

**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> Bladder urothelial (transitional cell) carcinoma	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN SITE</b> Bladder
	<b>NAME</b> Wu, Chin-Hsiu		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN ID</b> S111-05667A (PF22020)
	<b>DATE OF BIRTH</b> 01 November 1948		<b>ADDITIONAL RECIPIENT</b> None		<b>SPECIMEN TYPE</b> Slide Deck
	<b>SEX</b> Male		<b>MEDICAL FACILITY ID</b> 205872		<b>DATE OF COLLECTION</b> 14 February 2022
	<b>MEDICAL RECORD #</b> 47918183		<b>PATHOLOGIST</b> Not Provided		<b>SPECIMEN RECEIVED</b> 24 February 2022

## Biomarker Findings

**Microsatellite status** - MS-Stable  
**Tumor Mutational Burden** - 1 Muts/Mb

## Genomic Findings

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

**KRAS amplification**  
**MDM2 amplification**  
**CDKN2A/B CDKN2A loss**  
**KDM6A L1119del**

**2 Disease relevant genes with no reportable alterations: *FGFR2, FGFR3***

† See About the Test in appendix for details.

## Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 6)

### BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 1 Muts/Mb

### GENOMIC FINDINGS

**KRAS** - amplification

**7 Trials** see p. 6

**MDM2** - amplification

**4 Trials** see p. 8

### 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

### 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 - CDKN2A loss**..... p. 5    **KDM6A - L1119del**..... p. 5

**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.

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**Post-Sequencing Analysis:** 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531



PATIENT  
Wu, Chin-Hsiu

TUMOR TYPE  
Bladder urothelial (transitional  
cell) carcinoma  
COUNTRY CODE  
TW

REPORT DATE  
02 Mar 2022

ORDERED TEST #  
ORD-1308443-01

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 inhibitors<sup>1-3</sup>, including approved therapies nivolumab and pembrolizumab<sup>4</sup>. 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%,  $p=0.001$ )<sup>5</sup>.

### FREQUENCY & PROGNOSIS

MSI has been detected in 26-49% of urothelial carcinomas<sup>6-7</sup>; MSI-H has also been reported in multiple case studies of upper urinary tract urothelial carcinoma<sup>8</sup>. MSI, as determined through loss of MSH2 or MSH6 protein expression, correlated with non-invasive, well-differentiated bladder tumors and favorable overall survival<sup>6</sup>.

### 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>9</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>9-11</sup>. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers<sup>12-14</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>9,11,13-14</sup>.

## BIOMARKER

## Tumor Mutational Burden

## RESULT

1 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-L1<sup>15-17</sup>, anti-PD-1 therapies<sup>15-18</sup>, and combination nivolumab and ipilimumab<sup>19-24</sup>. In multiple studies of immune checkpoint inhibitors in urothelial carcinoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-L1<sup>15,25-29</sup> and anti-PD-1 immunotherapeutic agents<sup>30-31</sup>. For patients with metastatic urothelial carcinoma treated with the PD-L1 inhibitor atezolizumab, those with a

significantly increased mutational load (9.7 Muts/Mb or greater by this assay or others) were associated with response and longer OS compared with those with lower TMB<sup>15,25-27</sup>. Similarly, in a study of pembrolizumab in muscle invasive bladder cancer, the median TMB in responders was 12.3 Muts/Mb, versus 7.0 Muts/Mb in nonresponding patients<sup>31</sup>. The PD-1 inhibitor nivolumab led to increased ORR, PFS, and OS for patients with a TMB of 167 missense mutations/tumor or higher (~ equivalency = 9 Muts/Mb or higher as measured by this assay) compared with those harboring lower TMB in a study of metastatic urothelial cancer<sup>30</sup>.

### FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, the median somatic mutation burden was 5.5 mutations per megabase (mut/Mb)<sup>32</sup>. One study reported that the number of somatic mutations positively correlates with increased tumor stage and grade of bladder cancers<sup>33</sup>. For patients with metastatic urothelial carcinoma receiving atezolizumab, however, higher median

mutation load has been reported to be significantly associated with improved PFS and OS<sup>25-26,34</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>35-36</sup> and cigarette smoke in lung cancer<sup>37-38</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>39-40</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>41-45</sup>, and microsatellite instability (MSI)<sup>41,44-45</sup>. 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 in urothelial carcinoma<sup>15,25-29,46</sup>.

