

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 glioblastoma (GBM)	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Brain
	NAME Chang, Che Wen		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S112-13116 A (PF23037)
	DATE OF BIRTH 22 March 1956		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Male		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 25 March 2023
	MEDICAL RECORD # 29735635		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 19 April 2023

Biomarker Findings

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

Genomic Findings

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

EGFR L62R, amplification

PTEN L345fs*8

RB1 S318fs*13

TERT promoter -124C>T

TP53 C277fs*68

2 Disease relevant genes with no reportable alterations: **IDH1**, **PDGFRA**

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: **EGFR** amplification (p. 4), **TERT** promoter -124C>T (p. 6)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: Cetuximab (p. 8), Panitumumab (p. 8)
- 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: **TERT** promoter -124C>T (p. 6)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 4 Muts/Mb

GENOMIC FINDINGS

EGFR - L62R, amplification

7 Trials see p. 9

PTEN - L345fs*8

10 Trials see p. 11

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)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
none	Cetuximab
	Panitumumab
none	none

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

RB1 - S318fs*13 p. 5 **TP53** - C277fs*68 p. 7
TERT - promoter -124C>T p. 6

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

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

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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

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples⁶⁻⁸. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples⁶, although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs⁹. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM⁶, in GBMs with a previous lower grade astrocytoma⁷, and in giant cell GBM compared to classic GBM⁸.

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 tumor¹⁰. 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 PMS2¹⁰⁻¹². This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers¹³⁻¹⁵. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{10,12,14-15}.

BIOMARKER

Tumor Mutational Burden

RESULT

4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1¹⁶⁻¹⁸, anti-PD-1 therapies¹⁶⁻¹⁹, and combination nivolumab and ipilimumab²⁰⁻²⁵. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported^{16,26-27}. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations

have benefited from treatment with anti-PD-1²⁸⁻²⁹ or anti-PD-L1³⁰ 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

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (mut/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)³¹. 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 TMB³²⁻³³. Increased TMB has been reported to correlate with higher tumor grade in glioma³⁴ and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency

(bMMRD)²⁸, as well as with shorter OS of patients with diffuse glioma³⁵.

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 melanoma³⁶⁻³⁷ and cigarette smoke in lung cancer³⁸⁻³⁹, treatment with temozolomide-based chemotherapy in glioma⁴⁰⁻⁴¹, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes⁴²⁻⁴⁶, and microsatellite instability (MSI)^{42,45-46}. 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^{16,26-30}.

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GENOMIC FINDINGS

GENE

EGFR

ALTERATION

L62R, amplification

HGVS VARIANT

NM_005228.3: c.185T>G (p.L62R)

VARIANT CHROMOSOMAL POSITION

chr7:55210075

VARIANT ALLELE FREQUENCY (% VAF)

75.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer (NSCLC), EGFR activating mutations may predict sensitivity to EGFR-TKIs, including erlotinib⁴⁷, gefitinib⁴⁸⁻⁵¹, afatinib⁵²⁻⁵⁵, dacomitinib⁵⁶, and osimertinib^{53,57}; however, the data for patients with other tumor types are limited⁵⁸⁻⁶³. Patients with EGFR-mutated bithalamic glioma have reported responses to osimertinib⁶⁴⁻⁶⁵. In a case series of 11 patients with bithalamic gliomas with EGFR mutations, EGFR inhibitors, including osimertinib, showed improved survival; however, it showed a lack of significant clinical responses⁶¹. On the basis of preclinical data, EGFR mutations confer sensitivity to EGFR inhibitors, including osimertinib⁶¹. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy^{63,66-69}; however, a small subset of patients has experienced clinical benefit^{63,66-67}. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma⁷⁰⁻⁷³. There are conflicting data on the efficacy of anti-EGFR

antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS⁷⁴. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy⁷⁵⁻⁷⁶. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)⁷⁷. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)⁷⁸. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)⁷⁹⁻⁸². EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas in several genomic

studies of CNS tumors⁷⁹⁻⁸². In GBMs, Missense mutations in the EGFR extracellular domain have been found in 10-15% of cases and approximately half have a low-level amplification of the mutated allele⁸³⁻⁸⁴. In a study of IDH-wildtype GBM samples, EGFR alterations were detected in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event⁸⁵. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM⁸⁶⁻⁸⁷; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM⁸⁸.

