FOUNDATIONONE® CDx

Roche

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 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

* 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 F1CDx 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[2]"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.

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Current Gene List[2]

Genes with full coding exonic regons 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*					

SELECT REARRANGEMENTS[2]

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 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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