FOUNDATIONONE®CDx

PATIENT
Yeh, Kun-Lung

TUMOR TYPE
Brain astrocytoma
COUNTRY CODE
TW

REPORT DATE
24 May 2022
ORDERED TEST #
ORD-1362449-01

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 astrocytoma
NAME Yeh, Kun-Lung
DATE OF BIRTH 08 September 1987
SEX Male
MEDICAL RECORD # 47692717

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

SPECIMEN
SPECIMEN SITE Brain
SPECIMEN ID S110-31113 A (PF22059)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 19 October 2021
SPECIMEN RECEIVED 12 May 2022

Sensitivity for the detection of copy number alterations is reduced due to sample quality.
Sensitivity for the detection of alterations and genomic signatures is reduced and the TMB score may be underreported.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

BRAF N581Y
H3F3A K28M
KRAS G12V
ATRX S1585fs*16
FANCC W113*

α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***H3F3A*** **K28M** (p. 5)
- 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: ***H3F3A*** **K28M** (p. 5)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - Cannot Be Determined	**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)**
***BRAF* -** N581Y	none	none
10 Trials *see p. 8*		
***H3F3A* -** K28M	none	none
1 Trial *see p. 10*		
***KRAS* -** G12V	none	none
10 Trials *see p. 11*		

Electronically signed by Donna Ferguson, M.D. | 24 May 2022
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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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.

ATRX - S1585fs*16 ..... p. 7

FANCC - W113* ..... p. 7

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

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

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BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI-High has been reported in 3-8% of adult or pediatric astrocytomas and was generally not associated with Lynch syndrome[12-14]. Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[15-17]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[15], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[18]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[15], in GBMs with a previous lower grade astrocytoma[16], and in giant cell GBM compared to classic GBM[17].

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[19]. 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[19-21]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

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[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[22,32-33]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[34-35] or anti-PD-L1[36] 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

Astrocytomas harbor a median TMB of 1.8 mutations per megabase (muts/Mb), and 1.4% of cases have high TMB (>20 muts/Mb)[37]. 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[38-39]. Increased TMB has been reported to correlate with higher tumor grade in glioma[40] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[34], as well as with shorter OS of patients with diffuse glioma[41].

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[42-43] and cigarette smoke in lung cancer[7,44], treatment with temozolomide-based chemotherapy in glioma[45-46], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[47-51], and microsatellite instability (MSI)[47,50-51]. 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[22,32-36].

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GENE
BRAF

ALTERATION
N581Y

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1741A>T

VARIANT ALLELE FREQUENCY (% VAF)
34.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

BRAF and MEK inhibitors have shown efficacy for patients with activating BRAF alterations at the V600 codon; clinical outcomes are more limited for class 2 alterations in BRAF such as one or more of the alterations seen here. A retrospective study of immunotherapies in NSCLC reported a 69% DCR (9/13) for patients with class 2 mutations[52]. MEK inhibitors alone or in combination with RAF inhibitors also may be of benefit in these alterations[53-56]. Doublet RAF- and MEK-directed therapy may be more efficacious relative to either monotherapy; a retrospective analysis of BRAF-mutated melanoma observed 5/16 patient responses to BRAF inhibitor with MEK inhibitor therapy in BRAF class 2 tumors and 0/13 responses to BRAF inhibitor monotherapy[57]. A basket trial of single-agent BRAF-inhibitor vemurafenib (n=11)[58] and a trial in NSCLC (n=9)[59] also did not yield any responses for patients with class 2 tumors. In a basket trial of single-agent MEK-inhibitor trametinib, no responses were observed for patients with class 2 tumors (3 SDs, n=5)[60]. Investigational ERK inhibitors are also in development; a basket trial of ulixertinib reported 3 PRs for patients across class 2-mutated tumors[61]. A basket trial of second-generation investigational BRAF inhibitor PLX8394 reported 3 SDs and 4 PDs for patients with class 2 tumors[62]. In 2 Phase 1 studies evaluating the MEK-pan-RAF dual inhibitor CH5126766, 3 patients harboring BRAF V600E mutations experienced PRs, including 2 patients with melanoma[63] and 1 patient with low-grade serous ovarian carcinoma[64]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

