

Technical Specifications



Intended Use

FoundationOne[®]CDx (FICDx) 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 15 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, FICDx 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 FICDx 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)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	EGFR Tyrosine Kinase Inhibitors (TKI) approved by FDA*
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso [®] (osimertinib)
	<i>ALK</i> rearrangements	Alecensa [®] (alectinib), Alunbrig [®] (brigatinib), Xalkori [®] (crizotinib), or Zykadia [®] (ceritinib)
	<i>BRAF</i> V600E	Braftovi [®] (encorafenib) in combination with Mektovi [®] (binimetinib) or Tafinlar [®] (dabrafenib) in combination with Mekinist [®] (trametinib)
	<i>MET</i> single nucleotide variants (SNVs) and indels that lead to <i>MET</i> exon 14 skipping	Tabrecta [®] (capmatinib)
	<i>ROS1</i> fusions	Rozlytrek [®] (entrectinib)
Melanoma	<i>BRAF</i> V600E	BRAF Inhibitors approved by FDA*
	<i>BRAF</i> V600E and V600K	Mekinist [®] (trametinib) or BRAF/MEK Inhibitor Combinations approved by FDA*
	<i>BRAF</i> V600 mutation-positive	Tecentriq [®] (atezolizumab) in combination with Cotellic [®] (cobimetinib) and Zelboraf [®] (vemurafenib)
Breast Cancer	<i>ERBB2</i> (HER2) amplification	Herceptin [®] (trastuzumab), Kadcyla [®] (ado-trastuzumabemtansine), or Perjeta [®] (pertuzumab)
	<i>PIK3CA</i> C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray [®] (alpelisib)
Colorectal Cancer	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix [®] (cetuximab)
	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3 and 4) and <i>NRAS</i> wild-type (absence of mutations in exons 2, 3 and 4)	Vectibix [®] (panitumumab)
Ovarian Cancer	<i>BRCA1/2</i> alterations	Lynparza [®] (olaparib)
Cholangiocarcinoma	<i>FGFR2</i> fusions and select rearrangements	Pemazyre [™] (pemigatinib) or Truseltiq [™] (infigratinib)
Prostate Cancer	Homologous Recombination Repair (<i>HRR</i>) gene (<i>BRCA1</i> , <i>BRCA2</i> , <i>ATM</i> , <i>BARD1</i> , <i>BRIPI</i> , <i>CDK12</i> , <i>CHEK1</i> , <i>CHEK2</i> , <i>FANCL</i> , <i>PALB2</i> , <i>RAD51B</i> , <i>RAD51C</i> , <i>RAD51D</i> and <i>RAD54L</i>) alterations	Lynparza [®] (olaparib)
	<i>BRCA1</i> , <i>BRCA2</i> alterations	Akeega [®] (niraparib + abiraterone acetate)
Solid tumors	MSI-H	Keytruda [®] (pembrolizumab)
	TMB ≥ 10 mutations per megabase	Keytruda [®] (pembrolizumab)
	<i>NTRK1/2/3</i> fusions	Vitrakvi [®] (larotrectinib) or Rozlytrek [®] (entrectinib)

* 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>
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The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the Rubraca product label.



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 [†]
<i>EGFR</i> Exon 19 Deletions and L858R	98.1% (106/108)	99.4% (153/154)	cobas [®] <i>EGFR</i> Mutation Test v2
<i>EGFR</i> T790M	98.9% (87/88)	86.1% (93/108)	cobas [®] <i>EGFR</i> Mutation Test v1 cobas [®] <i>EGFR</i> Mutation Test v2
<i>ALK</i> Rearrangements	92.9% (78/84)	100% (75/75)	Ventana <i>ALK</i> (D5F3) CDx Assay Vysis <i>ALK</i> Break-Apart FISH Probe Kit
<i>KRAS</i>	100% (173/173)	100% (154/154)	therascreen [®] <i>KRAS</i> RGQ PCR Kit
<i>ERBB2</i> (HER2) Amplifications	89.4% (101/113)	98.4% (180/183)	Dako HER2 FISH PharmDx [®] Kit
<i>BRAF</i> V600	99.4% (166/167)	89.6% (121/135) [§]	cobas [®] <i>BRAF</i> V600 Mutation Test
<i>BRAF</i> V600E	99.3% (149/150)	99.2% (121/122)	
<i>BRAF</i> V600 dinucleotide [¶]	96.3% (26/27)	100% (24/24)	THxID [®] <i>BRAF</i> 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 FICDx and *BRAF* V600 negative samples to provide a better evaluation of V600 dinucleotide concordance.

Current Gene List²

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	ATRAX	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	NFKB1A	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	SOC1	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	RSP02	SDC4	SLC34A2	TERC**	TERC*** (PROMOTER ONLY)	TMPRSS2

** TERC is an ncRNA

*** Promoter region of TERC 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:

- 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).
- Current as of October 2023. Please visit www.foundationmedicine.com/f1cdx for the most up-to-date gene list.
- Refer to our full label for listing of intronic regions at <http://www.F1CDxLabel.com>.

