

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 anaplastic astrocytoma	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Brain
	NAME Chi, Ying-Hung		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S110-34918 B (PF21054)
	DATE OF BIRTH 25 January 1987		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Male		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 15 November 2021
	MEDICAL RECORD # 38827315		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 30 November 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

IDH1 R132G
ATRX E886fs*18
CDKN2A/B CDKN2B loss, CDKN2A loss
MTAP loss
TP53 R273C

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: **ATRX** E886fs*18 (p. 4), **IDH1** R132G (p. 3)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Ivosidenib** (p. 8)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: **IDH1** R132G (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: **IDH1** R132G (p. 3)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 3 Muts/Mb

GENOMIC FINDINGS

IDH1 - R132G

10 Trials see p. 9

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

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

Ivosidenib

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.

ATRX - E886fs*18.....	p. 4	MTAP - loss.....	p. 6
CDKN2A/B - CDKN2B loss, CDKN2A loss.....	p. 5	TP53 - R273C.....	p. 7

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

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

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BIOMARKER FINDINGS
BIOMARKER

Microsatellite status

RESULT

MS-Stable

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and

experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, $p=0.001$)⁵.

FREQUENCY & PROGNOSIS

MSI-High has been reported in 3-8% of adult or pediatric astrocytomas and was generally not associated with Lynch syndrome⁶⁻⁸. Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples⁹⁻¹¹. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples⁹, although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs¹². The frequency of MSI has been reported to be increased in relapsed compared to primary GBM⁹, in GBMs with a previous lower grade astrocytoma¹⁰, and in giant cell GBM compared to classic GBM¹¹.

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 tumor¹³. 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 PMS2¹³⁻¹⁵. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹⁶⁻¹⁸. 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

3 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-L1¹⁹⁻²¹, anti-PD-1 therapies¹⁹⁻²², and combination nivolumab and ipilimumab²³⁻²⁸. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported^{19,29-30}. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE

mutations have benefited from treatment with anti-PD-1³¹⁻³² or anti-PD-L1³³ therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Anaplastic astrocytoma harbors a median TMB of 1.8 mutations per megabase (mut/Mb), and 2% of cases have high TMB (>20 mut/Mb)³⁴. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB³⁵⁻³⁶. Increased TMB has been reported to correlate with higher tumor grade in glioma³⁷ and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency

(bMMRD)³¹, as well as with shorter OS of patients with diffuse glioma³⁸.

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 melanoma³⁹⁻⁴⁰ and cigarette smoke in lung cancer⁴¹⁻⁴², treatment with temozolomide-based chemotherapy in glioma⁴³⁻⁴⁴, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁴⁵⁻⁴⁹, and microsatellite instability (MSI)^{45,48-49}. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents^{19,29-33}.

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ORDERED TEST # ORD-1247965-01

GENOMIC FINDINGS

GENE

IDH1

ALTERATION

R132G

TRANSCRIPT ID

NM_005896

CODING SEQUENCE EFFECT

394C>G

VARIANT ALLELE FREQUENCY (% VAF)

40.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

IDH1 mutations that lead to production of 2-HG, most commonly R132 alterations, may predict sensitivity to IDH1-mutation-specific inhibitors such as ivosidenib⁵⁰. A Phase 1b/2 study of the IDH1 inhibitor olutasidenib for patients with IDH1-mutated glioma reported a DCR of 50% (n=24) with 1 PR⁵¹. A Phase 1 study of the pan-IDH1/IDH2 inhibitor vorasidenib for patients with IDH1- or IDH2-mutated glioma reported an ORR of 18.2% (4/22; RANO criteria) and median PFS of 31.4 months for non-enhancing cases and median PFS of 7.5 months for the overall glioma population (n=52)⁵². Preclinical studies suggested that IDH1 neomorphic mutations may also confer sensitivity to PARP inhibitors⁵³⁻⁵⁶. In a Phase 1

trial of the PD-L1 inhibitor atezolizumab in patients with glioblastoma (GBM), 2 of the 3 patients with IDH1-mutant tumors experienced clinical benefit (1 PR and 1 long-term SD); the third patient experienced short-term SD), whereas none of the 8 patients with IDH1-wild-type GBM experienced benefit (8/8 PD); significantly longer PFS and a trend toward longer OS were observed in the patients with IDH1-mutated tumors compared to the patients with IDH1-wild-type tumors³³. Preclinical data indicate that IDH1-mutated glioma may be sensitive to the glutaminase inhibitor telaglenastat in combination with radiotherapy⁵⁷.