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## GENOMIC FINDINGS

## GENE

# KRAS

ALTERATION  
amplification

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib<sup>47-52</sup>. Clinical evidence that KRAS amplification in the absence of a concurrent KRAS

activating mutation is sensitive to MEK inhibitors is limited. A Phase 2 study of selumetinib plus docetaxel in patients with gastric cancer reported 1/2 patients with KRAS amplification experienced a PR<sup>53</sup>. A patient with cervical cancer harboring both KRAS and PIK3CA amplification treated with the combination of trametinib and the AKT inhibitor GSK2141795 achieved a SD<sup>54</sup>.

### FREQUENCY & PROGNOSIS

KRAS amplification has been reported in 1-4% of bladder urothelial carcinomas<sup>55-56</sup>. Prognostic implications of KRAS amplification in the context of urothelial carcinoma have not been extensively investigated in the literature (PubMed, Nov 2021).

### 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<sup>48,57</sup>. In numerous cancer type-specific studies as well as a large-scale pan-cancer analysis, KRAS amplification was shown to correlate with increased expression<sup>58-61</sup>. Additionally, KRAS amplification correlated with sensitivity of cancer cell lines to KRAS knockdown, suggesting that amplified KRAS is an oncogenic driver<sup>61</sup>.

## GENE

# MDM2

ALTERATION  
amplification

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

MDM2 antagonists disrupt the MDM2-p53 interaction, thereby stabilizing p53<sup>62</sup>. Preclinical studies have suggested that the amplification of MDM2, in the absence of concurrent TP53 mutations, may increase sensitivity to these agents<sup>63-64</sup>. Preliminary Phase 1 studies of the MDM2-p53 antagonist alrizomadlin (APG-115) reported a PR in a patient with liposarcoma harboring an MDM2 amplification and wildtype for TP53 and SD in 21%-38% (6/28 and 5/13, respectively) of patients in genomically unselected solid tumors<sup>65-66</sup>. A Phase 2 trial of alrizomadlin in combination with pembrolizumab reported a PR in 1 of 3 patients with malignant peripheral nerve sheath tumor that had failed standard therapy, as well as PRs in patients with multiple types of solid tumors that had failed immunotherapy, including 1 out of 14 patients

with non-small cell lung cancer; 1 out of 5 patients with urothelial carcinoma; and 2 out of 5, 1 out of 5, and 1 out of 11 patients with mucosal, uveal, and cutaneous melanoma, respectively<sup>67</sup>. Phase 1b studies of the MDM2 inhibitor idasanutlin for refractory AML in combination with cytarabine or venetoclax reported anti-leukemic response rates of 33% (25/75) and 37% (11/30), respectively<sup>68-69</sup>; clinical benefit (58% ORR, 7/12) with idasanutlin monotherapy has been reported for patients with polycythemia vera<sup>70</sup>. The dual MDM2/MDM4 inhibitor ALRN-6924 led to an ORR of 27% (4/15) for patients with TP53 wildtype peripheral T-cell lymphoma in a Phase 2 study<sup>71</sup>; responses have also been observed in TP53 wildtype AML, MDS, Merkel cell carcinoma, colorectal cancer, and liposarcoma<sup>72-73</sup>.

### FREQUENCY & PROGNOSIS

MDM2 amplification has been reported in 5-9% of urothelial carcinoma cases<sup>32,74-79</sup>. Altered MDM2 protein expression in invasive urothelial carcinoma has been reported in several studies, with the reported frequency ranging from 9-61%<sup>74,80-83</sup>. One study reported that alteration of MDM2 or TP53 was not associated with outcomes of patients with bladder cancer<sup>79</sup>. Studies on correlation between MDM2 expression and

disease stage of urothelial cancer have yielded conflicting results; MDM2 expression alone does not appear to be a marker of clinical outcome in patients with urothelial carcinoma<sup>74,80-81</sup>.