Various studies have implicated BRAF alterations, including V600E and rearrangements, in the oncogenesis of pediatric low grade astrocytomas, including gangliogliomas[65-74]. BRAF alterations have been reported in 1-3% of gliomas including low grade gliomas[45,72,75-78] and glioblastomas (GBM)[79]. Studies have reported conflicting results as to whether BRAF mutations, including V600E, are more likely to be found in lower grade astrocytomas or higher grade glioblastomas[72,76,80], and the frequency of the BRAF V600E mutation in astrocytoma reported in the literature varies by cohort[81-83]. BRAF V600E is not strongly associated with prognosis in patients with astrocytoma[81,83]. While one study associated KIAA1549-BRAF fusion with improved prognosis in pediatric patients with low grade astrocytomas[84], others reported no significant association between BRAF rearrangements and outcome[85-88].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[89-90]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[91-92]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
H3F3A

ALTERATION
K28M

TRANSCRIPT ID
NM_002107

CODING SEQUENCE EFFECT
83A>T

VARIANT ALLELE FREQUENCY (% VAF)
44.4%

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[93-94], which is supported by increased expression of the ONC201 target DRD2 in H3F3A K28M-mutant versus wild-type gliomas[94]. 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[95]. 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[96]. Although other H3F3A mutations have been reported[39], 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[97], diffuse hemispheric glioma[98], glioblastomas[99-101], aggressive pediatric gliomas[102], pilocytic astrocytomas[103], gangliogliomas[104], glial and glioneuronal tumors[105], as well as in low-grade gliomas undergoing transformation and secondary high-grade gliomas[106]. 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[100]. 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[101,107]. 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[108]. 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[109-111]. H3F3B K37M (commonly known as K36M) has been identified in head and neck squamous cell carcinoma, specifically in tumors of the oral cavity[112]. Overexpression of H3F3A is associated with poor survival in lung adenocarcinomas, and is thought to promote cancer cell invasion[113].

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[107].

POTENTIAL DIAGNOSTIC IMPLICATIONS

H3F3A K27M mutation is characteristic of diffuse midline glioma, H3 K27M-altered (NCCN CNS Cancers Guidelines, v2.2021)[114-115].

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GENE
KRAS

ALTERATION
G12V

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>T

VARIANT ALLELE FREQUENCY (% VAF)
35.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[116-121]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[64]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study[122-123] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[124-125]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[126]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[127]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[128-129]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[130-131] . While clinical responses have been reported for patients with KRAS-mutated ovarian[132-135], cervical small cell neuroendocrine[136], or uterine cancer[134] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[137-140], pancreatic cancer[141-143], and NSCLC[138,144-145]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[146]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[147-149] and KRAS-mutated endometrioid adenocarcinoma[150].

FREQUENCY & PROGNOSIS

In the TCGA dataset, KRAS mutations or amplification was detected in 1.8% of glioblastomas (GBM)[79] and 2.8% of lower grade gliomas[75]. In other studies KRAS mutations were observed in 2 out of 125 pilocytic astrocytomas, 1 out 25 grade 1 and 2 astrocytomas[151-152], and 2 out of 94 patients with GBM[78]. While the importance of RAS signaling in astrocytomas has been established, there is very little information regarding clinical implications of KRAS alterations in human astrocytoma[151,153]. In mouse models of cancer, activating KRAS mutation in combination with AKT mutation was sufficient to induce GBM in astrocytes and neural progenitors[154]. Furthermore, mutant KRAS-driven signaling was required for the maintenance of mouse GBM tumors[155], suggesting that targeting KRAS signaling may be an appropriate therapeutic strategy in KRAS-driven GBMs.

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[117,156]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, and K117N have been characterized as activating and oncogenic[117,157-179].

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[115,180-182].

GENE
ATRX

ALTERATION
S1585fs*16

TRANSCRIPT ID
NM_000489

CODING SEQUENCE EFFECT
4753_4754TC>ATG

VARIANT ALLELE FREQUENCY (% VAF)
68.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