— Nontargeted Approaches —

IDH1/2 mutations are associated with improved survival outcomes for patients treated with radiation or alkylating chemotherapy (NCCN CNS Cancers Guidelines, v5.2020).

FREQUENCY & PROGNOSIS

IDH1 mutation is characteristic of low-grade gliomas and secondary glioblastoma, and is relatively rare in primary glioblastoma⁵⁸⁻⁶². In the TCGA datasets, IDH1 mutation has been found in 77% of lower grade glioma cases and in 5% of glioblastoma cases⁶³⁻⁶⁴. IDH1 mutations are highly prevalent in grade 2 and grade 3 astrocytoma, oligodendroglioma, and oligoastrocytoma, reported in 43-100% of grade 2 tumors and

45-93% of grade 3 tumors⁶⁵⁻⁶⁸. IDH1/2 mutations are a strong favorable prognostic marker for OS in Grade 2-3 glioma, particularly in combination with 1p/19q codeletion (NCCN CNS Cancers Guidelines, v5.2020). Several studies have found IDH1 mutations to be associated with improved prognosis and longer PFS and OS in patients with various types of glioma including anaplastic astrocytoma and GBM^{62,69-75}.

FINDING SUMMARY

The isocitrate dehydrogenases IDH1 and IDH2 encode highly homologous enzymes that are involved in the citric acid (TCA) cycle and other metabolic processes, playing roles in normal cellular metabolism and in protection against oxidative stress and apoptosis⁷⁶. R132 is located within the active site of IDH1 and is a hotspot for mutations in cancer⁷⁶⁻⁸⁰. Substitutions at IDH1 R132 alter the enzymatic activity of IDH1, resulting in the production of the oncometabolite, D-2-hydroxyglutarate (2-HG)⁷⁸⁻⁸², which promotes tumorigenesis^{78,83-86}.

POTENTIAL DIAGNOSTIC IMPLICATIONS

IDH1/2 mutation is associated with Grade 2 and 3 astrocytomas and oligodendrogliomas, and distinguishes secondary glioblastoma (GBM) from primary GBM (NCCN CNS Cancers Guidelines, v5.2020).

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GENOMIC FINDINGS

GENE

ATRX

ALTERATION

E886fs*18

TRANSCRIPT ID

NM_000489

CODING SEQUENCE EFFECT

2656_2659delGAGA

VARIANT ALLELE FREQUENCY (% VAF)

81.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical⁸⁷⁻⁸⁸ and limited clinical data⁸⁹, ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT⁸⁹. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan⁹⁰, combined PARP and ATR inhibition⁸⁸, or double-

strand break-induction with agents such as doxorubicin, irinotecan, and topotecan⁹¹; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT⁹². ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)⁹²⁻⁹⁴, 12.6% of pheochromocytomas and paragangliomas⁹⁵, and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma⁹⁶⁻¹⁰⁰. ATRX loss in PNET^{93,101} and melanoma¹⁰² and mutation in other neuroendocrine tumors⁹⁵ is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy⁹¹. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma^{67,103-105} and has been proposed as a distinguishing biomarker^{67,104-105}. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma⁹⁷⁻¹⁰⁰. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with

IDH1/2 mutation but no ATRX mutation⁶⁷. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS¹⁰⁶⁻¹⁰⁷.

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance¹⁰⁸⁻¹⁰⁹. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)^{92,107,110-111}. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function¹¹²⁻¹¹⁴; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors^{108,115}. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)¹¹⁶.

POTENTIAL DIAGNOSTIC IMPLICATIONS

ATRX mutations often co-occur with IDH1/2 mutations and may be indicative of Grade 2-3 astrocytoma or secondary glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v5.2020)¹¹⁷.

