FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Brain glioma (NOS)

REPORT DATE

ORDERED TEST #

PATIENT
DISEASE Brain glioma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

FDA Approved Content

Companion Diagnostic (CDx) Findings

A companion diagnostic provides essential information for the safe and effective of a corresponding drug or bio product. This table contains therapies associated with FoundationOne®CDx's FDA-app companion diagnostic indications.

GENOMIC FINDINGS	CD ICATED THERAP
No Companion Diagnostic (CDx) alterations for FoundationOne®CDx were detected.	

This patient with pediatric low-grade glioma has tested negative for BRAF fusions. In the clinical study supp is indication, F1CDx did not detect 24.3% (9/37) of BRAF fusions. Non-detection was attributed to sub-optimal quality metrics, incl ng low tumor purity, observed acro hole sample population. Therefore, physicians should consider additional testing for patients who are negative for BRAF fusions.

Tumor Profiling Results

FoundationOne®CDx is FDA-approved to provide tumor mutation profiling results for oncology patients with solid tumors.

GENOMIC FINDINGS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden 2 Muts/Mb §
CDKN2A loss §
CDKN2B loss §
DNMT3A R771*
EGFR amplification §
MTOR E1799K
TERT promoter -124C>T

*§ Refer to **appendix for limitation statements related to detection of any copy** number alterations, gene rearrangements, BRCA1/2 alterations, MSI, or TMB results in this section.*

*Please refer to **appendix for** Explanation **of Clinical** nce Classification and for variants of unknown significance (VUS).*

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ABOUT THE TEST FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

INTENDED USE

FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology 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) and tumor mutational burden (TMB) 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 the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. 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. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The F1CDx assay is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

TUMOR TYPE	BIOMARKER(S) DETECTED	THERAPY
Breast cancer	*AKT1* E17K; *PIK3CA* R88Q, N345K, C420R, E542K, E545A, E545D, E545Q, E545K, E545G, Q546E, Q546K, Q546R, Q546P, M1043V, M1043I, H1047Y, H1047R, H1047L and G1049R; and *PTEN* alterations	TRUQAP™ (capivasertib) in combination with FASLODEX® (fulvestrant)
	ERBB2 (HER2) amplification	HERCEPTIN® (trastuzumab)
		KADCYLA® (ado-trastuzumab emtansine)
		PERJETA® (pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	PIQRAY® (alpelisib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	PEMAZYRE® (pemigatinib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	ERBITUX® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3, and 4)	VECTIBIX® (panitumumab)
Melanoma	*BRAF* V600 mutation-positive	TECENTRIQ® (atezolizumab) in combination with COTELLIC® (cobimetinib) and ZELBORAF® (vemurafenib)
	BRAF V600E	BRAF Inhibitor Approved by FDA*
	BRAF V600E and V600K	BRAF/MEK Inhibitor Combinations Approved by FDA*
		MEKINIST® (trametinib)
Non-small cell lung cancer (NSCLC)	*ALK* rearrangements	ALECENSA® (alectinib)
		ALUNBRIG® (brigatinib)
		XALKORI® (crizotinib)
		ZYKADIA® (ceritinib)
	BRAF V600E	BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
		TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
	EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors (TKI) Approved by FDA*
	EGFR exon 20 T790M alterations	TAGRISSO® (osimertinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA® (capmatinib)
	ROS1 fusions	ROZLYTREK® (entrectinib)
Ovarian cancer	*BRCA1*, *BRCA2* alterations	LYNPARZA® (olaparib)

TABLE CONTINUED ON NEXT PAGE

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TABLE 1: COMPANION DIAGNOSTIC INDICATIONS CONTINUED

TUMOR TYPE	BIOMARKER(S) DETECTED	THERAPY
Prostate cancer	*BRCA1*, *BRCA2* alterations	AKEEGA® (niraparib + abiraterone acetate)
		LYNPARZA® (olaparib) in combination with abiraterone
	Homologous Recombination Repair (*HRR*) gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*) alterations	LYNPARZA® (olaparib)

**For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medicaldevices/productsan[illegible]rocedures/invitrodiagnostics/ucm30 431.htm*

