FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Yu Chun	Brain glioblastoma (GBM)	13 Dec 2022
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1517865-01

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

PATIENT
DISEASE Brain glioblastoma (GBM)
NAME Chen, Yu Chun
DATE OF BIRTH 18 December 1969
SEX Female
MEDICAL RECORD # 49084620

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S111-47319B
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 16 November 2022
SPECIMEN RECEIVED 06 December 2022

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.

FGFR3 amplification, FGFR3-TACC3 fusion
MTAP loss
CDKN2A/B CDKN2A loss, CDKN2B loss
TERT promoter -124C>T

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

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: *TERT* promoter -124C>T (p. 6)

- Targeted therapies with potential clinical benefit **approved in another tumor type**: Erdafitinib (p. 7)

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 8)

- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: *TERT* promoter -124C>T (p. 6)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	No therapies or clinical trials. See Biomarker Findings section	
Tumor Mutational Burden - 4 Muts/Mb	No therapies or clinical trials. See Biomarker Findings section	
GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
FGFR3 - amplification, FGFR3-TACC3 fusion 10 Trials see p. 8	none	Erdafitinib
MTAP - loss 1 Trial see p. 10	none	none

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

CDKN2A/B - CDKN2A loss, CDKN2B loss .... p. 5   *TERT -* promoter -124C>T .... p. 6

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 inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[10]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[10-12]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[13-15]. 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-L1[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. 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-1[28-29] or anti-PD-L1[30] 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 (muts/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 TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[35].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], 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

FGFR3

ALTERATION
amplification, FGFR3-TACC3 fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR3 may predict sensitivity to selective FGFR kinase inhibitors, including erdafitinib[47-49], pemigatinib[50], infigratinib[51-52], rogaratinib[53], Debio 1347[54-55], and derazantinib[56]; multikinase inhibitors such as pazopanib[57-58] and ponatinib[59-60]; and vofatamab, an antibody targeting FGFR3[61-63]. In the context of FGFR3 alterations, FGFR inhibitors, such as erdafitinib[47], pemigatinib[50], infigratinib[51], rogaratinib[53], and Debio 1347[64], have predominantly been studied in the context of urothelial carcinoma, resulting in ORRs of 25-40% and DCRs of 64-80%. Clinical benefit has been reported in patients with gliomas harboring FGFR3 fusions treated in a Phase 1 trial of erdafitinib[48,65], and a prolonged SD has been observed in a case study treated with Debio 1347[66]. For infigratinib, activity against non-urothelial tumors harboring FGFR3 alterations are limited[67], with responses reported in individuals with an FGFR3-amplified and -rearranged glioma or FGFR3-mutated head and neck squamous cell carcinoma with co-occurring FGF amplifications[68].

