FOUNDATIONONE® CDx

# Technical Specifications

## 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 when using the DNAx extraction method. The test is intended for detection of substitutions and indels in 324 genes, CNAs in 16 genes and select gene rearrangements, as well as genomic signatures including MSI and TMB using DNA isolated from FFPE tumor tissue specimens when using the CoExtraction method for DNA isolation. 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. 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. The F1CDx assay is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

### Table 1: Companion diagnostic indications

| TUMOR TYPES | BIOMARKERS | FDA-APPROVED THERAPY |
|---|---|---|
| Non-Small Cell Lung Cancer (NSCLC) | *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) |
| | *ALK* rearrangements | Alecensa®(alectinib), Alunbrig® (brigatinib), Xalkori® (crizotinib), or Zykadia® (ceritinib) |
| | *BRAF* V600E | Braftovi® (encorafenib) in combination with Mektovi® (binimetinib) or Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) |
| | *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping | Tabrecta® (capmatinib) |
| | *ROS1* fusions | Rozlytrek® (entrectinib) |
| Melanoma | *BRAF* V600E | BRAF Inhibitors approved by FDA* |
| | *BRAF* V600E and V600K | Mekinist® (trametinib) or BRAF/MEK Inhibitor Combinations approved by FDA* |
| | *BRAF* V600 mutation-positive | Tecentriq® (atezolizumab) in combination with Cotellic® (cobimetinib) and Zelboraf® (vemurafenib) |
| Breast Cancer | *ERBB2* (HER2) amplification | Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumabemtansine), or Perjeta® (pertuzumab) |
| | *PIK3CA* C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations | Piqray® (alpelisib) |
| | *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) |
| 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) |
| Ovarian Cancer | *BRCA1/2* alterations | Lynparza® (olaparib) |
| Cholangiocarcinoma | *FGFR2* fusions and select rearrangements | Pemazyre™ (pemigatinib) |
| Prostate Cancer | Homologous Recombination Repair *(HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L)* alterations | Lynparza® (olaparib) |
| | *BRCA1, BRCA2* alterations | Akeega® (niraparib + abiraterone acetate) |
| Solid tumors | MSI-H | Keytruda® (pembrolizumab) |
| | TMB ≥ 10 mutations per megabase | Keytruda® (pembrolizumab) |
| | *NTRK1/2/3* fusions | Vitrakvi® (larotrectinib) or Rozlytrek® (entrectinib) |
| | *RET* fusions | Retevmo® (selpercatinib) |

* For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools



## Summary of Clinical Studies

Follow-on CDx claims were based on a non-inferiority statistical testing approach using the enrichment design presented in the paper by Li (2016).[1] All studies passed the acceptance criteria specific in each study protocol.

| BIOMARKER | POSITIVE PERCENT AGREEMENT (PPA)‡ | NEGATIVE PERCENT AGREEMENT (NPA) | COMPARATOR METHOD† |
|---|---|---|---|
| *EGFR* Exon 19 Deletions and L858R | 98.1% (106/108) | 99.4% (153/154) | cobas® *EGFR* Mutation Test v2 |
| *EGFR* T790M | 98.9% (87/88) | 86.1% (93/108) | cobas® *EGFR* Mutation Test v1<br>cobas® *EGFR* Mutation Test v2 |
| *ALK* Rearrangements | 92.9% (78/84) | 100% (75/75) | Ventana *ALK* (D5F3) CDx Assay<br>Vysis *ALK* Break-Apart FISH Probe Kit |
| *KRAS* | 100% (173/173) | 100% (154/154) | therascreen® *KRAS* RGQ PCR Kit |
| *ERBB2* (HER2) Amplifications | 89.4% (101/113) | 98.4% (180/183) | Dako HER2 FISH PharmDx® Kit |
| *BRAF* V600 | 99.4% (166/167) | 89.6% (121/135)§ | cobas® *BRAF* V600 Mutation Test |
| *BRAF* V600E | 99.3% (149/150) | 99.2% (121/122) | |
| *BRAF* V600 dinucleotide§ | 96.3% (26/27) | 100% (24/24) | THxID® *BRAF* kit |