The median exon coverage for this sample is 2,270x

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TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs CoExtraction, an automated DNA/RNA co-extraction methodology for DNA extraction from routine FFPE biopsy or surgical resection specimens; 50-1000 ng of DNA 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 (refer to Table 2 and Table 3 for the complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® NovaSeq 6000, hybrid capture-selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and select genomic rearrangements (e.g., gene fusions). Rearrangements in one of the targeted genes included in Table 3 may be reported along with their uniquely identified genomic partners, which can be any gene in the genome even if not explicitly targeted by the assay. Additionally, genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) are reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

WARNINGS AND PRECAUTIONS

1. Alterations reported include somatic (non-inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
2. [illegible] may pose a risk to the patient when adequate tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
3. Reflex testing to an alternative FDA-approved companion diagnostic should be performed for patients who have a HER2 amplification result detected with a 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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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%.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation [illegible] the limits of detection of the assay.
4. Samples with <5% tumor [illegible] decreased sensitivity for detection of [illegible] alterations including *ERBB2*.
5. Clinical performance of Trigriphosimeric in patients with *EGFR* exon 20 T790M mutation detected at allele fraction <5% is ongoing and has not been established.
6. Due to differences in [illegible] and technologies, FoundationOne CDx assay may not identify and report approximately 6% (10/[illegible] copy number [illegible] and approximately 18% (3/17) of
7. Confirmatory [illegible] using a clinically validated assay should be performed for all copy number alterations and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use but used for clinical decision making.
8. For patients with solid tumors whose samples have MSI scores >0.0041 and <0.0124, an MSI "Cannot Be Determined" result is reported. Patients with this result should be retested with a validated orthogonal (alternative) method as these MSI scores represent a range of scores with low reliability. The likelihood of a patient receiving this result is ~3.29% within solid tumors.
9. Patients with solid tumors may also receive an MSI status reported as "Cannot Be Determined" due to a quality control (QC) failure. When all sample-level quality metrics are met, the rate of MSI "Cannot Be Determined" results due to a QC failure is 8.96%. Patients with this result should consider re-testing with FoundationOne CDx or an orthogonal (alternative) method, if clinically appropriate.
10. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at ≥5% allele frequency or greater (after filtering) and the final number is reported as [illegible]utations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor tested for a patient (e.g., primary vs. metastatic tumor content) and the testing platform used for 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.
11. 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.
12. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
13. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
14. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.
15. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not

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be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.

16. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
17. While the overall positive percent agreement between trial enrollment assays and F1CDx was 84% (37/44), thirty percent (30%) (6/20) of patients enrolled in the VITRAKVI clinical studies using RNA-based NGS detection were negative for *NTRK* fusions by F1CDx. Four of the six patients (4/6 or 60%) that were negative for *NTRK* fusions by F1CDx had a response to larotrectinib. Therefore, F1CDx may miss a subset of patients with solid tumors with *NTRK1/2/3* fusions who may derive benefit from VITRAKVI.
18. *NTRK2* fusions per the F1CDx CDx biomarker rules for *NTRK1/2/3* fusions were not well-represented in analytical validation studies.
19. While the overall positive percent agreement between trial enrollment assays and F1CDx was 63.6% (21/33), 52.4% (11/21) of patients enrolled in the ROZLYTREK clinical studies using RNA-based NGS detection were negative for *NTRK* fusions by F1CDx. 36.4% (4/11) of the patients enrolled using RNA-based NGS detection that were negative for *NTRK* fusions by F1CDx had a response to ROZLYTREK.
20. While the overall positive percent agreement between trial enrollment assays and F1CDx was 73.9% (34/46), 30.3% (10/33) of patients enrolled in the ROZLYTREK clinical studies using RNA-based NGS detection were negative for *ROS1* fusions by F1CDx. 50% (5/10) of the patients enrolled using RNA-based NGS detection that were negative for *ROS1* fusions by F1CDx had a response to ROZLYTREK.
21. Due to differences in technology, F1CDx, FISH, and IHC may identify slightly different populations when detecting *ALK* rearrangements. 6.5% of negatives by F1CDx may be positive by both IHC and FISH. See Section 3.4 of the device label for more information.
22. Certain gene fusions, and rearrangements (RE) including but not limited to *BRCA1* RE, *BRCA2* RE, *CDK12* RE, and indels in *PALB2* were not adequately validated in the site-to-site reproducibility study and may not be detected consistently by FoundationOne CDx.
23. Due to technological differences in detection, patients who are negative by F1CDx for *RET* fusions may derive benefit from RETSMO when determined to be positive by other test methods.
24. Additional clinical investigation for *NTRK1/2/3* fusions determined to be negative by F1CDx is recommended for cancers with high *NTRK1/ 2/3* fusion rates (e.g., soft tissue infantile fibrosarcoma, kidney mesoblastic nephroma, salivary gland secretory carcinoma (MASC), breast secretory carcinoma) such that patients may not forgo a potentially effective therapy.
25. F1CDx may miss a subset of patients with solid tumors with *NTRK3* fusions due to the design of the test not fully covering the *NTRK3* gene and common fusion partners.
26. This assay did not detect 24.3% (9/37) of *BRAF* fusions in the clinical validation study supporting this indication. Reduced sensitivity to detect *BRAF* fusions in the clinical validation samples was attributed to sub-optimal quality metrics, including low tumor purity, observed across the whole sample population. Physicians who receive a negative report for *BRAF* fusions for patients with pediatric low-grade glioma should consider following up with another test such that patients may not forgo a potentially effective therapy.