FREQUENCY & PROGNOSIS

FGFR3 mutation and amplification have been observed in 1% and 2.5% of glioblastoma (GBM) cases, respectively[69]. FGFR3 mutation has been observed in fewer than 1% of all astrocytomas in the COSMIC dataset (Mar 2022)[70]. FGFR3-TACC3 fusions have been reported in 1-8% of glioblastoma (GBM) cases[65,71-77] and 0-1% of lower-grade glioma cases[65,71,76]. In both GBM and lower-grade glioma, FGFR3-TACC3 fusions have been observed only in IDH1/2 wildtype cases (3.6% [21/588] of GBM cases in one study; 3/85 [3.5%] and 3/80 [3.8%] lower-grade glioma cases in 2 studies) but not in any samples harboring IDH1 or IDH2 mutations (0/126 lower-grade glioma cases in 1 study; 0/187 combined GBM and lower-grade glioma cases in another study)[65,76]. A case report described a patient with polymorphous low-grade neuroepithelial tumor harboring an FGFR3-TACC3 fusion[78]. FGFR3 has been reported to be expressed in GBM cell lines[79]. FGFR3 fusion was reported to be an independent predictor of longer OS in patients with IDH-wildtype glioma (stage II-IV combined cohort) or glioblastoma (GBM) specifically; however, OS of patients with IDH-wildtype, FGFR3 fusion-positive GBM was found to be significantly shorter than that of patients with IDH-mutated GBM[76]. Additionally, IDH-wildtype gliomas with FGFR3 fusions were reported to have a significantly lower rate of MGMT methylation than IDH-wildtype cases lacking such fusions[76]. In other studies, FGFR3 fusions were reported to be associated with recurrent histologic features in both low-grade and high-grade glioma, including monomorphous oligodendroglioma-like nuclei, endocrinoid networks of thin capillaries, and frequent microcalcifications[80-81]. However, due to the higher frequency of FGFR3 fusions in GBM compared to lower-grade glioma, as well as the limited long-term follow-up data for ostensibly low-grade but FGFR3-positive cases, guidelines have recommended cautious evaluation of clinical features and close monitoring of the course of the disease when a histologically low-grade tumor is found to harbor an FGFR3 fusion[81]. One retrospective analysis reported association between higher FGFR3 expression and longer OS in a combined cohort of patients with grade II-IV glioma[82].

FINDING SUMMARY

FGFR3 (Fibroblast growth factor receptor 3) encodes a receptor tyrosine kinase that typically promotes cell cycle progression and angiogenesis via activation of downstream signaling pathways, including RAS-MAPK and AKT; gain of function mutations in FGFRs have been reported in several cancer types[83-85]. FGFR3 has been reported to be amplified in cancer[86] and may be biologically relevant in this context[87-88]. FGFR3 fusions that retain the kinase domain (exons 11-17) have been shown to be activating and oncogenic[54,73]. Additionally, fusions that disrupt a binding site of the regulatory microRNA miR-99a in the FGFR3 3' UTR have been demonstrated to increase FGFR3 expression[71]. Rearrangements that include the N-terminal portion of FGFR3 (exons 1-17), such as observed here, are predicted to be activating and oncogenic.

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Brain glioblastoma (GBM)

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GENOMIC FINDINGS

ORDERED TEST # ORD-1517865-01

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A[89-90] or PRMT5 inhibition[90-92]. 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 loss[93]. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors[94], dual PRMT1 and PRMT5 inhibitors[95-97], and PRMT5 inhibitors that selectively bind the PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193[98]. In preclinical models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA[99-109]. 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 SD for 24% (13/55) of patients[110]. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed[111].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[112-113]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[114], gastrointestinal stromal tumors[115], mantle cell lymphoma (MCL)[116], melanoma[117-118], gastric cancer[119], myxofibrosarcoma[120], nasopharyngeal carcinoma[121], ovarian carcinoma[112] and non-small cell lung cancer[122]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[123] or in astrocytoma[124]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[125], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[126]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[127-128], esophageal cancer[129-130], osteosarcoma[131], and CRC[132].

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 activity[133-134]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[114,135-136], thereby reducing intracellular arginine methylation[90-92] and altering cell signaling[136-137]. 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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GENE

CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[138-141]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[142] and palbociclib treatment[143-144]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[145-151]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[152-153], the clinical relevance of p14ARF as a predictive biomarker is not clear. 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[64,146,148-149,154-155].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[156] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[69] than in those with lower grade gliomas (6%)[157]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[158-160]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[161]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[162]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[163]. 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[159,164]. 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 astrocytomas[165-166].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[167-168]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[169-170]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[171-172]. One or more alterations observed here are predicted to result in p16INK4a loss of function[173-194]. One or more alterations seen here are predicted to result in p14ARF loss of function[177,194-197]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[198].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[199]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[200-201]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[202-204]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[205-207]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253.2

CODING SEQUENCE EFFECT
-124C>T

VARIANT CHROMOSOMAL POSITION
chr5:1295228

VARIANT ALLELE FREQUENCY (% VAF)
32.5%

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 trials[208]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[209]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[210].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[211-212], 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 ependymomas[211-215]. 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%)[211,213]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[162]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[216]. 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[211,213,216-217]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v1.2022).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[218]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[219-221]. 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)[222-224], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[222].