No targeted therapies are available to directly address ATRX inactivation. Based on preclinical[183-184] and limited clinical data[185], 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[185]. Preclinical evidence also suggests that ATRX deficiency may impart sensitivity to synthetic lethal approaches involving PARP inhibition and irinotecan[186], combined PARP and ATR inhibition[184], or double-strand break-induction with agents such as doxorubicin, irinotecan, and topotecan[187]; 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[188]. ATRX mutation correlating with ALT has been reported in 10-20% of pancreatic neuroendocrine tumors (PNETs)[188-190], 12.6% of pheochromocytomas and paragangliomas[191], and 48% of adolescent and young adult (AYA) patients with glioblastoma (GBM) or neuroblastoma[192-196]. ATRX loss in PNET[189,197] and melanoma[198] and mutation in other neuroendocrine tumors[191] 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[187]. ATRX mutation or loss of expression is more frequent in Grade 2/3 astrocytoma and secondary GBM than primary GBM, oligodendroglioma, and oligoastrocytoma[199-202] and has been proposed as a distinguishing biomarker[200-202]. ATRX mutation has not been detected in concurrence with MYCN amplification in glioma and neuroblastoma[193-196]. 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[200]. 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[203-204].

FINDING SUMMARY

ATRX encodes a SWI/SNF chromatin remodeling protein implicated in histone variant H3.3 deposition, transcriptional regulation, and telomere maintenance[205-206]. ATRX inactivation or loss of expression is associated with alternative lengthening of telomeres (ALT)[188,204,207-208]. 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[209-211]; however, the loss of ATRX function is not sufficient to induce ALT, which requires other undetermined factors[205,212]. Germline mutations in ATRX give rise to alpha-thalassemia X-linked intellectual disability syndrome (ATR-X syndrome)[213].

GENE
FANCC

ALTERATION
W113*

TRANSCRIPT ID
NM_000136

CODING SEQUENCE EFFECT
339G>A

VARIANT ALLELE FREQUENCY (% VAF)
48.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address loss of FANCC activity. However, limited preclinical evidence[214-215] and clinical evidence in sarcoma[216] suggest that FANCC alterations may predict sensitivity to PARP inhibitors.

FREQUENCY & PROGNOSIS

Somatic mutations in FANCC are very infrequently observed in human malignancies (COSMIC, Jan 2022)[217].

FINDING SUMMARY

FANCC encodes a key component of an eight protein (FANCA/B/C/E/F/G/L/M) Fanconi anemia (FA) nuclear E3 ubiquitin ligase complex. This complex is involved in DNA repair and is essential for prevention of chromosome breakage caused by DNA damage[218]. Upon DNA damage or during the S-phase of the cell cycle, the FA complex is activated and recruited to the sites of DNA damage/DNA repair. The complex then activates FANCD2 and FANCL via monoubiquitination, leading to their co-localization with FANCD1/BRCA2, BRCA1, RAD51, PCNA, and other proteins at the DNA repair foci on chromatin. Germline mutations in FANCC cause Fanconi anemia, a clinically heterogeneous disorder involving various developmental abnormalities as well as predisposition to cancer; underlying these phenotypes are defects in DNA repair[219].

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
BRAF

ALTERATION
N581Y

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK. Limited clinical and preclinical studies indicate BRAF mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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)

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), California, Texas

NCT04913285

PHASE 1

A Study to Evaluate KIN-2787 in Subjects With BRAF Mutation Positive Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Perth (Australia), California, Tennessee, Virginia, Florida

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT02428712

PHASE 1/2

A Study of PLX8394 as a Single Agent in Patients With Advanced Unresectable Solid Tumors

TARGETS
BRAF, CRAF

LOCATIONS: Arizona, New York, Texas, Florida

NCT03434262

PHASE 1

SJDAWN: St. Jude Children's Research Hospital Phase 1 Study Evaluating Molecularly-Driven Doublet Therapies for Children and Young Adults With Recurrent Brain Tumors

TARGETS
CDK6, CDK4, MEK, SMO

LOCATIONS: Tennessee

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

GENE
KRAS

ALTERATION
G12V

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

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)

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Nedlands (Australia), Blacktown (Australia), Randwick (Australia), Melbourne (Australia), California, Texas

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS BCL2, BCL-XL, BCL-W, MEK

LOCATIONS: Massachusetts

NCT04214418

PHASE 1/2

Study of Combination Therapy With the MEK Inhibitor, Cobimetinib, Immune Checkpoint Blockade, Atezolizumab, and the AUTOphagy Inhibitor, Hydroxychloroquine in KRAS-mutated Advanced Malignancies

TARGETS PD-L1, MEK

LOCATIONS: Rhode Island, New York

NCT03434262

PHASE 1

SJDAWN: St. Jude Children's Research Hospital Phase 1 Study Evaluating Molecularly-Driven Doublet Therapies for Children and Young Adults With Recurrent Brain Tumors

TARGETS CDK6, CDK4, MEK, SMO

LOCATIONS: Tennessee

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.

