FOUNDATIONONE®CDx

PATIENT
Huang, Hsuan-Wen

TUMOR TYPE
Brain anaplastic astrocytoma
COUNTRY CODE
TW

REPORT DATE
19 Apr 2022
ORDERED TEST #
ORD-1341410-01

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 anaplastic astrocytoma
NAME Huang, Hsuan-Wen
DATE OF BIRTH 30 October 1993
SEX Female
MEDICAL RECORD # 41115246

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 S111-12810 A (PF22049)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 28 March 2022
SPECIMEN RECEIVED 12 April 2022

Biomarker Findings

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

Genomic Findings

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

FGFR1 N546K
H3F3A K28M
ATRX H1363fs*12
ERBB4 E542K
MCL1 amplification - equivocal†
PTPN11 T507K
TET2 E1151*

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***H3F3A* K28M** (p. 5)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: Infigratinib (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***H3F3A* K28M** (p. 5)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***TET2* E1151*** (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 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)**
***FGFR1* -** N546K	none	Infigratinib
10 Trials *see p. 11*		
***H3F3A* -** K28M	none	none
1 Trial *see p. 13*		

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

***TET2* -** E1151* ..... p. 9

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-High has been reported in 3-8% of adult or pediatric astrocytomas and was generally not associated with Lynch syndrome[6-8]. Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[9-11]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[9], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[12]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[9], in GBMs with a previous lower grade astrocytoma[10], and in giant cell GBM compared to classic GBM[11].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[13]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[13-15]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[16-18]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[13,15,17-18].

BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[19-21], anti-PD-1 therapies[19-22], and combination nivolumab and ipilimumab[23-28]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[19,29-30]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[31-32] or anti-PD-L1[33] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Anaplastic astrocytoma harbors a median TMB of 1.8 mutations per megabase (muts/Mb), and 2% of cases have high TMB (>20 muts/Mb)[34]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[35-36]. Increased TMB has been reported to correlate with higher tumor grade in glioma[37] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[31], as well as with shorter OS of patients with diffuse glioma[38].

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[39-40] and cigarette smoke in lung cancer[41-42], treatment with temozolomide-based chemotherapy in glioma[43-44], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[45-49], and microsatellite instability (MSI)[45,48-49]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[19,29-33].

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GENE
FGFR1

ALTERATION
N546K

TRANSCRIPT ID
NM_023110

CODING SEQUENCE EFFECT
1638C>A

VARIANT ALLELE FREQUENCY (% VAF)
29.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[50-52], pemigatinib[53], infigratinib[54-55], rogaratinib[56], Debio 1347[57-58], futibatinib[59], and derazantinib[60], or multikinase inhibitors such as pazopanib[61] and ponatinib[62-64]. In the context of FGFR1 mutation, clinical responses have been reported in patients with primary brain tumors[57,59] and lung squamous cell carcinoma[65] treated with FGFR inhibitors. In a phase 1 study of futibatinib, 2 patients with FGFR1-mutated primary brain tumors exhibited PRs[59]. A patient with FGFR1-mutated glioblastoma exhibited a PR when treated with infigratinib[66]. For pediatric patients with FGFR1-mutated gliomas, a case series reported 1 sustained PR for a patient with high grade glioma, and a sustained SD and 1 PD for patients with low grade gliomas following treatment with Debio 1347[57].

FREQUENCY & PROGNOSIS

In the Brain Lower Grade Glioma TCGA dataset and the Glioblastoma Multiforme TCGA dataset, mutation of FGFR1 has been found in less than 1% of cases[67-68]. In pediatric patients, FGFR1 alterations have been identified in 18% of low-grade gliomas[36], including 5/9 pilomyxoid astrocytomas, 8% of high-grade gliomas[36], and in 6% (4/64) of thalamic gliomas[69]. FGFR1 mutation has also been reported in 5% (5/96) of pilocytic astrocytomas[70]. Mutations in the FGFR1 kinase domain have been reported in both lower-grade gliomas and glioblastomas; one of these mutations has been described as an oncogenic mutation that disrupted autophosphorylation[71-73]. FGFR fusions were identified in 3/85 IDH1 and IDH2 wild-type gliomas, but were not found in any of 126 IDH1- or IDH2-mutant gliomas[74]. Patients with FGFR1-altered pilocytic astrocytomas have been associated with poor prognosis[75-76], although published data investigating the prognostic implications of FGFR1 alterations independent to co-occurring alterations in gliomas are limited (PubMed, Mar 2022)[69,77].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[78]. The FGFR1 alteration observed here has been characterized as activating and is predicted to be oncogenic[72,79-81].