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, v1.2022)[225]. 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, v1.2022)[226].

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| THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE |

Erdafitinib

Assay findings association

FGFR3
amplification, FGFR3-TACC3 fusion

AREAS OF THERAPEUTIC USE

Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) inhibitor. It is FDA approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have FGFR2 or FGFR3 alterations and have progressed after prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical evidence, FGFR3 fusions[48,65,227-228] and activating mutations[47-48,227] may confer sensitivity to erdafitinib.

SUPPORTING DATA

The interim analysis of the Phase 2 RAGNAR trial reported an ORR of 21% (6/29) for patients with FGFR-altered high grade glioma and 1 response for a patient with low-grade glioma (n=6)[229]. In a Phase 1 study of erdafitinib for patients with advanced solid tumors, 1 patient with glioblastoma harboring an FGFR3 fusion achieved a PR[48]. Another Phase 1 study reported that 2 patients with FGFR3 fusion-positive glioblastoma treated with erdafitinib experienced clinical benefit, including a 115-day SD and a minor response, respectively[65]. Erdafitinib has been primarily studied for the treatment of FGFR-altered urothelial carcinoma. A Phase 2 study evaluating erdafitinib for the treatment of patients with metastatic or unresectable urothelial carcinoma (mUC) previously treated with chemotherapy and harboring FGFR2/3 fusions or FGFR3 activating mutations reported an ORR of 40% (40/99, 3 CR), and a DCR of 80% (79/99)[47]. The interim analysis of the Phase 2 RAGNAR trial reported an ORR of 29% (52/178) for patients with FGFR-altered solid tumors treated with erdafitinib[229]. A Phase 1 trial of erdafitinib reported clinical responses for patients with various FGFR2- or FGFR3-altered solid tumors[48,65,230-231], including cholangiocarcinoma (27% ORR, 3/11), non-small cell lung cancer (NSCLC) (5% ORR, 1/21), breast (9% ORR, 3/34), and ovarian (9% ORR, 1/11), while other cancers including endometrial carcinoma and glioblastoma showed a low ORR (2%, 1/58)[232].

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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GENE
FGFR3

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR3.

ALTERATION
amplification, FGFR3-TACC3 fusion

NCT05019794 — PHASE 2

Infigratinib in Subjects With GC or GEJ With FGFR2 Amplification or Other Solid Tumors With Other FGFR Alterations

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Fuzhou (China), Hangzhou (China), Shanghai (China), Changzhou (China), Nanjing (China), Guangzhou (China), Wuan (China), Henan (China), Baoding (China), Taiyuan (China)

NCT04083976 — PHASE 2

A Study of Erdafitinib in Participants With Advanced Solid Tumors and Fibroblast Growth Factor Receptor (FGFR) Gene Alterations

TARGETS
FGFRs

LOCATIONS: Hangzhou (China), Shanghai (China), Nanjing (China), Guangzhou (China), Matsuyama (Japan), Hiroshima-shi (Japan), Chongqing (China), Beijing (China), Chengdu (China), Toyoake (Japan)

NCT05098847 — PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Shanghai (China)

NCT05024214 — PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

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CLINICAL TRIALS

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Osakasayama (Japan), Nagoya (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT04962867

PHASE 2

NCCH2006/MK010 Trial (FORTUNE Trial)

TARGETS
FGFR1, FGFR2, FGFR3

LOCATIONS: Higashi-Ku, Fukuoka (Japan), Sakyo-ku, Kyoto (Japan), Chuo-ku, Tokyo (Japan), Aoba-ku, Sendai, Miyagi (Japan), Kita-Ku, Sapporo, Hokkaido (Japan)

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Thessaloniki (Greece), Heraklion (Greece)