* For the most current information about the therapeutic products in this group, go to: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.
† Cobas® is a trademark of Roche Diagnostics Operations, Inc. Therascreen® is a trademark of Qiagen. PharmDx® is a registered trademark of Dako Denmark A/S. THxID® is a registered trademark of bioMérieux.
‡ The reference standard used to calculate PPA and NPA is defined as the consensus calls between the two comparator methods – PPA being when FoundationOne CDx and the comparator method(s) identified mutations in mutated patients and NPA being when FoundationOne CDx and the comparator method(s) did not identify mutations in non-mutated patients.
§ Sensitivity of dinucleotide detection of *BRAF* V600K and V600E was found to be significantly reduced in cobas® test, in particular for samples in which FoundationOne CDx detected the dinucleotides to be of lower than 40% mutant allele frequency (MAF), leading to low NPA values.
¶ A study using the THxID® *BRAF* kit (bioMérieux) was conducted with samples with *BRAF* V600 dinucleotide mutation detected by F1CDx and *BRAF* V600 negative samples to provide a better evaluation of V600 dinucleotide concordance.

## Current Gene List[2]

Genes with full coding exonic regions included in FoundationOne®CDx for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs).

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *ABL1* | *ACVR1B* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *ALOX12B* | *AMER1 (FAM123B)* | *APC* |
| *AR* | *ARAF* | *ARFRP1* | *ARID1A* | *ASXL1* | *ATM** | *ATR* | *ATRX* | *AURKA* |
| *AURKB* | *AXIN1* | *AXL* | *BAP1* | *BARD1** | *BCL2* | *BCL2L1* | *BCL2L2* | *BCL6* |
| *BCOR* | *BCORL1* | *BRAF* | *BRCA1** | *BRCA2** | *BRD4* | *BRIP1** | *BTG1* | *BTG2* |
| *BTK* | *C11ORF30 (EMSY)* | *CALR* | *CARD11* | *CASP8* | *CBFB* | *CBL* | *CCND1* | *CCND2* |
| *CCND3* | *CCNE1* | *CD22* | *CD274 (PD-L1)* | *CD70* | *CD79A* | *CD79B* | *CDC73* | *CDH1* |
| *CDK12** | *CDK4* | *CDK6* | *CDK8* | *CDKN1A* | *CDKN1B* | *CDKN2A* | *CDKN2B* | *CDKN2C* |
| *CEBPA* | *CHEK1** | *CHEK2** | *CIC* | *CREBBP* | *CRKL* | *CSF1R* | *CSF3R* | *CTCF* |
| *CTNNA1* | *CTNNB1* | *CUL3* | *CUL4A* | *CXCR4* | *CYP17A1* | *DAXX* | *DDR1* | *DDR2* |
| *DIS3* | *DNMT3A* | *DOT1L* | *EED* | *EGFR* | *EP300* | *EPHA3* | *EPHB1* | *EPHB4* |
| *ERBB2** | *ERBB3* | *ERBB4* | *ERCC4* | *ERG* | *ERRFI1* | *ESR1* | *EZH2* | *FAM46C* |
| *FANCA* | *FANCC* | *FANCG* | *FANCL** | *FAS* | *FBXW7* | *FGF10* | *FGF12* | *FGF14* |
| *FGF19* | *FGF23* | *FGF3* | *FGF4* | *FGF6* | *FGFR1* | *FGFR2* | *FGFR3* | *FGFR4* |
| *FH* | *FLCN* | *FLT1* | *FLT3* | *FOXL2* | *FUBP1* | *GABRA6* | *GATA3* | *GATA4* |
| *GATA6* | *GID4 (C17ORF39)* | *GNA11* | *GNA13* | *GNAQ* | *GNAS* | *GRM3* | *GSK3B* | *H3F3A* |
| *HDAC1* | *HGF* | *HNF1A* | *HRAS* | *HSD3B1* | *ID3* | *IDH1* | *IDH2* | *IGF1R* |
| *IKBKE* | *IKZF1* | *INPP4B* | *IRF2* | *IRF4* | *IRS2* | *JAK1* | *JAK2* | *JAK3* |
| *JUN* | *KDM5A* | *KDM5C* | *KDM6A* | *KDR* | *KEAP1* | *KEL* | *KIT* | *KLHL6* |