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide⁸⁹. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types⁹⁰⁻⁹². Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL DIAGNOSTIC IMPLICATIONS

The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2022)⁹³.

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GENOMIC FINDINGS

GENE

PTEN

ALTERATION

L345fs*8

HGVS VARIANT

NM_000314.4: c.1032_1033dup (p.L345Rfs*8)

VARIANT CHROMOSOMAL POSITION

chr10:89725048

VARIANT ALLELE FREQUENCY (% VAF)

42.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway⁹⁴⁻⁹⁷. Clinical studies in glioblastoma have not observed an association between PTEN deficiency and response to everolimus or temsirolimus⁹⁸⁻¹⁰⁰. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors¹⁰¹⁻¹⁰⁵, and clinical benefit has been observed for patients with PTEN-altered breast

cancer including triple negative breast cancer¹⁰⁶, ovarian cancer¹⁰⁷, uterine leiomyosarcoma¹⁰⁸, and endometrial cancer¹⁰⁵ treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity¹⁰⁹⁻¹¹⁰.

FREQUENCY & PROGNOSIS

Studies in the literature have indicated that PTEN alterations (mutation or homozygous deletion) occur most frequently in glioblastoma (GBM), less frequently in anaplastic astrocytoma, and rarely in lower grade glioma subtypes including low grade astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma^{88,111-117}. One study detected PTEN mutation in 42% (97/232) and loss in 10% (24/232) of IDH-wildtype GBM samples analyzed⁸⁵. In the TCGA dataset, PTEN mutation was observed in 23% of GBM cases and PTEN deletion was reported in 7% of cases⁸⁰, while in the Lower Grade Glioma TCGA dataset, PTEN mutation was observed in 4% of cases and homozygous deletion observed in 1.2% of cases¹¹⁸. Decreased PTEN expression is associated with the higher grade GBM tumors¹¹⁹. Loss of PTEN correlated with significantly worse prognosis in all grades of gliomas^{114,120}.

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis⁹⁵. Alterations such as seen here may disrupt PTEN function or expression^{116,121-161}.

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome¹⁶²⁻¹⁶³. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients^{162,164}. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder¹⁶². Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE

RB1

ALTERATION

S318fs*13

HGVS VARIANT

NM_000321.2: c.951_954del (p.S318Nfs*13)

VARIANT CHROMOSOMAL POSITION

chr13:48941637-48941641

VARIANT ALLELE FREQUENCY (% VAF)

54.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of limited clinical data¹⁶⁵ and strong preclinical data¹⁶⁶⁻¹⁶⁹, RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer

(SCLC). A clinical study evaluating the Aurora kinase A inhibitor alisertib for patients with prostate cancer did not find an association between RB1 deletion and clinical benefit¹⁷⁰. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members¹⁷¹ and activation of the NOTCH pathway¹⁷².

FREQUENCY & PROGNOSIS

In the TCGA datasets, RB1 mutation or homozygous deletion was observed in 9% of glioblastomas⁸⁰ and 2.5% of lower grade glioma cases¹¹⁸. In one study, loss of RB1 transcript expression was observed in 10.6% of glioblastomas and occurred more frequently in the proneural subtype¹⁷³. One study reports that mutation of RB1 is correlated with shorter survival in glioblastoma patients¹⁷⁴. Several studies suggest that RB1, PTEN, and/or TP53 mutations are early events in the

development of glioblastoma¹⁷⁵⁻¹⁷⁷.

FINDING SUMMARY

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle¹⁷⁸⁻¹⁷⁹. Alterations such as seen here may disrupt RB1 function or expression¹⁸⁰⁻¹⁸⁶.