ORDERED TEST # ORD-1247965-01

GENOMIC FINDINGS

GENE

CDKN2A/B

ALTERATION

CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib¹¹⁸⁻¹²¹. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment¹²²⁻¹²³, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents¹²⁴⁻¹³⁰; 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 inhibitors¹³¹⁻¹³², the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib^{125,127-128,133-135}.

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas¹³⁶ and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)⁶⁴ than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)¹³⁷⁻¹³⁸. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)¹³⁹⁻¹⁴¹. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples¹⁴². Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression^{140,143}. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas¹⁴⁴⁻¹⁴⁵.

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b¹⁴⁶⁻¹⁴⁷. 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 control¹⁴⁸⁻¹⁴⁹. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition¹⁵⁰⁻¹⁵¹. One or more alterations observed here are predicted to result in p16INK4a loss of function¹⁵²⁻¹⁷³. One or more alterations seen here are predicted to result in p14ARF loss of function^{156,173-176}. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b¹⁷⁷.

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 cancer¹⁷⁸. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma¹⁷⁹⁻¹⁸⁰. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases¹⁸¹⁻¹⁸³. 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 tumors¹⁸⁴⁻¹⁸⁶. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENOMIC FINDINGS

GENE

MTAP

ALTERATION

loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors¹⁸⁷. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss¹⁸⁸. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition^{187,189-190}, MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors¹⁹¹; dual PRMT1 and PRMT5 inhibition may be more effective¹⁹²⁻¹⁹⁴. In preclinical cancer models, MTAP inactivation showed increased

sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells¹⁹⁵⁻²⁰⁵. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients²⁰⁶.

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers²⁰⁷⁻²⁰⁸; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma²⁰⁹, gastrointestinal stromal tumors²¹⁰, mantle cell lymphoma (MCL)²¹¹, melanoma²¹²⁻²¹³, gastric cancer²¹⁴, myxofibrosarcoma²¹⁵, nasopharyngeal carcinoma²¹⁶, ovarian carcinoma²⁰⁷ and non-small cell lung cancer²¹⁷. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia²¹⁸ or in astrocytoma²¹⁹. However, MTAP has also

been reported to be overexpressed in colorectal cancer (CRC) samples²²⁰, and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM²²¹. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma²²²⁻²²³, esophageal cancer²²⁴⁻²²⁵, osteosarcoma²²⁶, and CRC²²⁷.

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity²²⁸⁻²²⁹. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment^{209,230-231}, thereby reducing intracellular arginine methylation^{187,189,232} and altering cell signaling^{231,233}. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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GENOMIC FINDINGS

GENE

TP53

ALTERATION

R273C

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

817C>T

VARIANT ALLELE FREQUENCY (% VAF)

83.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib²³⁴⁻²³⁷, or p53 gene therapy and immunotherapeutics such as SGT-53²³⁸⁻²⁴² and ALT-801²⁴³. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type²⁴⁴. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²⁴⁵. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²⁴⁶. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²⁴⁷. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel²⁴⁸. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell

carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations²⁴⁹. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²⁴². Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model²⁵⁰. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246²⁵¹⁻²⁵³. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR²⁵⁴. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies²⁵⁵⁻²⁵⁶; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies²⁵⁷⁻²⁵⁸. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 18-40% of astrocytoma samples, and preferentially in anaplastic astrocytoma; one study reported TP53 loss of function and partially/fully functional mutations in 15% and 25% of anaplastic astrocytomas, respectively²⁵⁹⁻²⁶⁴. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)²⁶⁵. One study reported that TP53 alterations were associated with poorer OS (12.9 months altered vs. 19.7 months wildtype, HR=1.58, p=0.0054) in IDH-wildtype GBM²⁶⁶. Mutation of TP53 is thought to be an early step in the tumorigenesis of astrocytomas, which can progress into anaplastic astrocytoma and then glioblastoma through gain of other genetic abnormalities such as loss of CDKN2A or RB1, followed by loss of PTEN²⁶⁷.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²⁶⁸. Alterations such as seen here may disrupt TP53 function or expression²⁶⁹⁻²⁷³.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Sep 2021)²⁷⁴. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁷⁵⁻²⁷⁷, including sarcomas²⁷⁸⁻²⁷⁹. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁸⁰ to 1:20,000²⁷⁹. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30²⁸¹. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion²⁸²⁻²⁸⁷. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁸²⁻²⁸³. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁸⁸. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{286,289-290}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