| *KMT2A (MLL)* | *KMT2D (MLL2)* | *KRAS* | *LTK* | *LYN* | *MAF* | *MAP2K1 (MEK1)* | *MAP2K2 (MEK2)* | *MAP2K4* |
| *MAP3K1* | *MAP3K13* | *MAPK1* | *MCL1* | *MDM2* | *MDM4* | *MED12* | *MEF2B* | *MEN1* |
| *MERTK* | *MET* | *MITF* | *MKNK1* | *MLH1* | *MPL* | *MRE11A* | *MSH2* | *MSH3* |
| *MSH6* | *MST1R* | *MTAP* | *MTOR* | *MUTYH* | *MYC* | *MYCL (MYCL1)* | *MYCN* | *MYD88* |
| *NBN* | *NF1* | *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOTCH1* | *NOTCH2* | *NOTCH3* |
| *NPM1* | *NRAS* | *NT5C2* | *NTRK1* | *NTRK2* | *NTRK3* | *P2RY8* | *PALB2** | *PARK2* |
| *PARP1* | *PARP2* | *PARP3* | *PAX5* | *PBRM1* | *PDCD1 (PD-1)* | *PDCD1LG2 (PD-L2)* | *PDGFRA* | *PDGFRB* |
| *PDK1* | *PIK3C2B* | *PIK3C2G* | *PIK3CA* | *PIK3CB* | *PIK3R1* | *PIM1* | *PMS2* | *POLD1* |
| *POLE* | *PPARG* | *PPP2R1A* | *PPP2R2A* | *PRDM1* | *PRKAR1A* | *PRKCI* | *PTCH1* | *PTEN** |
| *PTPN11* | *PTPRO* | *QKI* | *RAC1* | *RAD21* | *RAD51* | *RAD51B** | *RAD51C** | *RAD51D** |
| *RAD52* | *RAD54L** | *RAF1* | *RARA* | *RB1* | *RBM10* | *REL* | *RET* | *RICTOR* |
| *RNF43* | *ROS1* | *RPTOR* | *SDHA* | *SDHB* | *SDHC* | *SDHD* | *SETD2* | *SF3B1* |
| *SGK1* | *SMAD2* | *SMAD4* | *SMARCA4* | *SMARCB1* | *SMO* | *SNCAIP* | *SOCS1* | *SOX2* |
| *SOX9* | *SPEN* | *SPOP* | *SRC* | *STAG2* | *STAT3* | *STK11* | *SUFU* | *SYK* |
| *TBX3* | *TEK* | *TET2* | *TGFBR2* | *TIPARP* | *TNFAIP3* | *TNFRSF14* | *TP53* | *TSC1* |
| *TSC2* | *TYRO3* | *U2AF1* | *VEGFA* | *VHL* | *WHSC1 (MMSET)* | *WHSC1L1* | *WT1* | *XPO1* |
| *XRCC2* | *ZNF217* | *ZNF703* | | | | | | |

* *Genes with copy number alteration reporting are limited to CDx variants when using the CoExtraction method as part of the FDA-approved Intended Use*

## Select Rearrangements[2,3]

Genes with select intronic regions for the detection of gene rearrangements, one gene with a promoter region and one non-coding RNA gene.

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

** *TERC is an ncRNA*
*** *Promoter region of TERT is interrogated*

FoundationOne®CDx is a qualitative next-generation sequencing based in vitro diagnostic test for advanced cancer patients with solid tumors and is for prescription use only. The test analyzes 324 genes as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) and is a companion diagnostic to identify patients who may benefit from treatment with specific therapies in accordance with the approved therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the test does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Some patients may require a biopsy. For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com.

**References:**


1. Li M. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study. Statistics in Biopharmaceutical Research 8, 355-363 (2016).
2. Current as of November 2023. Please visit www.*foundationmedicine.com/f1cdx* for the most up-to-date gene list.
3. Refer to our full label for listing of intronic regions at *http://www.F1CDxLabel.com.*


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