FOUNDATIONONE® CDx

Broad clinical utility built on extensive validation[1-4]

Clinical summary

Our tissue-based comprehensive genomic profiling service for all solid tumours[1,2,4]

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Based on our analytically and clinically validated, FDA-approved comprehensive platform[1,3]

High concordance with FDA-approved companion diagnostics (CDx)[4]

GENOMIC FINDINGS	POSITIVE PERCENT AGREEMENT (PPA)*	NEGATIVE PERCENT AGREEMENT (NPA)*	COMPARATOR TEST METHOD
EGFR Exon 19 Deletions and L858R Alterations	98.1% (106/108)	99.4% (153/154)	cobas® *EGFR* Mutation Test v2
EGFR T790M Alterations	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 Alterations	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

- FoundationOne®CDx is concordant with FDA-approved FoundationFocus™ CDx for BRCA 1/2[4]

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. FoundationFocus is a trademark of Foundation Medicine, Inc.
*The reference standard used to calculate positive percent agreement (PPA) and negative percent agreement (NPA) is defined as the consensus calls between the two comparator methods or comparator runs. Agreement calculations solely using consensus calls may overestimate the performance of FoundationOne CDx.
†Sensitivity of dinucleotide detection of *BRAF* V600K and V600E was found to be significantly reduced in the cobas® test, in particular for samples in which FoundationOne CDx detected the dinucleotides to be of lower than 40% MAF, leading to low NPA values.
‡A study using the THxIDTM *BRAF* kit (bioMérieux) was conducted with samples with *BRAF* V600 dinucleotide mutation detected by FoundationOne CDx and *BRAF* V600 negative samples to provide a better evaluation of V600 dinucleotide concordance.

FOUNDATIONONE®CDx

High concordance with externally validated NGS method*[4]

	POSITIVE PERCENT AGREEMENT (PPA)	NEGATIVE PERCENT AGREEMENT (NPA)
All short variants	94.6%	99.9%
Substitutions	96.6%	99.9%
Insertions & deletions	83.4%	99.9%

High concordance with FoundationOne®†[4]

	POSITIVE PERCENT AGREEMENT (PPA)	NEGATIVE PERCENT AGREEMENT (NPA)
All variants	98.6%	99.9%
All short variants	99.1%	99.9%
Substitutions	99.4%	99.9%
Insertions & deletions	97.0%	99.9%
All copy number variants	94.3%	99.9%
Amplifications	94.0%	99.9%
Losses	94.8%	99.8%
Rearrangements	100.0%	99.9%

- FoundationOne is our pioneering lab-developed test used in over 180,000 patients[5,6]

*The detection of alterations by FoundationOne CDx was compared to results of an externally validated next-generation sequencing assay (evNGS). Overall there were 157 overlapping genes between the two assays. The comparison between short alterations, including base substitutions and short indels, detected by FoundationOne CDx and the orthogonal method included 188 samples from 46 different tumours. Differences in variants of unknown significance (VUS) alteration calls between the platform were noted, and are expected based on differences in filtering employed by FoundationOne CDx and evNGS. Negative predictive value and positive predictive value were also calculated and were found to be different than percent agreement because the two platforms filter VUS differently. Discordant alterations not related to VUS filtering were primarily caused by deletions with low allelic fraction in homopolymer regions. The FoundationOne CDx variant calling pipeline imposes a filter based on MAF of ≥0.10 for indels in homopolymer regions to reduce the likelihood of calling false positives resulting from artifacts introduced by the technology. As such, the difference observed was due to varying filter thresholds between the two platforms.
†To support the use of retrospective data generated using FoundationOne, a concordance study was conducted with FoundationOne CDx. This study evaluated a test set of 165 specimens. PPA and NPA between FoundationOne CDx and FoundationOne, using the FoundationOne assay as the reference method, was calculated for all alterations, as well as for alterations binned by type: short variants, copy number alterations (CNAs) and rearrangements. A total of 2325 variants, including 2026 short variants, 266 CNAs and 33 rearrangements were included in the study.
NGS, next-generation sequencing.

Broad clinical utility across common cancers

% patients with genomic alterations that the FoundationOne CDx platform is clinically validated to detect	Benefits vs other tests
Melanoma[7–12] **39%-94% patients** *BRAF* V600E 36% - 75% *BRAF* V600K 2% - 19%	Identifies 37% more patients with clinically relevant *BRAF* alterations compared with PCR, IHC and other NGS testing methods[40]
Colorectal cancer[13–20] **61%-75% patients** *KRAS* wildtype 59% - 70% *NRAS* wildtype 2% - 5%	Identifies up to 12% more patients with resistance-associated KRAS alterations compared with traditional PCR-based methods[41]
NSCLC[21–31] **20%-39% patients** *EGFR* exon 19 deletions 8% - 17% *EGFR* exon 21 *L858R* 6% - 11% *EGFR* exon 20 *T790M* 1% at diagnosis *EGFR* exon 20 *T790M* 33% - 62% acquired resistance *ALK* rearrangements 5% - 8% *BRAF* V600E 1% - 2%	Identifies up to 35% and 17% more patients with *ALK* fusions and *EGFR* alterations, respectively, compared with traditional FISH and PCR-based methods[42,43]
Ovarian[32–35] **13%-28% patients** *BRCA1* 8% - 19% *BRCA2* 5% - 9%	Identifies patients with *BRCA1/2* alterations who may benefit from PARP inhibitors*[4]
Breast[36–39] **13%-23% patients** *ERBB2 (HER2)* amplification	Identifies patients with *ERBB2* alterations who may benefit from HER2 therapy[4] Detects drug resistance mechanisms, including various *ESR1* and *RB1* alterations[4] that may inform patient management regarding hormone therapy and CDK4/6 inhibitors[44,45]

* FoundationOne CDx does not distinguish between germline and somatic alterations.
FISH, fluorescence in situ hybridisation. IHC, immunohistochemistry. NGS, next-generation sequencing. NSCLC, non-small cell lung cancer. PCR, polymerase chain reaction.

FOUNDATIONONE®CDx

Comprehensive analysis of the tumour genome in a single test[4]

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

Assesses 324 cancer-related genes[4]

Genes with full coding exonic regions included in FoundationOne CDx:
For detection of substitutions, insertion-deletions and copy-number alterations

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*	*FGFR1*	*FGFR2*	*FGFR3*
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:
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*	*KM2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT (promoter only)*†	
TMPRSS2								

In the same test reports:[4]
- Tumour mutational burden
- Microsatellite instability

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

FOUNDATIONONE® CDx

Broad clinical utility built on extensive validation[1–4]

Extensive validation[1-3]

» Based on our analytically and clinically validated, FDA-approved comprehensive platform[1,3]
» High concordance with FDA-approved companion diagnostics and with NGS methods[4]

Broad clinical utility

» Clinically relevant results across common cancers: colorectal cancer, melanoma, NSCLC, ovarian and breast[7–39]

324 GENES TMB+MSI

Goes beyond common genomic alterations[4]

» Assesses 324 cancer-relevant genes[4]
» Reports TMB and MSI[4]

Intended use statement

FoundationOne®CDx 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 tumour mutational burden (TMB) and microsatellite instability (MSI) 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 therapies in accordance with approved therapeutic product labeling. Additionally, FoundationOne CDx is intended to provide tumour mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

For more information, please contact your Roche representative
Email: europe.foundationmedicine@roche.com
Phone: +49 7624 14 2098

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