ASSAY CONFIGURATION SPECIFIC TO THIS ISSUED REPORT

MR Suite Version (RG) 8.5.1
MR Reporting Config Version 69
Analysis Pipeline Version v3.37.0
Computational Biology Suite Version 6.33.2
Sequencer Type: NovaSeq 6000
Extraction Method: CoExtraction

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APPENDIX Genes assayed in FoundationOne®CDx

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

TABLE 2 | 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***	*BT*	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*
CBL	***CCND1***	***CCND2***	***CCND3***	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD7*
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*	*E R*	*EMSY (C11orf30)*	***EP300***	***EPHA3***	***EPHB1***
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ER*	***ERRFI1***	*ESR1*
EZH2	*ANCA*	*ANCC*	*ANC*	*ANCL*	*AS*	***FBXW7***	
4	*9*			*4*	*6*	*1*	*R2*
GR3	*R4*		*L CN*	*L T1*	*L T3*	*OXL2*	*UBF1*
ATA4	*A TA6*	*D4 (C17orf39)*	*NA11*	*NA13*	*GNAQ*	*GNAS*	*GRM3*
- A (H3F3A)	*D AC*		*NF1A*	*RAS*	*ID3*	*IRS2*	*D,*
R	*KBKE*	*KZF1*	*NPP4B*	*RF2*	*RF4*	*AK1*	*AK2*
AK3	*UN*	*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***	*M C*	*M CL (M CL1)*	*M CN*	*MYD88*	*NBN*	*NF1*
NF2	***NFE2L2***	***NFKBIA***	***NKX2-***	***NOTCH1***	*NOTCH2*	*NOTCH3*	*NPM1*
NRAS	*NSD2 (WHSC1 or MMSET)*	***NSD3 (WHSC1L1)***	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	***PAX5***
PBRM1	*PDCD1 (PD-)*	*PDCD1L (PD-L2)*	*P2RY8*	*PALB2*	*PARP1*	*PARP2*	***PARP3***
PIK3C2B	***PIK3C2G***	***PIK3CA***	*PIK3CB*	*PIK3R1*	*PIM1*	*PDGFRA*	*PDGFRB*
PDK1	*POLD1*	*POLE*	***PPARG***	***PPP2R1A***	***PPP2R2A***	*PRDM1*	*PRKAR1A*
PRKCI	*PMS2*	*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*	*SF3*
SGK1	***SMAD2***	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STA*	*STAT*	*STK11*
SUFU	***SYK***	***TBX3***	***TEK***	*TENT5C (FAM46C)*	*TET2*	*T BR2*	*TIPARP*
TNFAIP3	***TNFRSF14***	***TP53***	***TSC1***	*TSC2*	*TYRO3*	*U2AF1*	*VE A*
VHL	*WT1*	***XPO1***	*XRCC*	*ZNF217*	*ZNF7*		

TABLE 3 | DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	***BCL2***	*BCR*	***BRAF***	*BRCA1*	*BRCA2*	*CD74*	*E R*
ETV4	***ETV5***	***ETV6***	***EWSR1***	***EZR***	*R1*	*R2*	*R3*
KIT	*KMT2A (MLL)*	***MSH2***	***MYB***	*MY*	***NOTCH2***	*NTRK1*	*NTRK2*
NUTM1	*PDGFRA*	*RAF1*	*RARA*	***RET***	***ROS1***	*RSPO*	*SDC4*
SLC34A2	*TERC***	*TERT****	*TMPRSS*				

**TERC is an NCRNA

***Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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PATIENT
DISEASE Brain glioma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN SITE
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

FDA Approved Content

Companion Diagnostic (CDx) Findings

A companion diagnostic provides essential information for the safe and effective u a corresponding drug or cal product. This table contains therapies associated with FoundationOne®CDx's FDA-approved companion diagnostic indications.

