

Technical Specifications



Intended Use

FoundationOne CDx™ (FICDx) 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) 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. 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 a single-site assay performed at Foundation Medicine, Inc.

Table 1: Companion diagnostic indications

INDICATIONS	BIOMARKER	FDA-APPROVED THERAPY*
Non-Small Cell Lung Cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif® (afatinib), Iressa® (gefitinib), or Tarceva® (erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso® (osimertinib)
	<i>ALK</i> rearrangements	Alecensa® (alectinib), Xalkori® (crizotinib), or Zykadia® (ceritinib)
	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib)
Melanoma	<i>BRAF</i> V600E	Tafinlar® (dabrafenib) or Zelboraf® (vemurafenib)
	<i>BRAF</i> V600E and V600K	Mekinist® (trametinib) or Cotellic® (cobimetinib), in combination with Zelboraf® (vemurafenib)
Breast Cancer	<i>ERBB2</i> (HER2) amplification	Herceptin® (trastuzumab), Kadcyla® (ado-trastuzumab-emtansine), or Perjeta® (pertuzumab)
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	Rubraca® (rucaparib)

* Tarceva® is the registered trademark of OSI Pharmaceuticals, LLC. Zelboraf®, Herceptin®, Perjeta®, Kadcyla®, and Cotellic® are registered trademarks of Genentech, Inc. Gilotrif® is a registered trademark of Boehringer Ingelheim International GmbH. Iressa® and Tagrisso® are registered trademarks of the AstraZeneca group of companies. Xalkori® is a registered trademark of Pfizer Inc. Zykadia®, Tafinlar®, and Mekinist® are registered trademarks of Novartis AG Corporation Switzerland. Erbix® is a registered trademark of ImClone LLC, a wholly owned subsidiary of Eli Lilly and Company. Alecensa® is a registered trademark of Chugai Seiyaku Kabushiki Kaisha. Vectibix® is a registered trademark of Immunex Corporation. Rubraca® is a registered trademark of Clovis Oncology, Inc.



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

* 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	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	ERRF1	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	NTSC2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2	PARK2
PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-L1)	PDCD1LG2 (PD-L2)		PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKARIA	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	SOC3
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFB2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1 (MMSET)	WHSC1L1	WT1
XPO1	XRCC2	ZNF217	ZNF703					

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	NOTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT (promoter only)**	
TMPSR2								

*TERC is non-coding RNA gene. **TERT is gene with promoter region.

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Reference

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 December 12, 2017. Please visit www.foundationmedicine.com/flcdx for the most up-to-date gene list.
3. Refer to our full label for listing of intronic regions at www.foundationmedicine.com/flcdx.

