FOUNDATIONONE®CDx

PATIENT
Hsu, Ching-Tzu

TUMOR TYPE
Brain meningioma
COUNTRY CODE
TW

REPORT DATE
23 Feb 2022
ORDERED TEST #
ORD-1302978-01

**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** Brain meningioma
**NAME** Hsu, Ching-Tzu
**DATE OF BIRTH** 22 December 1974
**SEX** Female
**MEDICAL RECORD #** 46429587

**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** Brain
**SPECIMEN ID** S110-40615A (PF22019)
**SPECIMEN TYPE** Slide Deck
**DATE OF COLLECTION** 21 December 2021
**SPECIMEN RECEIVED** 15 February 2022

**Sensitivity for the detection of copy number alterations is reduced due to sample quality.**

## Biomarker Findings

**Microsatellite status -** MS-Stable
**Tumor Mutational Burden -** 0 Muts/Mb

## Genomic Findings

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

***AKT1*** E17K
***MUTYH*** splice site 892-2A>G

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Everolimus** (p. 6)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 7)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH* splice site 892-2A>G** (p. 5)

| BIOMARKER FINDINGS | THERAPY AND CLINICAL TRIAL IMPLICATIONS |
|---|---|
| **Microsatellite status -** MS-Stable | **No therapies or clinical trials.** see Biomarker Findings section |
| **Tumor Mutational Burden -** 0 Muts/Mb | **No therapies or clinical trials.** see Biomarker Findings section |

| GENOMIC FINDINGS | THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE) | THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE) |
|---|---|---|
| ***AKT1* -** E17K | none | Everolimus 2B |
| **10 Trials** see p. 7 | | Temsirolimus |

2B *NCCN category*

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

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

***MUTYH* -** splice site 892-2A>G ..... p. 5

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



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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.*



**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

# 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[1-3], including approved therapies nivolumab and pembrolizumab[4]. 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

The reported incidence of MSI in meningioma has varied significantly between studies[6-12]. The prognostic significance of MSI in meningioma is unknown (PubMed, Aug 2021).

### 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[13]. 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[13-15]. 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[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18].

BIOMARKER

# Tumor Mutational Burden

**RESULT**
0 Muts/Mb

### POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[19-21], anti-PD-1 therapies[19-22], and combination nivolumab and ipilimumab[23-28]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[19-22,29]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[19]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[30] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[20]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[22,29]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

### FREQUENCY & PROGNOSIS

Meningioma harbors a median TMB of 1.8 mutations per megabase (muts/Mb), and 0.9% of cases have high TMB (>20 muts/Mb)[31]. Grade 2 or 3 meningiomas have been associated with a higher mutation rate than Grade 1 meningiomas; meningiomas were reported to have a smaller number of somatic alterations relative to other tumor types[32].

### 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[33-34] and cigarette smoke in lung cancer[35-36], treatment with temozolomide-based chemotherapy in glioma[37-38], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[39-43], and microsatellite instability (MSI)[39,42-43]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[20-21,29].