ALK
P278L

BRD4
V1110del

EPHB4
I942M

ERBB3
C1078R

FANCC
A325T

FGF3
R210W

RAD51
T132A

Electronically signed by Donna Ferguson, M.D. | 24 May 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B 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*	*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)

Electronically signed by Donna Ferguson, M.D. | 24 May 2022
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

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 6.2.0

The median exon coverage for this sample is 682x

Electronically signed by Donna Ferguson, M.D. | 24 May 2022
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1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
4. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
5. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
6. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
7. Rizvi NA, et al. Science (2015) pmid: 25765070
8. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
9. Hochster et al., 2017; ASCO Abstract 673
10. Fleming et al., 2018; ASCO Abstract 5585
11. Bang et al., 2018; ASCO Abstract 92
12. Alonso M, et al. Cancer Res. (2001) pmid: 11280776
13. Rodríguez-Hernández I, et al. PLoS ONE (2013) pmid: 24073290
14. Vladimirova V, et al. Neuropathol. Appl. Neurobiol. (2008) pmid: 18053027
15. Martinez R, et al. Oncology (2004) pmid: 15331927
16. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
17. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
18. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
19. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
20. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
21. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
22. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
23. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
24. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
25. Cristescu R, et al. Science (2018) pmid: 30309915
26. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
27. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
28. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
29. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
30. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
31. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
32. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
33. Touat M, et al. Nature (2020) pmid: 32322066
34. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
35. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
36. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
37. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
38. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
39. Johnson A, et al. Oncologist (2017) pmid: 28912153
40. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
41. Wang L, et al. BMC Cancer (2020) pmid: 32164609
42. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
43. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
44. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
45. Johnson BE, et al. Science (2014) pmid: 24336570
46. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
47. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
48. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
49. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
50. Nature (2012) pmid: 22810696
51. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
52. Marin-Acevedo et al., 2021; ASCO Abstract e21016
53. Nikanjam M, et al. Mol Cancer Ther (2021) pmid: 33722853
54. Nebhan CA, et al. Oncologist (2021) pmid: 33861486
55. Gautschi O, et al. J Thorac Oncol (2015) pmid: 26200454
56. Negrao MV, et al. J Thorac Oncol (2020) pmid: 32540409
57. Menzer C, et al. J. Clin. Oncol. (2019) pmid: 31580757
58. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
59. Mazieres J, et al. Ann. Oncol. (2020) pmid: 31959346
60. Johnson DB, et al. Clin Cancer Res (2020) pmid: 31924734
61. Sullivan RJ, et al. Cancer Discov (2018) pmid: 29247021
62. Janku et al., 2021; AACR Abstract CT212
63. Martinez-Garcia M, et al. Clin. Cancer Res. (2012) pmid: 22761467
64. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
65. Rodriguez FJ, et al. Annu Rev Pathol (2013) pmid: 23121055
66. Gronych J, et al. J. Clin. Invest. (2011) pmid: 21403401
67. Koelsche C, et al. Neuropathol. Appl. Neurobiol. (2014) pmid: 23822828