GENOMIC FINDINGS	CDx-IN ED THERAPIES
BRAF V600E	Ojemda™ (Tovorafenib)

Tumor Profiling Results

FoundationOne®CDx is FDA-approved to provide tum profiling results for o y patients with solid tumors.

ENOMIC FINDINGS & BIOMARKER S IDENTIFIED

Results reported in this section are not prescriptive or conclusive for d use of any product. See *professional services* section for additional information.

Microsatellite status MS-Stable §
Tumor Mutational Burden Muts/Mb §
BRAF V600E
CBL W408S
CDKN2A loss §
CDKN2B loss §
MTAP loss §

§ Refer to appendix for limitatio ents related to lterations, gene rearrangements, BRCA1/2 alterations, MSI, or TMB results in this section.

Please refer to appendix for Explanat linico cance Classification a ariants of unknown significance (VUS).

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ABOUT THE TEST FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

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INTENDED USE

FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology 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) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to [illegible] patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling [illegible] F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidel[illegible]n onco[illegible] patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive [illegible]ed use of a[illegible]c therapeutic product.

The F1CDx assay is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

TUMOR TYPE	BIOMARKER(S) DETECTED	THERAPY
Breast cancer	*AKT1* E17K; *PIK3CA* R88Q, N345K, C420R, E542K, E545A, E545D, E545Q, E545K, E545G, Q546E, Q546K, Q546R, Q546P, M1043V, M1043I, H1047Y, H1047R, H1047L and G1049R; and *PTEN* alterations	TRUQAP™ (capivasertib) in combination with FASLODEX® (fulvestrant)
	ERBB2 (HER2) amplification	HERCEPTIN® (trastuzumab)
		KADCYLA® (ado-trastuzumab emtansine)
		PERJETA® (pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	PIQRAY® (alpelisib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	[illegible]® (pemigatinib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	ERBITUX® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3, and 4)	VECTIBIX® (panitumumab)
Melanoma	*BRAF* V600 mutation-positive	TECENTRIQ® (atezolizumab) in combination with COTELLIC® (cobimetinib) and ZELBORAF® (vemurafenib)
	[illegible] V600E	BRAF Inhibitor Approved by FDA*
	BRAF V600E and V600K	BRAF/MEK Inhibitor Combinations Approved by FDA*
		MEKINIST® (trametinib)
Non-small cell lung cancer (NSCLC)	*ALK* rearrangements	ALECENSA® (alectinib)
		ALUNBRIG® (brigatinib)
		XALKORI® (crizotinib)
		ZYKADIA® (ceritinib)
	BRAF V600E	BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
		TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
	EGFR exon 19 deletions and *EGFR* exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors (TKI) Approved by FDA*
	EGFR exon 20 T790M alterations	TAGRISSO® (osimertinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA® (capmatinib)
	ROS1 fusions	ROZLYTREK® (entrectinib)
Ovarian cancer	*BRCA1*, *BRCA2* alterations	LYNPARZA® (olaparib)

TABLE CONTINUED ON NEXT PAGE

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TABLE 1: COMPANION DIAGNOSTIC INDICATIONS CONTINUED

TUMOR TYPE	BIOMARKER(S) DETECTED	THERAPY
Prostate cancer	*BRCA1*, *BRCA2* alterations	AKEEGA® (niraparib + abiraterone acetate)
		LYNPARZA® (olaparib) in combination with abiraterone
	Homologous Recombination Repair (*HRR*) gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*) alterations	LYNPARZA® (olaparib)

**For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medicaldevices/productsan[illegible]rocedures/invitrodiagnostics/ucm30 431.htm*