NCT04424966

PHASE NULL

Infigratinib in Recurrent Glioblastoma Patients

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Arizona

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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FOUNDATIONONE®**CDx**

PATIENT
Chen, Yu Chun

TUMOR TYPE
Brain glioblastoma (GBM)

REPORT DATE
13 Dec 2022

ORDERED TEST #   ORD-1517865-01

CLINICAL TRIALS

GENE
MTAP

ALTERATION
loss

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05245500	PHASE 1/2
Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion	TARGETS PRMT5-MTA

LOCATIONS: Colorado, Massachusetts, New York, Tennessee, Texas

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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.

ARID1A	*CHEK2*	*KMT2A (MLL)*	*MSH3*
P109S	T533A	A53V	P63_P64insAAPPAP
PDCD1 (PD-1)	*PDGFRB*	*PIK3R1*	*ROS1*
A202_R203insGA	V51I	A483P	T326R
TEK			
rearrangement			

PATIENT	TUMOR TYPE	REPORT DATE
Chen, Yu Chun	Brain glioblastoma (GBM)	13 Dec 2022

APPENDIX	Genes Assayed in FoundationOne®CDx

ORDERED TEST # ORD-1517865-01

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	ERRFI1	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	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	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
P2RY8	PALB2	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
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	SOCS1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)		TET2	TGFBR2
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	RSPO2	SDC4	SLC34A2	TERC*	TERT**	TMPRSS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Homologous Recombination status

Loss of Heterozygosity (LOH) score

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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

Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST 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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations
1. In the 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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PATIENT
Chen, Yu Chun

TUMOR TYPE
Brain glioblastoma (GBM)

REPORT DATE
13 Dec 2022

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.

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

3. 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 ≥ 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.

4. 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.

5. 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.

6. 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.

7. 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

PATIENT
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TUMOR TYPE
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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
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