POTENTIAL DIAGNOSTIC IMPLICATIONS

In pediatric gliomas lacking typical BRAF and NF1 driver alterations, RAS/MAPK hyperactivation arising from non-KIAA1549 fusions with BRAF, non-V600 BRAF mutations, FGFR1/2 fusions, FGFR1 mutations, RAF1 fusions, KRAS mutations, or MYB or MYBL1 rearrangements are typical of the WHO entity diffuse low-grade glioma, MAPK pathway-altered[73,82-84].

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GENE
H3F3A

ALTERATION
K28M

TRANSCRIPT ID
NM_002107

CODING SEQUENCE EFFECT
83A>T

VARIANT ALLELE FREQUENCY (% VAF)
40.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Prospective data from pooled clinical studies and preclinical evidence suggest that H3F3A K28M mutation predicts benefit from the investigational selective dopamine receptor D2 (DRD2) antagonist ONC201[85-86], which is supported by increased expression of the ONC201 target DRD2 in H3F3A K28M-mutant versus wild-type gliomas[86]. Among adult patients with recurrent H3F3A K28M-mutant gliomas, ONC201 achieved a DCR of 64% (7/11) and a 6-month PFS rate of 36% (5/14), with 3 patients experiencing complete and durable regressions of thalamic lesions[87]. Data from pooled ONC201 monotherapy trials showed that 31% (9/29) of patients with recurrent H3F3A K28M-mutated glioma remain progression free at 6.5 months median follow-up[88]. Although other H3F3A mutations have been reported[36], it is unclear whether these therapeutic strategies would be relevant in gliomas with H3F3A mutations other than K28M.

FREQUENCY & PROGNOSIS

Recurrent mutations in the histone tail of H3F3A, at sites involved in critical post-translational modifications, have been reported at high frequency in pediatric and young adult brain tumors, including diffuse midline gliomas[89], diffuse hemispheric glioma[90], glioblastomas[91-93], aggressive pediatric gliomas[94], pilocytic astrocytomas[95], gangliogliomas[96], glial and glioneuronal tumors[97], as well as in low-grade gliomas undergoing transformation and secondary high-grade gliomas[98]. These mutations were commonly found concurrently with mutations in TP53 or in ATRX and DAXX, which form a complex required for H3.3 recruitment to DNA, and were mutually exclusive with IDH1 mutations, which indirectly affect methylation of critical H3.3 residues[92]. H3F3A K28M (also known as K27M) is a poor prognostic marker in glioma (NCCN CNS Cancers Guidelines, v2.2021). H3F3A G35 mutations are associated with disease onset during adolescence, whereas K28 mutations affect younger children and predict poorer IOS[93,99]. H3F3A K28M mutation has also been identified in 58% of adult midline gliomas, and is associated with shorter OS for patients with brainstem gliomas but not for patients with thalamic gliomas[100]. Mutations of H3F3A or H3F3B, the other gene encoding histone H3.3, have also been detected in giant cell tumor of bone and chondroblastoma, with low mutation frequencies in other tumors of cartilage and bone[101-103]. H3F3B K37M (commonly known as K36M) has been identified in head and neck squamous cell carcinoma, specifically in tumors of the oral cavity[104]. Overexpression of H3F3A is associated with poor survival in lung adenocarcinomas, and is thought to promote cancer cell invasion[105].

FINDING SUMMARY

H3F3A encodes the histone 3 variant H3.3. Histones form part of the nucleosome complex around which DNA is coiled in the cell. H3F3A mutations affecting different hotspot residues, such as G35 (commonly referred to as G34 in the literature) and K28 (commonly known as K27), form different subgroups based on methylation and gene expression differences, the region of the brain affected, and clinical parameters[99].

POTENTIAL DIAGNOSTIC IMPLICATIONS

H3F3A K27M mutation is characteristic of diffuse midline glioma, H3 K27M-altered (NCCN CNS Cancers Guidelines, v2.2021)[82,106].

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GENE
ATRX

ALTERATION
H1363fs*12

TRANSCRIPT ID
NM_000489

CODING SEQUENCE EFFECT
4089delT

VARIANT ALLELE FREQUENCY (% VAF)
43.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical[107-108] and limited clinical data[109], ATRX alterations may confer sensitivity to combination strategies involving WEE1 inhibition. In a Phase 2 study evaluating the WEE1 inhibitor adavosertib plus irinotecan for the treatment of pediatric patients with neuroblastoma, prolonged SD was reported for 44% (4/9) of patients with ATRX-deficient tumors and responses were seen in two tumors that had evidence of ALT[109]. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan[110], combined PARP and ATR inhibition[108], or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan[111]; however, these approaches have not been demonstrated clinically.