POTENTIAL GERMLINE IMPLICATIONS

Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year¹⁸⁷. Germline mutations in RB1 account for approximately 40% of RB tumors¹⁸⁸ and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma¹⁸⁹⁻¹⁹⁰. In the appropriate clinical context, germline testing of RB1 is recommended.

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GENOMIC FINDINGS

GENE

TERT

ALTERATION
promoter -124C>T

HGVS VARIANT
NM_198253.2: c.-124C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295228

VARIANT ALLELE FREQUENCY (% VAF)
48.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials¹⁹¹; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth¹⁹². A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer

reported no improvement in PFS or OS¹⁹³.

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas¹⁹⁴⁻¹⁹⁵, most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas¹⁹⁴⁻¹⁹⁸. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)^{194,196}. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed⁸⁵. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM¹⁹⁹. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM^{194,196,199-200}. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length²⁰¹. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells²⁰²⁻²⁰⁴. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)²⁰⁵⁻²⁰⁷, as well as tandem mutations at positions -124/-125 bp and -138/-139 bp²⁰⁵.

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v2.2022)²⁰⁸. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2022)⁹³.

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GENOMIC FINDINGS

GENE

TP53

ALTERATION

C277fs*68

HGVS VARIANT

NM_000546.4: c.828del (p.C277Vfs*68)

VARIANT CHROMOSOMAL POSITION

chr17:7577109-7577110

VARIANT ALLELE FREQUENCY (% VAF)

68.3%

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 adavosertib²⁰⁹⁻²¹² or p53 gene therapy such as SGT-53²¹³⁻²¹⁷. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype²¹⁸. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²¹⁹. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²²⁰. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²²¹. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel²²². A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck

squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations²²³. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring²²⁴. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²¹⁷. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR²²⁵. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)²²⁶.

FREQUENCY & PROGNOSIS

In the TCGA dataset, TP53 alterations have been reported in 35% of glioblastomas (GBMs), with a high incidence in pediatric and secondary GBMs and a low incidence in primary GBMs²²⁷⁻²²⁸. One study detected TP53 alterations in 31% (73/232) of IDH-wildtype GBM samples analyzed, with most of the events being mutations⁸⁵. 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, respectively²²⁹⁻²³⁴. Some studies suggest that the presence of a TP53 mutation is correlated with a favorable prognosis in patients with glioblastoma (GBM)²³⁵. 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 GBM⁸⁵. 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 PTEN²³⁶.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²³⁷. Alterations such as seen here may disrupt TP53 function or expression²³⁸⁻²⁴².

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁴³⁻²⁴⁵, including sarcomas²⁴⁶⁻²⁴⁷. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁴⁸ to 1:20,000²⁴⁷. 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 30²⁴⁹. 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 expansion²⁵⁰⁻²⁵⁵. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁵⁰⁻²⁵¹. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁵⁶. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{254,257-258}. 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

Cetuximab

Assay findings association

EGFR

L62R, amplification

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies⁷⁴.

SUPPORTING DATA

A Phase 2 trial of cetuximab with the anti-VEGF monoclonal antibody bevacizumab for patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone²⁵⁹. However, another Phase 2 study demonstrated that for patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly longer PFS and numerical (although not statistically significant) improvement in OS²⁶⁰. In addition, a case report for an EGFR-amplified patient with GBM treated with cetuximab using intraarterial cerebral infusion (SIACI) in combination with chemotherapy reported a stable response without recurrence at 6 months²⁶¹.

Panitumumab

Assay findings association

EGFR

L62R, amplification

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies⁷⁴.

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with

doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs²⁶².

Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer²⁶³⁻²⁶⁵ and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit²⁶⁶⁻²⁶⁸ and others have reported no benefit²⁶⁹⁻²⁷¹. A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility²⁷². Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)²⁷³⁻²⁷⁴; biliary tract cancers, including cholangiocarcinoma²⁷⁵⁻²⁷⁶; and renal cell carcinoma (RCC)²⁷⁷.