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) 7.4.0

The median exon coverage for this sample is 820x

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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Martinez R, et al. Oncology (2004) pmid: 15331927
7. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
8. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
9. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
10. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
11. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
12. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
13. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
14. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
15. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
16. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
17. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
18. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
19. Cristescu R, et al. Science (2018) pmid: 30309915
20. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
21. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
22. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
23. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
24. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
25. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
26. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
27. Touat M, et al. Nature (2020) pmid: 32322066
28. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
29. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
30. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
31. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
32. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
33. Johnson A, et al. Oncologist (2017) pmid: 28912153
34. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
35. Wang L, et al. BMC Cancer (2020) pmid: 32164609
36. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
37. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
38. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
39. Rizvi NA, et al. Science (2015) pmid: 25765070
40. Johnson BE, et al. Science (2014) pmid: 24336570
41. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
42. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
43. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
44. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
45. Nature (2012) pmid: 22810696
46. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
47. Loriot Y, et al. N. Engl. J. Med. (2019) pmid: 31340094
48. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
49. Karkera JD, et al. Mol. Cancer Ther. (2017) pmid: 28416604
50. Necchi et al., 2018; ESMO Abstract 900P
51. Pal SK, et al. Cancer Discov (2018) pmid: 29848605
52. Pal SK, et al. Cancer (2020) pmid: 32208524
53. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
54. Nakanishi Y, et al. Mol. Cancer Ther. (2015) pmid: 25589496
55. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
56. Papadopoulos KP, et al. Br. J. Cancer (2017) pmid: 28972963
57. Bellmunt J, et al. Br. J. Cancer (2018) pmid: 30220708
58. Palma N, et al. Eur. Urol. (2015) pmid: 25766722
59. Gozgit JM, et al. Mol. Cancer Ther. (2012) pmid: 22238366
60. Liao RG, et al. Cancer Res. (2013) pmid: 23786770
61. Bellmunt et al., 2018; ASCO Abstract 4534
62. Necchi et al., 2019; ASCO GU Abstract 409
63. Siefker-Radtke et al., 2019; ASCO Abstract 4511
64. Voss et al., 2017; ASCO Abstract 2500
65. Di Stefano AL, et al. Clin. Cancer Res. (2015) pmid: 25609060
66. Farouk Sait S, et al. JCO Precis Oncol (2021) pmid: 34250399
67. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
68. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
69. Brennan CW, et al. Cell (2013) pmid: 24120142
70. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
71. Parker BC, et al. J. Clin. Invest. (2013) pmid: 23298836
72. Stransky N, et al. Nat Commun (2014) pmid: 25204415
73. Singh D, et al. Science (2012) pmid: 22837387
74. Wu YM, et al. Cancer Discov (2013) pmid: 23558953
75. Bao ZS, et al. Genome Res. (2014) pmid: 25135958
76. Di Stefano AL, et al. Neuro Oncol (2020) pmid: 32413119
77. Schittenhelm J, et al. Neurooncol Pract (2021) pmid: 33898054
78. Huse JT, et al. Acta Neuropathol (2017) pmid: 27812792
79. Loilome W, et al. J. Neurooncol. (2009) pmid: 19340397
80. Bielle F, et al. Brain Pathol. (2018) pmid: 28976058
81. Acta Neuropathol Commun (2020) pmid: 32085805
82. Wang Z, et al. Oncotarget (2016) pmid: 27829236
83. Powers CJ, et al. Endocr. Relat. Cancer (2000) pmid: 11021964
84. Eswarakumar VP, et al. Cytokine Growth Factor Rev. (2005) pmid: 15863030
85. Wesche J, et al. Biochem. J. (2011) pmid: 21711248
86. Gao J, et al. Sci Signal (2013) pmid: 23550210
87. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
88. Beroukhim R, et al. Nature (2010) pmid: 20164920
89. Kalev P, et al. Cancer Cell (2021) pmid: 33450196
90. Marjon K, et al. Cell Rep (2016) pmid: 27068473
91. Mavrakis KJ, et al. Science (2016) pmid: 26912361
92. Kryukov GV, et al. Science (2016) pmid: 26912360
93. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
94. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
95. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
96. Srour N, et al. Cancer Cell (2019) pmid: 31287990
97. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
98. Smith CR, et al. J Med Chem (2022) pmid: 35041419
99. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
100. Tang B, et al. Cancer Res. (2018) pmid: 29844120
101. Munshi PN, et al. Oncologist (2014) pmid: 24928612
102. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
103. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
104. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
105. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
106. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
107. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
108. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
109. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
110. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
111. Alhalabi O, et al. Nat Commun (2022) pmid: 35379845
112. Wei R, et al. Sci Rep (2016) pmid: 27929028
113. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
114. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
115. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
116. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
117. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
118. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
119. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
120. Li CF, et al. Oncotarget (2014) pmid: 25426549
121. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
122. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
123. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
124. Becker AP, et al. Pathobiology (2015) pmid: 26088413
125. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
126. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
127. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
128. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
129. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
130. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
131. Zhi L, et al. J Cancer (2016) pmid: 27994653
132. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
133. Limm K, et al. PLoS ONE (2016) pmid: 27479139
134. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
135. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
136. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
137. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
138. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
139. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
140. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
141. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
142. Fennell DA, et al. Lancet Oncol (2022) pmid: 35157829
143. Elvin JA, et al. Oncologist (2017) pmid: 28283584
144. Gao J, et al. Curr Oncol (2015) pmid: 26715889
145. Gopalan et al., 2014; ASCO Abstract 8077
146. Peguero et al., 2016; ASCO Abstract 2528
147. Konecny et al., 2016; ASCO Abstract 5557
148. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
149. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
150. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
151. Johnson DB, et al. Oncologist (2014) pmid: 24797823
152. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
153. Gamble LD, et al. Oncogene (2012) pmid: 21725357

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PATIENT
Chen, Yu Chun

TUMOR TYPE
Brain glioblastoma (GBM)