### FINDING SUMMARY

MDM2 encodes an E3 ubiquitin protein ligase, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins<sup>84-86</sup>. MDM2 acts to prevent the activity of the tumor suppressor p53; therefore, overexpression or amplification of MDM2 may be oncogenic<sup>87-88</sup>. Overexpression or amplification of MDM2 is frequent in cancer<sup>89</sup>. Although two retrospective clinical studies suggest that MDM2 amplification may predict a short time-to-treatment failure on anti-PD-1/PD-L1 immune checkpoint inhibitors, with 4/5 patients with MDM2 amplification<sup>90</sup> and 2/3 patients with MDM2 or MDM4 amplification<sup>91</sup> experiencing tumor hyperprogression, amplification of MDM2 or MDM4 was not associated with shorter progression-free survival (PFS) in a retrospective analysis of non-small cell lung cancer (NSCLC) outcomes with immune checkpoint inhibitors (hazard ratio of 1.4, p=0.44)<sup>92</sup>. The latter study reported PFS of >2 months for 5/8 patients with MDM2/MDM4 amplification<sup>92</sup>.

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## GENOMIC FINDINGS

## GENE

## CDKN2A/B

## ALTERATION

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 palbociclib<sup>93-96</sup>. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment<sup>97-98</sup>, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents<sup>99-105</sup>; 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 inhibitors<sup>64,106</sup>, the clinical relevance of p14ARF as a predictive biomarker is not clear.

### FREQUENCY & PROGNOSIS

In the Bladder Urothelial Carcinoma TCGA dataset, concurrent homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of cases, and CDKN2A mutation has been found in 5.5% of cases<sup>32</sup>. Loss of CDKN2A/B or loss of p14ARF, p16INK4a, or p15INK4b protein expression occurs frequently in bladder urothelial carcinoma, with reports of frequency ranging from 18% to 77%<sup>107-115</sup>. Several studies have associated loss of CDKN2A/B or loss of p16INK4a and p15INK4b expression with disease progression, decreased recurrence-free disease, and poor prognosis in patients with urothelial carcinoma, although results have been inconsistent<sup>55,107-108,110,113,116-118</sup>.

### FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b<sup>119-120</sup>. 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 control<sup>121-122</sup>. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition<sup>123-124</sup>. One or more alterations observed here are predicted to result in p16INK4a loss of function<sup>125-146</sup>. One or more alterations seen here are predicted to result in p14ARF loss of function<sup>129,146-149</sup>.

### 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 cancer<sup>150</sup>. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma<sup>151-152</sup>. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases<sup>153-155</sup>. 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 tumors<sup>156-158</sup>. In the appropriate clinical context, germline testing of CDKN2A is recommended.

## GENE

## KDM6A

## ALTERATION

L1119del

## TRANSCRIPT ID

NM\_021140

## CODING SEQUENCE EFFECT

3354\_3356delTCT

## VARIANT ALLELE FREQUENCY (% VAF)

20.5%

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

There are no therapies available to address KDM6A alterations in cancer.

### FREQUENCY & PROGNOSIS

KDM6A mutations have been reported in 3.9% of samples analyzed, with the highest incidence in tumors of the urinary tract (31%), liver (7.3%), endometrium (6.7%), salivary gland (6.0%), and pancreas (5.1%) (COSMIC, Jan 2022)<sup>159</sup>. KDM6A mutations or copy number alterations have also been identified in medulloblastoma (8.9%)<sup>160</sup>, adenoid cystic carcinoma (6.7%)<sup>161</sup>, and metastatic prostate cancer (10%)<sup>162</sup>. KDM6A inactivation has been found as a recurrent tumorigenic event in

male T-cell acute lymphoblastic leukemia (T-ALL), and loss of KDM6A increased the sensitivity of T-ALL cells to therapies targeting histone H3 lysine 27 methylation in preclinical assays<sup>163</sup>. However, KDM6A overexpression has been noted in breast cancer and renal cell carcinoma, and correlated with inferior prognosis in patients with breast cancer<sup>164-166</sup>.