Ivosidenib

Assay findings association
IDH1
R132G

AREAS OF THERAPEUTIC USE

Ivosidenib is an isocitrate dehydrogenase 1 (IDH1) inhibitor that is FDA approved to treat patients with a susceptible IDH1 mutation in relapsed or refractory acute myeloid leukemia (AML) or previously treated locally advanced or metastatic cholangiocarcinoma. It is also approved as a first-line treatment for patients with AML and a susceptible IDH1 mutation who are not eligible for intensive induction chemotherapy or who are ≥ 75 years old. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of extensive clinical evidence in AML²⁹¹ and

cholangiocarcinoma²⁹²⁻²⁹³ and limited clinical data in myelodysplastic syndrome (MDS)²⁹¹ and glioma^{50,294}, IDH1 R132 mutation may confer sensitivity to ivosidenib.

SUPPORTING DATA

In a Phase 1 study of ivosidenib for patients with IDH1-mutated advanced solid tumors, 1 patient achieved PR in the non-enhancing glioma population (ORR=2.9% [1/35]); for patients with non-enhancing glioma and enhancing glioma, SD rates were 85.7% (30/35) and 45.2% (14/31), respectively, and median PFS was 13.6 months and 1.4 months, respectively^{50,294}.

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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CLINICAL TRIALS

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and

should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require

medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see [clinicaltrials.gov](https://www.foundationmedicine.com/genomic-testing#support-services). Or visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

GENE
IDH1
ALTERATION
 R132G

RATIONALE
 IDH1 mutations may predict sensitivity to IDH1 inhibitors. On the basis of preclinical data, IDH1 mutations may also confer sensitivity to PARP

inhibitors in solid tumors. Preclinical data indicate that IDH1 mutations may predict sensitivity to glutaminase inhibitors.

NCT04740190
PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
 PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT02264678
PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
 ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

NCT03772561
PHASE 1

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

TARGETS
 PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966
PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
 CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116
PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
 ATR, PARP

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

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NCT03907969
PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
 PARP, DNA-PK

LOCATIONS: Newcastle upon Tyne (United Kingdom), London (United Kingdom), Connecticut, Texas

NCT03830918
PHASE 1/2

Niraparib and Temozolomide in Treating Patients With Extensive-Stage Small Cell Lung Cancer With a Complete or Partial Response to Platinum-Based First-Line Chemotherapy

TARGETS
 PARP

LOCATIONS: California

NCT03914742
PHASE 1/2

BGB-290 and Temozolomide in Treating Patients With Recurrent Gliomas With IDH1/2 Mutations

TARGETS
 PARP

LOCATIONS: California, Michigan, Missouri, Ohio, Pennsylvania, Massachusetts, Connecticut, Maryland, Virginia

NCT03212274
PHASE 2

Olaparib in Treating Patients With Advanced Glioma, Cholangiocarcinoma, or Solid Tumors With IDH1 or IDH2 Mutations

TARGETS
 PARP

LOCATIONS: California, Wisconsin, Missouri, Kansas

NCT03221400
PHASE 1/2

PEN-866 in Patients With Advanced Solid Malignancies

TARGETS
 PARP, HSP90

LOCATIONS: Nevada, Colorado, Michigan, Oklahoma, Arkansas, Tennessee, Pennsylvania, Maryland, Virginia

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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.

FANCA
R591Q

IDH2
R188Q

KMT2A (MLL)
A53V

MAP3K1
R1023H

PDCD1 (PD-1)
A80V

SMARCA4
K546del

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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	ATRAX	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	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	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.

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. 2021. 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-

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APPENDIX

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. 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 = 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; 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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APPENDIX
About FoundationOne®CDx

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 5.2.0

The median exon coverage for this sample is 952x

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