FREQUENCY & PROGNOSIS

Somatic mutation of ATRX has been reported in a number of solid tumor types, often associated with ALT[112]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[112-114], 12.6% of pheochromocytomas and paragangliomas[115], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[116-120]. ATRX loss in PNET[113,121] and melanoma[122] and mutation in other neuroendocrine tumors[115] is associated with poor prognosis. Pediatric patients with high-grade glioma and ATRX mutation were shown to have more aggressive disease but are more responsive to treatment with double-strand break therapy[111]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[123-126] and has been proposed as a distinguishing biomarker[124-126]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[117-120]. Low-grade gliomas with both IDH1/2 mutation and ATRX mutation are associated with worse prognosis than those with IDH1/2 mutation but no ATRX mutation[124]. Loss of ATRX protein expression has been reported in 33-39% of incidences of leiomyosarcoma (LMS) associating with ALT, a poor prognostic factor across all LMS subtypes, and with poor prognosis in extrauterine LMS but not in uterine LMS[127-128].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[129-130]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[112,128,131-132]. Alterations that disrupt the ADD domain (aa 167-270) or helicase domain (aa 2010-2280) of ATRX are predicted to result in loss of ATRX function[133-135]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[129,136]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[137].

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GENE
ERBB4

ALTERATION
E542K

TRANSCRIPT ID
NM_005235

CODING SEQUENCE EFFECT
1624G>A

VARIANT ALLELE FREQUENCY (% VAF)
50.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The ERBB family kinase inhibitors afatinib and lapatinib, the EGFR inhibitors erlotinib and gefitinib, and the Bruton tyrosine kinase inhibitor ibrutinib have been shown to inhibit ERBB4 at clinically achievable concentrations[138-143]. However, whether these inhibitors would be clinically effective for patients with ERBB4 mutation is unclear. Retrospective analyses of the Phase 3 LUX-Lung 8 trial reported that patients with squamous non-small cell lung cancer (NSCLC) harboring mutations in ERBB family members exhibited long-term benefit following afatinib treatment compared with patients with ERBB-wildtype tumors; there was no difference for patients treated with erlotinib[144-145]. A meta-analysis showed that patients with ERBB4-mutated NSCLC treated with immune checkpoint inhibitors exhibited longer PFS and OS compared with patients who had ERBB4-wildtype tumors (p=0.036 and p=0.0378)[146].

FREQUENCY & PROGNOSIS

ERBB4 mutations have been identified in various solid tumors, including stomach (13%), salivary gland (11%, 2/18), esophageal (9%), lung (8-9%), endometrioid (6%), colorectal (5%), head and neck (5%), and gallbladder carcinomas (3.9%, 2/51), and melanoma (1.8%)[146-151]. In hematological malignancies, ERBB4 mutations are rare, and have been reported at low frequency in diffuse large B-cell lymphoma (DLBCL)(2.2%-5.7%), chronic lymphocytic leukemia (CLL)(0.6-1.1%), and multiple myeloma (0.5%)[152-158]. ERBB4 amplification has been predominantly detected in gastric tumors (67%)[159]. ERBB4 fusions have been identified infrequently in solid tumors and peripheral T-cell lymphoma, although evidence for ERBB4 fusions as driver alterations is generally limited[160-163]. Expression of N-terminally truncated oncogenic ERBB4 variants has been reported in ALK fusion-negative anaplastic large cell lymphomas[164]. ERBB4 mutation correlates with poorer survival for patients with colorectal cancer (CRC)[165]. Increased ERBB4 expression has been associated with worse clinical outcomes for patients with CRC[166-167], bone sarcoma[168], esophageal squamous cell carcinoma (SCC)[169], oral SCC[170], metastatic Ewing sarcoma[171], gastric cancer[172], osteosarcoma[173], or triple-negative breast cancer[174]. In contrast, high ERBB4 expression has been described as a positive prognostic factor in breast cancer[175-177], ovarian cancer[178], cervical carcinomas[179], hormone-sensitive and castrate-resistant prostate cancer[180], and EGFR-negative intrahepatic cholangiocarcinoma[181].

FINDING SUMMARY

ERBB4 (also known as HER4) encodes a member of the ErbB receptor tyrosine kinase family that plays a role in cell proliferation and apoptosis[182]. Activating alterations are predicted to be oncogenic, and gain-of-function mutations have been identified throughout the gene[147,182-184]. The variants N181S, V348L, P854Q, and T926M have demonstrated similar activity as wildtype ERBB4 in limited preclinical studies[183,185]. A single-nucleotide polymorphism in ERBB4 has been associated with increased risk of non-small cell lung cancer (NSCLC) in the Chinese Han population[186].