68. Nicolaides TP, et al. Clin. Cancer Res. (2011) pmid: 22038996
69. Huillard E, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22586120
70. Dahiya S, et al. Case Rep Med (2012) pmid: 22548077
71. Korshunov A, et al. Acta Neuropathol. (2009) pmid: 19543740
72. Schindler G, et al. Acta Neuropathol. (2011) pmid: 21274720
73. Donson AM, et al. Brain Pathol. (2014) pmid: 24238153
74. Dougherty MJ, et al. Neuro-oncology (2010) pmid: 20156809
75. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
76. Basto D, et al. Acta Neuropathol. (2005) pmid: 15791479
77. Chi AS, et al. J. Neurooncol. (2012) pmid: 22821383
78. Knobbe CB, et al. Acta Neuropathol. (2004) pmid: 15517309
79. Brennan CW, et al. Cell (2013) pmid: 24120142
80. Horbinski C, et al. Neuro-oncology (2012) pmid: 22492957
81. Bannykh SI, et al. Clin. Neuropathol. () pmid: 25066317
82. Theeler BJ, et al. Neuro-oncology (2014) pmid: 24470550
83. Chappé C, et al. Brain Pathol. (2013) pmid: 23442159
84. Hawkins C, et al. Clin. Cancer Res. (2011) pmid: 21610142
85. Colin C, et al. Neuropathol. Appl. Neurobiol. (2013) pmid: 23278243
86. Jones DT, et al. Cancer Res. (2008) pmid: 18974108
87. Lin A, et al. J. Neuropathol. Exp. Neurol. (2012) pmid: 22157620
88. Horbinski C, et al. Acta Neuropathol. (2010) pmid: 20044755
89. Holderfield M, et al. Nat. Rev. Cancer (2014) pmid: 24957944
90. Burotto M, et al. Cancer (2014) pmid: 24948110
91. Davies H, et al. Nature (2002) pmid: 12068308
92. Kandoth C, et al. Nature (2013) pmid: 24132290
93. Arrillaga-Romany I, et al. Oncotarget (2017) pmid: 29108308
94. Prabhu VV, et al. Clin. Cancer Res. (2018) pmid: 30559168
95. Chi et al., 2018; SNO abstract ACTR-34
96. Arrillaga et al., 2019; ASCO abstract 3005
97. Solomon DA, et al. Brain Pathol. (2016) pmid: 26517431
98. Fontebasso AM, et al. Acta Neuropathol (2013) pmid: 23417712
99. Pandit et al., 2016; ISPNO Abstract HG-58
100. Schwartzentruber J, et al. Nature (2012) pmid: 22286061
101. Venneti S, et al. Acta Neuropathol. (2014) pmid: 25200322
102. Wu G, et al. Nat. Genet. (2012) pmid: 22286216
103. Hochart A, et al. Ann Clin Transl Neurol (2015) pmid: 25909089
104. Joyon N, et al. Neuropathol. Appl. Neurobiol. (2017) pmid: 27219822
105. Nguyen AT, et al. Neuropathol. Appl. Neurobiol. (2015) pmid: 25389051
106. Mistry M, et al. J. Clin. Oncol. (2015) pmid: 25667294
107. Sturm D, et al. Cancer Cell (2012) pmid: 23079654
108. Feng J, et al. Hum. Pathol. (2015) pmid: 26297251
109. Behjati S, et al. Nat. Genet. (2013) pmid: 24162739
110. Kervarrec T, et al. Mod Pathol (2017) pmid: 28059095
111. Righi A, et al. Hum Pathol (2017) pmid: 28899740
112. Papillon-Cavanagh S, et al. Nat. Genet. (2017) pmid: 28067913
113. Park SM, et al. Nat Commun (2016) pmid: 27694942
114. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
115. Pfister SM, et al. Cancer Discov (2022) pmid: 34921008
116. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
117. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
118. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
119. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
120. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
121. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
122. Krebs et al., 2021; AACR Abstract CT019
123. Shinde et al., 2020; AACR Abstract CT143
124. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
125. Mainardi S, et al. Nat Med (2018) pmid: 29808006
126. Koczywas et al., 2021; AACR Abstract LB001
127. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
128. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) pmid: 30683722
129. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
130. Hofmann et al., 2021; AACR Abstract CT210
131. Gort et al., 2020; ASCO Abstract TPS3651
132. Monk BJ, et al. J Clin Oncol (2020) pmid: 32822286
133. Farley J, et al. Lancet Oncol. (2013) pmid: 23261356
134. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
135. Han C, et al. Gynecol Oncol Rep (2018) pmid: 29946554
136. Lyons YA, et al. Gynecol Oncol Rep (2014) pmid: 26075998
137. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
138. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
139. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
140. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
141. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152

