.

For more information on potential biological and clinical significance, see the Biomarker and Genomic Findings sections.

#### BIOMARKER FINDINGS

**Microsatellite status** -  
Cannot Be Determined

**Tumor Mutational Burden** -  
Cannot Be Determined

#### THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

**No therapies or clinical trials are associated with the Genomic Findings for this sample.**

If you have questions or comments about this result, please contact your local Customer Service team  
<https://www.rochefoundationmedicine.com/home/contact-us.html>

#### 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.

**SMAD4** - G386D ..... p. 5

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**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-1658385-01

**BIOMARKER FINDINGS**
**BIOMARKER**

# Microsatellite status

**RESULT**

Cannot Be Determined

**POTENTIAL TREATMENT STRATEGIES**
**— Targeted Therapies —**

On the basis of clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)<sup>1-2</sup> may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), retifanlimab, and pembrolizumab<sup>3-9</sup>, as well as PD-L1-targeting agents atezolizumab, avelumab, and durvalumab (alone or in

combination with tremelimumab)<sup>10-11</sup>. As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

**FREQUENCY & PROGNOSIS**

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)<sup>12-19</sup>, colorectal cancers (CRCs; 10-15%)<sup>2,20-23</sup>, and gastric cancers (12-35%)<sup>24-27</sup> and at lower frequencies in many other tumor types, including esophageal<sup>28</sup>, small bowel<sup>29-33</sup>, hepatobiliary<sup>34-40</sup>, prostate<sup>41-43</sup>, and urinary tract carcinomas<sup>44-46</sup>. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy<sup>47</sup>. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting<sup>12,15-16,18,48-50</sup>. However, studies specifically analyzing early stage endometrial

cancer have reported a correlation between MSI-H and decreased survival<sup>14,17,19,49</sup>, thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

**FINDING SUMMARY**

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor<sup>22</sup>. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2<sup>22,51-52</sup>. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

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## BIOMARKER FINDINGS

## BIOMARKER

# Tumor Mutational Burden

## RESULT

Cannot Be Determined

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1<sup>53-55</sup>, anti-PD-1 therapies<sup>53-56</sup>, and combination nivolumab and ipilimumab<sup>57-62</sup>. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors<sup>53-56,63-67</sup>. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB  $\geq 10$  Muts/Mb (as measured by this assay) compared with those with TMB  $< 10$  Muts/Mb in a large cohort that included multiple tumor types<sup>63</sup>; similar findings were observed in the KEYNOTE 028 and 012 trials<sup>56</sup>. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores  $\geq 10$  Muts/Mb were associated with prolonged time to treatment failure compared with

scores  $< 10$  muts/Mb (HR=0.68)<sup>67</sup>. 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  $\geq 10$  Muts/Mb independent of blood TMB at any cutpoint in matched samples<sup>68</sup>. 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  $\geq 16$  Muts/Mb than those with TMB  $\geq 10$  and  $< 16$  Muts/Mb<sup>66</sup>. 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 chemotherapy<sup>69</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>54</sup>. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

## FREQUENCY & PROGNOSIS

Carcinomas that have been reported to harbor the highest frequencies of elevated TMB include colorectal (CRC) (8-25%)<sup>23,70</sup>, endometrial (7-24%)<sup>71</sup>, intestinal type gastric (20%)<sup>72</sup>, and non-small cell lung carcinoma (NSCLC; 8-13%)<sup>73-74</sup>. In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis<sup>75</sup>, as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of

high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)<sup>73</sup>. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC<sup>75-76</sup>, several other large studies did find a strong link<sup>77-80</sup>. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations<sup>23,70</sup> and with microsatellite instability (MSI)<sup>70</sup>, which in turn has been reported to correlate with better prognosis<sup>20,81-87</sup>. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma<sup>71,88-90</sup> and bladder cancer<sup>91</sup>, it is also linked with improved prognosis in patients with these tumor types<sup>71</sup>.

## FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma<sup>92-93</sup> and cigarette smoke in lung cancer<sup>8,94</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>95-96</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>23,71,97-99</sup>, and microsatellite instability (MSI)<sup>23,71,99</sup>. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types<sup>54-56,63</sup>. However, the TMB level in this sample could not be determined with confidence.

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GENOMIC FINDINGS

GENE  
**SMAD4**

ALTERATION  
G386D

HGVS VARIANT  
NM\_005359.5:c.1157G>A (p.G386D)

VARIANT CHROMOSOMAL POSITION  
chr18:48593406

VARIANT ALLELE FREQUENCY (% VAF)  
5.9%

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 A<sup>100</sup> and the Wnt/beta-catenin pathway<sup>101</sup>.

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with improved responses to chemotherapeutic agents in

patients with pancreatic cancer<sup>102-104</sup> and non-small cell lung cancer (NSCLC)<sup>105</sup>. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy<sup>106</sup> and adjuvant chemoradiotherapy<sup>107</sup>.

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)<sup>108</sup>, pancreatic acinar cell carcinoma (26%)<sup>109</sup>, cholangiocarcinoma (25%)<sup>110</sup>, small intestine cancer (20%)<sup>111</sup>, appendiceal adenocarcinoma (14-20% mutation; 57% deletion)<sup>112-113</sup>, colorectal adenocarcinoma (CRC; 14%)<sup>23</sup>, esophageal adenocarcinoma (14%)<sup>114</sup>, and stomach adenocarcinoma (13%)<sup>115</sup>. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)<sup>116</sup> and intraductal papillary mucinous neoplasms (IPMN)<sup>117</sup>; 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 IPMNs<sup>118</sup>. SMAD4 gene alterations have been associated with reduced OS for patients with pancreatic adenocarcinoma<sup>119</sup>. Reduced SMAD4 expression has been associated

with worse prognosis in various cancer types, including CRC<sup>120-122</sup>, appendiceal mucinous neoplasm<sup>123</sup>, gastric adenocarcinoma<sup>124-125</sup>, esophageal adenocarcinoma<sup>126</sup>, esophageal squamous cell carcinoma<sup>127</sup>, breast cancer<sup>128</sup>, and prostate cancer<sup>129</sup>.

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling<sup>130-131</sup>. 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 inactivating<sup>132-145</sup>.

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome<sup>146-148</sup>, which is associated with an increased risk of gastrointestinal cancers<sup>149</sup>. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65<sup>150</sup>. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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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.

**MSH6**

 NM\_000179.2:  
 c.4068\_4071dup  
 (p.K1358Dfs\*2)  
 chr2:48033981

**PRDM1**

 NM\_001198.3: c.1735G>A  
 (p.V579I)  
 chr6:106553770

**TSC1**

 NM\_000368.4: c.1960C>G  
 (p.Q654E)  
 chr9:135781005

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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, Cipalstraat 3, 2440 Geel, Belgium. 

## ABOUT FOUNDATIONONE CDx

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details:  
[www.rochefoundationmedicine.com/f1cdxtech](http://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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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](http://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](http://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

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ORDERED TEST # ORD-1658385-01

APPENDIX

About FoundationOne®CDx

- MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as “MS-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](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

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ORDERED TEST # ORD-1658385-01

**APPENDIX**

About FoundationOne®CDx

distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

**VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS**

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1*, *CBL*, *DNMT3A*, *IDH2*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear 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) 7.10.0

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**ORDERED TEST #** ORD-1658385-01

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