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GENE
## *AKT1*

**ALTERATION**
E17K

**TRANSCRIPT ID**
NM_001014431

**CODING SEQUENCE EFFECT**
49G>A

**VARIANT ALLELE FREQUENCY (% VAF)**
36.0%

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

Mutations that activate AKT1 may predict activity of AKT1 inhibitors in various tumor types. Phase 3 trials of AKT inhibitor combination treatments for patients with advanced breast cancer (capivasertib) and prostate cancer (ipatasertib) are furthest in development[44], and basket trials have also shown responses in a variety of other solid tumors[45-46]. An NCI-MATCH subprotocol of capivasertib for patients with breast cancer (18 patients) and other tumor types (17 patients) reported an ORR of 29% (10/35) with 1 CR experienced by a patient with endometrioid endometrial adenocarcinoma and PRs experienced by 7 patients with breast cancer, 1 patient with uterine leiomyosarcoma, and 1 patient with oncocytic carcinoma of the parotid gland[46]. A patient with AKT1 E17K mutation-positive meningothelial meningioma treated with capivasertib experienced stable disease and a minor radiographic response lasting over 1 year[47]. On the basis of clinical data in solid tumors, AKT1 activating mutations may be sensitive to mTOR inhibitors such as everolimus and temsirolimus[48-52]. In an exploratory analysis, a study for patients with AKT1-mutated hormone-receptor-positive (HR+), HER2-negative breast cancer treated with the investigational ATP-competitive MTOR-inhibitor sapanisertib and exemestane or fulvestrant reported a positive association between best overall response (CR+PR) and AKT1-mutated status (n=11) compared with patients with AKT1-wildtype status (n=42) (p<0.03)[53]. In a retrospective analysis of clinical outcomes for patients with HR+ breast cancer, AKT1 E17K was associated with significantly increased median duration of treatment with everolimus-containing regimens[54].

## FREQUENCY & PROGNOSIS

AKT1 mutation has been reported in 11.5% of meningioma samples analyzed (COSMIC, Mar 2021)[55]. The AKT1 E17K mutation has been reported to occur mainly in Grade 1 meningiomas, and only rarely in Grades 2 or 3, cited in 7-11% of Grade 1 cases[32,56]. AKT1 E17K mutations have been shown to be mutually exclusive with NF2 mutations in meningiomas[32]. Increased AKT1 activity has also been detected in meningiomas, with one study identifying AKT1 activity (p-AKT) in 45% and 8% of anaplastic and atypical meningiomas, respectively, as compared to 5% in benign meningioma tissue[57-58]. AKT1 E17K was associated with shorter time to recurrence for patients with meningioma when compared with wildtype AKT1 tumors (P=0.046)[59].

## FINDING SUMMARY

AKT1 encodes an intracellular serine/threonine kinase and is one of three members of the AKT gene family. AKT activation promotes cell survival via inhibition of apoptosis and also contributes to cell proliferation through several interactions with the cell cycle machinery; inappropriate activation of AKT can therefore lead to tumor formation[60]. Missense mutations and in-frame duplications that occur in the pleckstrin homology (PH) domain of AKT1, as seen here, have been shown to transform cells and activate AKT signaling and are therefore considered to be oncogenic[61-67].



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GENE
# *MUTYH*

**ALTERATION**
splice site 892-2A>G

**TRANSCRIPT ID**
NM_001048171

**CODING SEQUENCE EFFECT**
892-2A>G

**VARIANT ALLELE FREQUENCY (% VAF)**
45.8%

## POTENTIAL TREATMENT STRATEGIES

**— Targeted Therapies —**

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

## FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2022)[55]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[68-69]. There is conflicting data regarding the impact of monoallelic mutations on the risk of developing CRC[70-72]. Patients with MUTYH-mutant CRC were reported to have significantly improved overall survival compared to patients without MUTYH mutation[73].

## FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[74]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[68-69,75-77]. Numerous other MUTYH mutations have also been shown to result in loss of function[75-78].

## POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with MUTYH-associated polyposis (ClinVar, Sep 2021)[79]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[68,80-82]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[68]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[83-87]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[69]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.



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# Everolimus

*Assay findings association*

**AKT1**
E17K

### AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

AKT1 activating mutations may predict sensitivity to mTOR inhibitors. A clinicogenomic registry study showed significantly increased median duration of treatment with everolimus-containing regimens for patients with AKT1 E17K-mutated breast cancer compared with AKT1-wildtype disease[54]. Individual patients with AKT1-mutated endometrial cancer[48-49], papillary thyroid cancer[50], ovarian cancer[51], or thymoma[52] have achieved objective response or disease control with mTOR inhibitor treatment.