REPORT DATE
13 Dec 2022

APPENDIX   References

ORDERED TEST #   ORD-1517865-01

154. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
155. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
156. Ceccarelli M, et al. Cell (2016) pmid: 26824661
157. Jonsson P, et al. Clin. Cancer Res. (2019) pmid: 31263031
158. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
159. Sottoriva A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23412337
160. Weber RG, et al. Oncogene (2007) pmid: 16909113
161. Nakamura M, et al. Brain Pathol. (2001) pmid: 11303791
162. Yan et al. 2020; DOI:10.1200/PO.19.00385
163. Chakravarti A, et al. Clin. Cancer Res. (2001) pmid: 11489817
164. Feng J, et al. Cancer (2012) pmid: 21713760
165. Raabe EH, et al. Clin. Cancer Res. (2011) pmid: 21636552
166. Liu W, et al. J. Exp. Clin. Cancer Res. (2011) pmid: 21843312
167. Quelle DE, et al. Cell (1995) pmid: 8521522
168. Mutat. Res. (2005) pmid: 15878778
169. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
170. Oncogene (1999) pmid: 10498883
171. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
172. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
173. Ruas M, et al. Oncogene (1999) pmid: 10498896
174. Jones R, et al. Cancer Res. (2007) pmid: 17909018
175. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
176. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
177. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
178. Gombart AF, et al. Leukemia (1997) pmid: 9324288
179. Yang R, et al. Cancer Res. (1995) pmid: 7780957
180. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
181. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942

182. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
183. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
184. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
185. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
186. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
187. Koh J, et al. Nature (1995) pmid: 7777061
188. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
189. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
190. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
191. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
192. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
193. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
194. Rutter JL, et al. Oncogene (2003) pmid: 12853981
195. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
196. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
197. Zhang Y, et al. Cell (1998) pmid: 9529249
198. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
199. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
200. Adv Exp Med Biol (2010) pmid: 20687502
201. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
202. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
203. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
204. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
205. Kaufman DK, et al. Neurology (1993) pmid: 8414022
206. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
207. Chan AK, et al. Clin Neuropathol () pmid: 28699883

208. Nat Rev Clin Oncol (2017) pmid: 27245281
209. Duperret EK, et al. Mol Ther (2018) pmid: 29249395
210. Chiappori AA, et al. Ann Oncol (2015) pmid: 25467017
211. Killela PJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23530248
212. Killela PJ, et al. Oncotarget (2014) pmid: 24722048
213. Nonoguchi N, et al. Acta Neuropathol. (2013) pmid: 23955565
214. Liu X, et al. Cell Cycle (2013) pmid: 23603989
215. Koelsche C, et al. Acta Neuropathol. (2013) pmid: 24154961
216. Arita H, et al. Acta Neuropathol. (2013) pmid: 23764841
217. Reitman ZJ, et al. Acta Neuropathol. (2013) pmid: 24217890
218. Shay JW, et al. Semin. Cancer Biol. (2011) pmid: 22015685
219. Shay JW, et al. Eur. J. Cancer (1997) pmid: 9282118
220. Kim NW, et al. Science (1994) pmid: 7605428
221. Hanahan D, et al. Cell (2000) pmid: 10647931
222. Horn S, et al. Science (2013) pmid: 23348503
223. Huang FW, et al. Science (2013) pmid: 23348506
224. Vinagre J, et al. Nat Commun (2013) pmid: 23887589
225. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
226. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
227. Siefker-Radtke et al., 2018; ASCO Abstract 4503
228. Park et al., 2019; ASCO Abstract 4117
229. Loriot et al., 2022; ASCO Abstract 3007
230. Qin A, et al. J Thorac Oncol (2019) pmid: 30267839
231. Soria et al., 2016; ASCO Abstract 4074
232. Bahleda R, et al. Clin. Cancer Res. (2019) pmid: 31088831

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