The median exon coverage for this sample is 2,270x

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TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs CoExtraction, an automated DNA/RNA co-extraction methodology for DNA extraction from routine FFPE biopsy or surgical resection specimens; 50-1000 ng of DNA 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 (refer to Table 2 and Table 3 for the complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® NovaSeq 6000, hybrid capture-selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and select genomic rearrangements (e.g., gene fusions). Rearrangements in one of the targeted genes included in Table 3 may be reported along with their uniquely identified genomic partners, which can be any gene in the genome even if not explicitly targeted by the assay. Additionally, genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) are reported.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/f1cdx

WARNINGS AND PRECAUTIONS

1. Alterations reported include somatic (non-inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
2. [illegible] may pose a risk to the patient when adequate tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
3. Reflex testing to an alternative FDA-approved companion diagnostic should be performed for patients who have a *ERBB2* amplification result detected with a 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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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%.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation [illegible] the limits of detection of the assay.
4. Samples with <5% tumor [illegible] decreased sensitivity for detection of [illegible] alterations including *ERBB2*.
5. Clinical performance of Trastuzumab [illegible] in patients with *EGFR* exon 20 T790M mutation detected at allele fraction <5% is ongoing and has not been established.
6. Due to differences in [illegible] and technologies, FoundationOne CDx assay may not identify and report approximately 6% (10/[illegible] copy number [illegible] and approximately 18% (3/17) of
7. Confirmatory [illegible] using a clinically validated assay should be performed for all copy number alterations and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use but used for clinical decision making.
8. For patients with solid tumors whose samples have MSI scores >0.0041 and <0.0124, an MSI "Cannot Be Determined" result is reported. Patients with this result should be retested with a validated orthogonal (alternative) method as these MSI scores represent a range of scores with low reliability. The likelihood of a patient receiving this result is ~3.29% within solid tumors.
9. Patients with solid tumors may also receive an MSI status reported as "Cannot Be Determined" due to a quality control (QC) failure. When all sample-level quality metrics are met, the rate of MSI "Cannot Be Determined" results due to a QC failure is 8.96%. Patients with this result should consider re-testing with FoundationOne CDx or an orthogonal (alternative) method, if clinically appropriate.
10. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at ≥5% allele frequency or greater (after filtering) and the final number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor tested for a patient (e.g., primary vs. metastatic tumor content) and the testing platform used for 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.
11. 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.
12. The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
13. Alterations in polyT homopolymer runs may not be reliably detected in BRCA1/2.
14. Certain large rearrangements in BRCA1/2 including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.
15. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not

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be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.

16. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
17. While the overall positive percent agreement between trial enrollment assays and F1CDx was 84% (37/44), thirty percent (30%) (6/20) of patients enrolled in the VITRAKVI clinical studies using RNA-based NGS detection were negative for *NTRK* fusions by F1CDx. Four of the six patients (4/6 or 60%) that were negative for *NTRK* fusions by F1CDx had a response to larotrectinib. Therefore, F1CDx may miss a subset of patients with solid tumors with *NTRK1/2/3* fusions who may derive benefit from VITRAKVI.
18. *NTRK2* fusions per the F1CDx CDx biomarker rules for *NTRK1/2/3* fusions were not well-represented in analytical validation studies.
19. While the overall positive percent agreement between trial enrollment assays and F1CDx was 63.6% (21/33), 52.4% (11/21) of patients enrolled in the ROZLYTREK clinical studies using RNA-based NGS detection were negative for *NTRK* fusions by F1CDx. 36.4% (4/11) of the patients enrolled using RNA-based NGS detection that were negative for *NTRK* fusions by F1CDx had a response to ROZLYTREK.
20. While the overall positive percent agreement between trial enrollment assays and F1CDx was 73.9% (34/46), 30.3% (10/33) of patients enrolled in the ROZLYTREK clinical studies using RNA-based NGS detection were negative for *ROS1* fusions by F1CDx. 50% (5/10) of the patients enrolled using RNA-based NGS detection that were negative for *ROS1* fusions by F1CDx had a response to ROZLYTREK.
21. Due to differences in technology, F1CDx, FISH, and IHC may identify slightly different populations when detecting *ALK* rearrangements. 6.5% of negatives by F1CDx may be positive by both IHC and FISH. See Section 3.4 of the device label for more information.
22. Certain gene fusions, and rearrangements (RE) including but not limited to *BRCA1* RE, *BRCA2* RE, *CDK12* RE, and indels in *PALB2* were not adequately validated in the site-to-site reproducibility study and may not be detected consistently by FoundationOne CDx.
23. Due to technological differences in detection, patients who are negative by F1CDx for *RET* fusions may derive benefit from RETEVMO when determined to be positive by other test methods.
24. Additional clinical investigation for *NTRK1/2/3* fusions determined to be negative by F1CDx is recommended for cancers with high *NTRK1/ 2/3* fusion rates (e.g., soft tissue infantile fibrosarcoma, kidney mesoblastic nephroma, salivary gland secretory carcinoma (MASC), breast secretory carcinoma) such that patients may not forgo a potentially effective therapy.
25. F1CDx may miss a subset of patients with solid tumors with *NTRK3* fusions due to the design of the test not fully covering the *NTRK3* gene and common fusion partners.
26. This assay did not detect 24.3% (9/37) of *BRAF* fusions in the clinical validation study supporting this indication. Reduced sensitivity to detect *BRAF* fusions in the clinical validation samples was attributed to sub-optimal quality metrics, including low tumor purity, observed across the whole sample population. Physicians who receive a negative report for *BRAF* fusions for patients with pediatric low-grade glioma should consider following up with another test such that patients may not forgo a potentially effective therapy.