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

GENE

EGFR

ALTERATION

L62R, amplification

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination

therapies. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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)

NCT04946968

PHASE 2

Phase-2 Dacomitinib Study on Patients With EGFR-Driven Advanced Solid Tumours With Low EGFR-AS1 lncRNA Expr or Other Novel Emerging Biomarkers

TARGETS

ERBB4, EGFR, ERBB2

LOCATIONS: Singapore (Singapore)

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRP α , in Subjects With Advanced Solid and Hematologic Cancers

TARGETS

CD20, EGFR, SIRP-alpha

LOCATIONS: Heidelberg (Australia), Melbourne (Australia), Manchester (United Kingdom), Edmonton (Canada), Madrid (Spain), Salamanca (Spain), Malaga (Spain), Toronto (Canada)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS

MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT02800486

PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbix) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS

EGFR

LOCATIONS: New York

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CLINICAL TRIALS
NCT02861898
PHASE 1/2

Super-selective Intra-arterial Repeated Infusion of Cetuximab for the Treatment of Newly Diagnosed Glioblastoma

TARGETS
 EGFR

LOCATIONS: New York

NCT04670679
PHASE 1

A Dose Escalation/Expansion Study of ERAS-601 in Patients With Advanced or Metastatic Solid Tumors

TARGETS
 SHP2, EGFR

LOCATIONS: Perth (Australia), Melbourne (Australia), Nevada, California, Missouri, Texas, Massachusetts, New York, Tennessee

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CLINICAL TRIALS

GENE
PTEN

ALTERATION
L345fs*8

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors

of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

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), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT04740190

PHASE 2

Talazoparib - Carboplatin for Recurrent High-grade Glioma With DDRd

TARGETS
PARP

LOCATIONS: Hong Kong (Hong Kong)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

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)

NCT05076513

PHASE NULL

Trial of Niraparib in Participants With Newly-diagnosed Glioblastoma and Recurrent Glioma

TARGETS
PARP

LOCATIONS: Arizona

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CLINICAL TRIALS
NCT04614909
PHASE NULL

Phase 0/2 Study of Pamiparib in Newly Diagnosed and rGBM

TARGETS
 PARP

LOCATIONS: Arizona

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)

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

NCT04991480
PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
 PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

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APPENDIX
Variants of Unknown Significance

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

MSH2

NM_000251.1: c.505A>G
(p.I169V)
chr2:47637371

NFKBIA

NM_020529.2: c.365A>G
(p.N122S)
chr14:35872538

NOTCH3

NM_000435.2: c.4039G>C
(p.G1347R)
chr19:15288700

SPEN

NM_015001.2: c.10616C>A
(p.P3539H)
chr1:16264413

ZNF217

NM_006526.2: c.2235C>A
(p.N745K)
chr20:52193068

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APPENDIX

Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B or WTX)	
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFA1	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCCD1 (PD-1)	PDCCD1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51
RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFBP2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPR2SS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status
 Loss of Heterozygosity (LOH) score
 Microsatellite (MS) status
 Tumor Mutational Burden (TMB)

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APPENDIX
About FoundationOne®CDx

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Ciplstraat 3, 2440 Geel, Belgium. 

ABOUT FOUNDATIONONE CDx

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

Please refer to technical information for performance specification details:
www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLE

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

detection of alterations in a total of 324 genes.

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical

methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

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About FoundationOne®CDx

- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
 - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score $\geq 16\%$ will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
 - The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and

extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
- Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
- Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal

hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

*Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *PALB2*, *PMS2*, *POLE*, *RAD51C*, *RAD51D*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TSC2*, and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

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APPENDIX

About FoundationOne®CDx

tumor sequencing is germline or somatic.
 Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking

into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version (RG) 7.8.0

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ORDERED TEST # **ORD-1611453-01**
APPENDIX **References**

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