

Technical Specifications

Clinical Background

Cancers have long been categorised and treated based on the anatomic site of origin of the cancer, e.g., lung, breast, colon, skin, etc. Increasingly, oncologists and pathologists are also focusing on the genomic alterations, in the genes that drive a cancer.

As we understand more about these underlying DNA alterations, cancer may be treated with targeted therapies that specifically attack those changes in a patient's tumour. FoundationOne® CDx provides a comprehensive genomic profile to support multidisciplinary discussion and joint decision making with patients.

Technical Information and Test Overview

This table refers to the technical information and test overview based on a inferiority testing approach using the enrichment design presented in the paper by Li (2016).¹

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 cobas® EGFR Mutation Test v2
ALK Rearrangements	92.9% (78/84)	100% (75/75)	Ventana ALK (D5F3) CDx Assay Vysis ALK Break-Apart FISH Probe Kit
KRAS	100% (173/173)	100% (154/154)	therascreen® KRAS RQq 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

* 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 nonmutated 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.

Methods

FoundationOne® CDx is a comprehensive genomic profile that applies next-generation sequencing to identify all 4 types of genomic alterations across all genes known to be unambiguous drivers of solid tumours with high accuracy. The test simultaneously sequences the coding region of 324 cancer-related genes including introns from 36 genes often rearranged or altered in cancer to a typical median depth of coverage of greater than 500X. Each covered read represents a unique DNA fragment to enable the highly sensitive and specific detection of genomic alterations that occur at low frequencies due to tumour heterogeneity, low tumour purity and small tissue samples. FoundationOne® CDx detects all classes of genomic alterations, including base substitutions, insertions and deletions (indels), copy number alterations (CNAs) and rearrangements using a small, routine FFPE sample (including core or fine needle biopsies).

Reporting

If a clinically relevant alteration is found in any one of the genes on the current gene list, the report will identify the gene and alteration and will provide an interpretation that is specific to the patient's tumour as defined by the submitting pathologist.

The genes listed on the front page of the report are found to have one or more clinically relevant alterations. In some cases, pertinent negatives are displayed on the front of the report; these are genes that have no alterations but are particularly relevant for the specific tumour type (e.g., KRAS in colon cancer, EGFR in lung cancer). The complete list of genes that are tested appears in the "Current Gene List" table on page 2, in the appendix of each FoundationOne® CDx report.

Variants of Unknown Significance (VUS)

Often an alteration is detected in one of the genes included on FoundationOne® CDx, but that specific alteration has not yet been adequately characterised in the scientific literature. We include these variants in the report so that they may be acted upon in the future should clinical evidence emerge.

Equivocal

Designation signifies that there is some, but not unambiguous, evidence of amplification or homozygous loss of a gene.

Subclonal

Designation signifies that the FoundationOne® CDx analytical methodology has identified the presence of the alteration in less than 10% of the estimated tumour DNA.

FoundationOne® CDx Includes Genes That Are Commonly Tested for in All Solid Tumours

FoundationOne® CDx is a comprehensive and fully informative genomic profile that can reveal all classes of actionable alterations, including those in cancer-driving genes that are rarely or never tested for in solid tumours. The FoundationOne® CDx report often reveals additional genomic information - including evidence linking targeted medicines to identified genomic alterations - to inform multidisciplinary decision making and discussions with patients.

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	ERFF1	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	MKKN1	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	PKD1	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	TGFB2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1 (MMSET)	WHSC1L1	WT1
XPO1	XRCC2	ZNF217	ZNF703					

SELECT REARRANGEMENTS²

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	EWRSR1	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 non-coding RNA gene. **TERT is gene with promoter region

FoundationOne[®] CDx is a next-generation sequencing based service for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumour mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour tissue specimens.

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 Data on File M-GB-00001549 September 2020

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