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GENE
MCL1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to target MCL1 amplification, but MCL1 inhibitors including AMG 176, AMG 397, AZD5991, and S64315 (MIK665) are in early clinical development[187-190]. Limited preclinical data suggest that MCL1 expression alone may not be predictive of sensitivity to MCL1 inhibitors, but BH3 profiling may be a better predictor of MCL1 dependence[188,190-192]. Clinical and preclinical data indicate that increased MCL1 expression may be associated with resistance to BCL2-targeted agents such as venetoclax, navitoclax, or ABT-737[193-200]. In one study, amplification of the genomic locus containing MCL1 was acquired upon disease progression in patients with multiple myeloma treated with venetoclax[201]. Combined inhibition of MCL1 and BCL2 may be more effective[188-190,202-203]. Indirect approaches using therapeutic agents that reduce MCL1 expression are also being investigated[204]. Preclinical studies demonstrate that investigational cyclin-dependent kinase inhibitors targeting CDK9, such as dinaciclib, alvocidib, and voruciclib, suppress gene transcription, reduce MCL1 expression levels, and synergize with BCL2 inhibitors to induce apoptosis[205-212]. Preclinical studies in multiple types of cancer cells have also shown that the multikinase inhibitor sorafenib indirectly downregulates MCL1 and cooperates with BCL2-targeting agents[213-216], and a heavily pretreated patient with metastatic triple-negative breast cancer (TNBC) and MCL1 gene amplification responded to sorafenib in combination with several other therapies[217]. Preclinical studies of patient-derived tumor cells suggest that increased MCL1 levels may confer resistance to antitubulin therapies such as paclitaxel[218], and MCL1 amplification was reported to be more frequent in patients with TNBC and primary resistance to neoadjuvant chemotherapy[219].

FREQUENCY & PROGNOSIS

MCL1 amplification has been reported at the highest incidence in lung adenocarcinoma (16%)[220], breast invasive carcinoma (15%)[221], hepatocellular carcinoma (15%), and bladder urothelial carcinoma (13%)[222] and at lower frequencies in other solid tumor types (cBioPortal, 2022)[223-224]. MCL1 mutations have been reported in fewer than 1% of solid and hematologic cancers (COSMIC, 2022)[225]. In patients with NSCLC, MCL1 amplification was significantly associated with shorter overall survival (hazard ratio 1.39)[226]; high MCL1 protein expression alone was not prognostic in NSCLC[227-229], whereas overexpression of both MCL1 and MYC was linked with poor survival[230]. High MCL1 expression has also been associated with poor prognosis in ovarian[231-232] and colorectal[233] cancers. The prognostic significance of MCL1 expression in breast cancer is not clear[234-235].

FINDING SUMMARY

MCL1 (myeloid cell leukemia 1) encodes a member of the BCL2 family that regulates apoptosis[236]. Focal amplification of MCL1 has been reported in lung, breast, and other cancer types, and the survival of cells with MCL1 amplification is dependent on MCL1 expression[237]. In non-small cell lung cancer (NSCLC), MCL1 amplification was significantly associated with increased MCL1 mRNA expression[226]. Although several MCL1 phosphorylation site mutations have been characterized[238], cancer-associated MCL1 mutations have not been reported (PubMed, Jan 2022).

GENE
PTPN11

ALTERATION
T507K

TRANSCRIPT ID
NM_002834

CODING SEQUENCE EFFECT
1520C>A

VARIANT ALLELE FREQUENCY (% VAF)
23.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

SHP-2 has been reported to activate the RAS-MEK-ERK, PI3K-AKT-mTOR, and SRC kinase pathways[239-242]. Based on a case study of a patient with histiocytic sarcoma harboring an activating PTPN11 mutation who experienced a PR to trametinib[243], as well as preclinical data[244-246], PTPN11 activation may predict sensitivity to MEK inhibitors in histiocytic neoplasms.

FREQUENCY & PROGNOSIS

In the Brain Lower Grade Glioma and Glioblastoma Multiforme TCGA datasets, PTPN11 mutations have been reported in fewer than 1% of cases (cBioPortal, Jan 2022)[223-224]. PTPN11 mutations in glioma subtypes have also been reported in the scientific literature, and recurrent activating PTPN11 mutations have been detected in pilocytic astrocytomas[70,247-248]. PTPN11 mutations in glioblastoma have been associated with young patient age[249], but their prognostic significance in gliomas in general have not been extensively studied (PubMed, Aug 2021). While both oncogenic and tumor suppressor roles for PTPN11 has been described, its role in glioblastoma tumorigenesis is likely to be oncogenic[70,247,250-251].