### SUPPORTING DATA

A patient with meningioma with pulmonary metastases experienced a clinical and radiographic response to everolimus treatment[88]. A study of 3 patients with NF2 meningioma treated with everolimus reported no responses or progressive disease[89]. A preclinical study reported that everolimus and temsirolimus both inhibited meningioma cell growth and resulted in a 70% decrease in tumor growth in orthotopic and subcutaneous xenograft mouse models[90]. Other preclinical studies of meningioma cells in vitro have shown that everolimus synergized with octreotide to inhibit cell proliferation and reduce cell viability[91-92]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[93], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[94].

# Temsirolimus

*Assay findings association*

**AKT1**
E17K

### AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

AKT1 activating mutations may predict sensitivity to mTOR inhibitors. A clinicogenomic registry study showed significantly increased median duration of treatment with everolimus-containing regimens for patients with AKT1 E17K-mutated breast cancer compared with AKT1-wildtype disease[54]. Individual patients with AKT1-mutated endometrial cancer[48-49], papillary thyroid cancer[50], ovarian cancer[51], or thymoma[52] have achieved objective response or disease control with mTOR inhibitor treatment.

### SUPPORTING DATA

Clinical data on the efficacy of temsirolimus for the treatment of meningioma are limited (PubMed, Oct 2021). A Phase 1 trial of bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced solid tumors showed that the combination was well tolerated and resulted in six-month SD in 21% of patients, with a 21% rate of partial or complete remission[95]. In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), temsirolimus showed clinical benefit, but further studies are warranted[96]. A Phase 2 study of temsirolimus in patients with KRAS-mutant colorectal cancer reported limited efficacy; however, all patients who exhibited tumor reduction were found to have low levels of mutated KRAS in plasma samples[97]. A Phase 2 clinical trial in patients with pancreatic cancer reported that temsirolimus monotherapy had limited efficacy, and may have contributed to disease progression[98]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[99].

**NOTE** Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.



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**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. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

**GENE**
*AKT1*

**ALTERATION**
E17K

**RATIONALE**
AKT1 amplification or mutation may lead to activation of AKT signaling and therefore may result in sensitivity to AKT pathway inhibitors.

Inhibitors of AKT and the downstream protein mTOR are under investigation in clinical trials.

## 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)

## NCT03239015

**PHASE 2**

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

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

**LOCATIONS:** Shanghai (China)

## NCT04337463

**PHASE NULL**

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

**TARGETS**
mTORC1, mTORC2, PD-1

**LOCATIONS:** Chongqing (China), Chengdu (China)

## NCT04803318

**PHASE 2**

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

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

**LOCATIONS:** Guangzhou (China)

## NCT03772561

**PHASE 1**

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

**TARGETS**
PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

## NCT04632992

**PHASE 2**

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

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

**LOCATIONS:** Alaska, Washington, Oregon, California, Idaho

## NCT03994796

**PHASE 2**

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

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

**LOCATIONS:** Washington, Oregon, Idaho, Montana

## NCT03673787

**PHASE 1/2**

A Trial of Ipatasertib in Combination With Atezolizumab

**TARGETS**
AKTs, PD-L1

**LOCATIONS:** Sutton (United Kingdom)

## NCT03065062

**PHASE 1**

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

**TARGETS**
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

**LOCATIONS:** Massachusetts

## NCT03217669

**PHASE 1**

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

**TARGETS**
IDO1, mTOR

**LOCATIONS:** Kansas

**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.

***CIC***
Q907E

***DIS3***
N630D

***EPHA3***
A731V

***GNAS***
P53L

***MAP3K1***
L78P

***MRE11A***
F13L

***PIK3C2B***
A1004S



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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* | *ERRFI1* | *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* | *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* | *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)* | *NT5C2* | *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* | *SOCS1* |
| *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* | *RSPO2* | *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)



Electronically signed by Erik Williams, M.D. | 23 February 2022
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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. CE

## 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 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). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

### Limitations

1. In the 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-

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. 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.
4. 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.
5. 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.
6. 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 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 |

MR Suite Version 6.0.0

The median exon coverage for this sample is 843x



Electronically signed by Erik Williams, M.D. | 23 February 2022
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