FOUNDATIONONE®

Technical Information and Test Overview

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 and that may be less toxic and more effective than traditional cytotoxic treatments.

Technical Information	Base Substitutions[1]	Indels[1]	Copy Number Alterations[1]	Rearrangements
Sensitivity	>99% MAF ≥5%	>97% MAF ≥10%	>95% CN ≥8 or 0 ≥30% tumour nuclei	≥90%[2] >99% for ALK fusion[3] ≥20% tumour nuclei
Specificity (PPV)	>99%	>99%	>99%	>99%
Typical Median depth of coverage (each covered read is of a unique DNA fragment to enable detection of alterations at low frequency)	500[1]			
Sample requirements	≥40 µm tissue, of which a minimum of 20% is of malignant origin, on 8 to 10 unstained slides or in an FFPE block. Needle biopsy is also acceptable.			
Turn-around time	14 day average*			

* As measured from the date the Foundation Medicine laboratory receives a sample that meets requirements.

Methods

FoundationOne® is a Comprehensive Genomic Profile that applies next-generation sequencing in a unique manner 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 315 cancer-related genes plus introns from 28 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® 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.

The genes listed on the front page of the report are found to have one or more clinically relevant alterations. All other genes are not found to have any 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® report and at www.foundationone.com/genelist.

Variants of Unknown Significance (VUS)

Often an alteration is detected in one of the genes included on FoundationOne®, 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 when there is some, but not unambiguous, evidence of amplification or homozygous loss of a gene.

Subclonal

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

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

FoundationOne® 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® report often reveals alterations that may lead to additional treatment options for physicians and their patients to consider.

* The analytic validation of FoundationOne®, based on a prior version of the assay (236 genes, 19 select rearrangements) was published in Nature Biotechnology[1] and established the performance specifications required to deliver the high level of accuracy routinely obtained for all classes of genomic alteration by FoundationOne®. This updated version of FoundationOne® met these performance specifications by demonstrating high concordance with genomic profiles of ninety four clinical specimens previously profiled on the validated version of FoundationOne®.

1 G. Frampton, et al., "Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing". Nat Biotechnol. 2013 Oct 20.
2 Based on analysis of coverage and re-arrangement structure in the COSMIC database for solid tumour fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.
3 Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay.
4 Current as of August 18th, 2014. Please visit www.foundationmedicine.com/genelist for the most current gene list.

Current Gene List[4]

FoundationOne® identifies all classes of alterations in each of the genes listed below.

As a pan-cancer test, FoundationOne® is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature.

CURRENT GENE LIST

ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	

SELECT REARRANGEMENTS

ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

Roche Singapore Pte Ltd | 3 Biopolis Drive | #03-11 Synapse | Singapore 138623
Phone: +65 6880 5399 | email: APAC.foundation@roche.com

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