FINDING SUMMARY

PTPN11 encodes the protein tyrosine-protein phosphatase non-receptor type 11, also known as SHP-2. PTPN11 plays a critical role in both embryonic development and cancer[252]. PTPN11 is also known to be somatically mutated in a variety of cancers, where both oncogenic and tumor suppressor roles for PTPN11 have been described[247,250-251]. The N-terminal SRC homology 2 (SH2) domain (aa 6-102) negatively regulates SHP-2 activity by binding to the active site of the SHP-2 protein tyrosine phosphatase (PTP) domain (aa 247-521)[253]. Alterations that disrupt this interaction or affect the specificity and structure of the SH2 and PTP domains, such as seen here, have been characterized as activating[241,250,254-266] and are predicted to be oncogenic[241,250,255-258,267-270].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in PTPN11 have been found in the developmental disorder Noonan syndrome, which predisposes individuals to various cancers, including embryonal rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia[256,271-275].

GENE
TET2

ALTERATION
E1151*

TRANSCRIPT ID
NM_017628

CODING SEQUENCE EFFECT
3451G>T

VARIANT ALLELE FREQUENCY (% VAF)
53.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2022)[223-224]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2022).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[276-277]. Alterations such as seen here may disrupt TET2 function or expression[278-282].

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 expansion[283-288]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[283-284]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[289]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[287,290-291]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Donna Ferguson, M.D. | 19 April 2022
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Infigratinib

Assay findings association

FGFR1
N546K

AREAS OF THERAPEUTIC USE

Infigratinib is a TKI that inhibits FGFR1, FGFR2, and FGFR3. It is FDA approved for the treatment of patients with unresectable locally advanced or metastatic cholangiocarcinoma who have FGFR2 rearrangements or fusions and have progressed after prior therapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on individual responses in patients with FGFR1-mutated glioblastoma[66] and lung squamous cell carcinoma[65], FGFR1 mutation may predict sensitivity to infigratinib.

SUPPORTING DATA

A Phase 2 study of infigratinib for patients with recurrent high-grade gliomas harboring FGFR alterations, reported a 9.5% (2/21) ORR, 1.7 month median PFS, and 6.7 month median OS[66]. Disease control greater than one year was observed in 4 patients, including a PR in a patient with FGFR1-mutated glioma, and SD in patients with glioma harboring FGFR1 mutation, FGFR3 mutation, or FGFR3-TACC3 fusion[66].

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

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
N546K

NCT04169672

PHASE 2

Study of Surufatinib Combined With Toripalimab in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Shanghai (China), Beijing (China)

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

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)

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)

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), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington, Hospitalet de Llobregat (Spain)

NCT03547037

PHASE 1

A Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of JNJ-63723283, an Anti-Programmed Cell Death (PD)-1 Monoclonal Antibody, as Monotherapy or in Combination With Erdafitinib in Japanese Participants With Advanced Solid Cancers

TARGETS
PD-1, FGFRs

LOCATIONS: Chuo-Ku (Japan), Kashiwa (Japan)

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: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT04424966

PHASE NULL

Infigratinib in Recurrent Glioblastoma Patients

TARGETS
FGFR3, FGFR1, FGFR2

LOCATIONS: Arizona

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Macquarie Park (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), Colorado, Minnesota, Arizona, Ohio, Florida

NCT02549937

PHASE 1/2

A Multi-Center, Open-Label Study of Sulfatinib(HMPL-012) in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs

LOCATIONS: Milano (Italy), California, Colorado, Texas, New York, Tennessee, Virginia, Florida

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GENE
H3F3A

ALTERATION
K28M

RATIONALE
On the basis of clinical and preclinical data, H3F3A K28M mutation may predict response to antagonists of dopamine receptors D2.

NCT03295396	**PHASE 2**
ONC201 in Adults With Recurrent H3 K27M-mutant Glioma	**TARGETS** DRD2, CLLP, DRD3

LOCATIONS: California, Minnesota, New York, Pennsylvania, Texas, North Carolina

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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.

FGFR3
D580N

MLH1
R217C

MTOR
H1744Y

NOTCH3
E739K

NTRK1
R220Q

PDGFRA
L112F

SPEN
T796S

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV1*
ETV4	*ETV5*	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*
KMT2A (MLL)	*MSH2*	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*
RAF1	*RARA*	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***
TMPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

MR Suite Version 6.1.0

The median exon coverage for this sample is 759x

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