### FINDING SUMMARY

KDM6A encodes a histone H3 lysine 27 demethylase UTX, which functions as a transcriptional regulator<sup>167</sup>. A significant number of inactivating KDM6A mutations have been found across multiple tumor types, suggesting a role as a tumor suppressor<sup>167</sup>.

**ORDERED TEST #** ORD-1308443-01

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

**GENE**
**KRAS**
**RATIONALE**

KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway

components, including MEK inhibitors.

**ALTERATION**

amplification

**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)

**NCT03284502**
**PHASE 1**

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

**TARGETS**

MEK, RAFs

**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)

**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), Texas

**NCT02407509**
**PHASE 1**

Phase I Trial of RO5126766

**TARGETS**

RAFs, MEK, mTOR

**LOCATIONS:** London (United Kingdom), Sutton (United Kingdom)

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CLINICAL TRIALS

**NCT04800822****PHASE 1**

PF-07284892 in Participants With Advanced Solid Tumors

**TARGETS**

SHP2, ROS1, ALK, MEK, BRAF, EGFR

LOCATIONS: California, Michigan, New York, Tennessee, Texas

**NCT03162627****PHASE 1**

Selumetinib and Olaparib in Solid Tumors

**TARGETS**

MEK, PARP

LOCATIONS: Texas

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**CLINICAL TRIALS**
**GENE**
**MDM2**
**ALTERATION**

amplification

**RATIONALE**

Inhibitors of the MDM2-p53 interaction are being tested in clinical trials. Overexpression or

amplification of MDM2 may increase sensitivity to these agents, but more data are required.

**NCT04589845**
**PHASE 2**

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

**TARGETS**

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

**LOCATIONS:** Zhongzheng Dist. (Taiwan), Taipei City (Taiwan), Taoyuan County (Taiwan), Tainan (Taiwan), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing (China), Chengdu City (China)

**NCT03449381**
**PHASE 1**

This Study Aims to Find the Best Dose of BI 907828 in Patients With Different Types of Advanced Cancer (Solid Tumors)

**TARGETS**

MDM2

**LOCATIONS:** Tokyo, Chuo-ku (Japan), Berlin (Germany), Tübingen (Germany), Leuven (Belgium), Barcelona (Spain), Ottawa (Canada), Connecticut, New York, Tennessee, Florida

**NCT03611868**
**PHASE 1/2**

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

**TARGETS**

MDM2, PD-1

**LOCATIONS:** Brisbane (Australia), South Brisbane (Australia), Bedford Park (Australia), Heidelberg (Australia), California, Arizona, Missouri, Arkansas, Pennsylvania, New York

**NCT03725436**
**PHASE 1**

ALRN-6924 and Paclitaxel in Treating Patients With Advanced, Metastatic, or Unresectable Solid Tumors

**TARGETS**

MDM2, MDM4

**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.

**IDH2**  
M397V

**MLH1**  
V61I

**PARP3**  
A235V and H146Y

**SMO**  
R199W

**ZNF703**  
L63H

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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)	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	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73
CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R
CTCF	CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2	DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FAM46C	FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12
FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3
FGFR4	FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3
GATA4	GATA6	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDMSA	KDMS5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKKN1	MLH1	MPL	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	NSD3 (WHSC1L1)	NTSC2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI	PTCH1
PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	REL	RET
RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC	SDHD	SETD2
SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOC3
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	WT1	XPO1
XRCC2	ZNF217	ZNF703						

**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TMPRSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated

**ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS**

Loss of Heterozygosity (LOH) score

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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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 PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

### THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

#### Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

#### Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification - equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss - equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

### Ranking of Therapies and Clinical Trials

#### Ranking of Therapies in Summary Table

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

#### Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

### NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) ([www.nccn.org](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. 2022. 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 fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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About FoundationOne®CDx

- Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- 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.
  - 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 = 1<sup>st</sup> Quartile to 3<sup>rd</sup> 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; 291656669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PALB2*, *PMS2*, *POLE*, *RAD51C*, *RAD51D*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TSC2*, and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

## VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

#### LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

#### NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

#### NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

#### TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

#### SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
mut/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 6.0.0

**The median exon coverage for this sample is 869x**

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**APPENDIX**
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