ASSAY CONFIGURATION SPECIFIC TO THIS ISSUED REPORT

MR Suite Version (RG) 8.5.1
MR Reporting Config Version 69
Analysis Pipeline Version v3.37.0
Computational Biology Suite Version 6.33.2
Sequencer Type: NovaSeq 6000
Extraction Method: CoExtraction

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APPENDIX Genes assayed in FoundationOne®CDx

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

TABLE 2 | 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***	*BT*	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*
CBL	***CCND1***	***CCND2***	***CCND3***	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD7*
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*	*E R*	*EMSY (C11orf30)*	***EP300***	***EPHA3***	***EPHB1***
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ER*	***ERRFI1***	*ESR1*
EZH2	*ANCA*	*ANCC*	*ANC*	*ANCL*	*AS*	***FBXW7***	
4	*9*			*4*	*6*	*1*	*R2*
GR3	*R4*		*L CN*	*L T1*	*L T3*	*OXL2*	*UBP1*
ATA4	*A TA6*	*D4 (C17orf39)*	*NA11*	*NA13*	*GNAQ*	*GNAS*	*GRM3*
- A (H3F3A)	*D AC*		*NF1A*	*RAS*	*3B1*	*ID3*	*D*
R	*KBKE*	*KZF1*	*NPP4B*	*RF2*	*RF4*	*IRS2*	*AK1*
AK3	*UN*	*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***	***M C***	*M CL (M CL1)*	*M CN*	*MYD88*	*NBN*	*NF1*
NF2	***NFE2L2***	***NFKBIA***	***NKX2-***	***NOTCH1***	*NOTCH2*	*NOTCH3*	*NPM1*
NRAS	*NSD2 (WHSC1 or MMSET)*	***NSD3 (WHSC1L1)***	***NT5C2***	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*
PALB2	*PARP1*	*PARP2*	***PARP3***	***PAX5***	*PBRM1*	*PDCD1 (PD-)*	*PDCD1L (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*	*SF3*
SGK1	***SMAD2***	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STA*	*STAT*	*STK11*
SUFU	***SYK***	***TBX3***	***TEK***	*TENT5C (FAM46C)*	*TET2*	*T BR2*	*TIPARP*
TNFAIP3	***TNFRSF14***	***TP53***	***TSC1***	*TSC2*	*TYRO3*	*U2AF1*	*VE A*
VHL	*WT1*	***XPO1***	*XRCC*	*ZNF217*	*ZNF7*		

TABLE 3 | DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	***BCL2***	*BCR*	***BRAF***	*BRCA1*	*BRCA2*	*CD74*	*E R*
ETV4	***ETV5***	***ETV6***	***EWSR1***	***EZR***	*R1*	*R2*	*R3*
KIT	*KMT2A (MLL)*	***MSH2***	***MYB***	*MY*	***NOTCH2***	*NTRK1*	*NTRK2*
NUTM1	*PDGFRA*	*RAF1*	*RARA*	***RET***	***ROS1***	*RSPO*	*SDC4*
SLC34A2	*TERC***	*TERT****	*TMPRSS*				

**TERC is an NCRNA

***Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Tumor Mutational Burden (TMB)

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