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142. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
143. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
144. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
145. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
146. Liu JF, et al. Gynecol. Oncol. (2019) pmid: 31118140
147. Spreafico et al., 2014; ASCO Abstract 5506
148. Juric et al., 2014; ASCO Abstract 9051
149. Banerji et al., 2014; ASCO Abstract e13559
150. Shapiro GI, et al. Invest New Drugs (2019) pmid: 31020608
151. Cin H, et al. Acta Neuropathol. (2011) pmid: 21424530
152. Janzarik WG, et al. Neuropediatrics (2007) pmid: 17712732
153. Mellinghoff IK, et al. Curr. Top. Microbiol. Immunol. (2012) pmid: 22015553
154. Holland EC, et al. Nat. Genet. (2000) pmid: 10802656
155. Holmen SL, et al. Cancer Res. (2005) pmid: 16166301
156. Kahn S, et al. Anticancer Res. () pmid: 3310850
157. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
158. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
159. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
160. Sci. STKE (2004) pmid: 15367757
161. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
162. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
163. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
164. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
165. Kim E, et al. Cancer Discov (2016) pmid: 27147599
166. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
167. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
168. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
169. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
170. Scheffzek K, et al. Science (1997) pmid: 9219684
171. Scholl C, et al. Cell (2009) pmid: 19490892
172. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
173. Tyner JW, et al. Blood (2009) pmid: 19075190
174. Valencia A, et al. Biochemistry (1991) pmid: 2029511
175. White Y, et al. Nat Commun (2016) pmid: 26854029
176. Wiest JS, et al. Oncogene (1994) pmid: 8058307
177. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
178. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
179. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
180. Ryall S, et al. Cancer Cell (2020) pmid: 32289278
181. Qaddoumi I, et al. Acta Neuropathol. (2016) pmid: 26810070
182. Zhang J, et al. Nat. Genet. (2013) pmid: 23583981
183. Liang J, et al. Cancer Res (2020) pmid: 31551363
184. Garbarino J, et al. Transl Oncol (2021) pmid: 34118569
185. Cole et al., 2021; AACR Abstract CT059
186. George SL, et al. EBioMedicine (2020) pmid: 32846370
187. Koschmann C, et al. Sci Transl Med (2016) pmid: 26936505
188. Heaphy CM, et al. Science (2011) pmid: 21719641
189. Singhi et al., 2015; USCAP Abstract 1797
190. Jiao Y, et al. Science (2011) pmid: 21252315
191. Fishbein L, et al. Nat Commun (2015) pmid: 25608029
192. Morosini et al., 2014; ASCO Abstract 11008
193. Cheung NK, et al. JAMA (2012) pmid: 22416102
194. Molenaar JJ, et al. Nature (2012) pmid: 22367537
195. Pugh TJ, et al. Nat. Genet. (2013) pmid: 23334666
196. Cheung NK, et al. Nat. Rev. Cancer (2013) pmid: 23702928
197. Marinoni I, et al. Gastroenterology (2014) pmid: 24148618
198. Qadeer ZA, et al. J. Invest. Dermatol. (2014) pmid: 24468746
199. Kannan K, et al. Oncotarget (2012) pmid: 23104868
200. Haberler C, et al. Clin. Neuropathol. () pmid: 24559763
201. Reuss DE, et al. Acta Neuropathol. (2015) pmid: 25427834
202. Sahm F, et al. Acta Neuropathol. (2014) pmid: 25143301
203. Singhi et al., 2015; USCAP Abstract 93
204. Liau JY, et al. Am. J. Surg. Pathol. (2015) pmid: 25229770
205. Clynes D, et al. Trends Biochem. Sci. (2013) pmid: 23916100
206. Ratnakumar K, et al. Epigenetics (2013) pmid: 23249563
207. Lovejoy CA, et al. PLoS Genet. (2012) pmid: 22829774
208. Bower K, et al. PLoS ONE (2012) pmid: 23185534
209. Nan X, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17296936
210. Garrick D, et al. Gene (2004) pmid: 14729260
211. Eustermann S, et al. Nat. Struct. Mol. Biol. (2011) pmid: 21666677
212. Flynn RL, et al. Science (2015) pmid: 25593184
213. Gibbons RJ, et al. Cell (1995) pmid: 7697714
214. Ghosh S, et al. Am. J. Pathol. (2014) pmid: 24200853
215. Lombardi AJ, et al. Clin. Cancer Res. (2015) pmid: 25609062
216. Piha-Paul et al., 2018; AACR-NCI-EORTC Abstract A096
217. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
218. Moldovan GL, et al. Annu. Rev. Genet. (2009) pmid: 19686080
219. Deakyne JS, et al. Biochemistry Mosc. (2011) pmid: 21568838

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