FOUNDATIONONE®

FoundationOne® Technical Information

CLINICAL BACKGROUND

Cancers are categorised and treated based mainly on the anatomic site of origin of the cancer, e.g. lung, breast, colon, skin, etc. Increasingly, there is a focus on understanding the genomic alterations that drive cancer.[1,2] The Catalogue of Somatic Mutations in Cancer (COSMIC) database now holds data for >28,000 whole genomes from >1 million tumour samples and describes >4 million coding mutations.[3]

As we understand more about these underlying DNA alterations, cancer may be treated with targeted therapies that specifically address the specific alterations in a patient's tumour.[1]

METHODS

FoundationOne® is a Comprehensive Genomic Profile that applies a next-generation sequencing with hybrid capture-based target enrichment approach to identify somatic genomic alterations in genes known to be unambiguous drivers of solid tumours. Each profile 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 >500X. Each covered read represents an individual 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 and rearrangements using a small, routine clinical sample (including core or fine-needle biopsies).

All FoundationOne® samples are simultaneously profiled for tumour mutation burden (TMB) and microsatellite instability (MSI) status.[4] TMB is determined by measuring the number of somatic mutations occurring in sequenced genes on the FoundationOne® profile and extrapolating to the genome as a whole.[4] MSI is determined by assessing indel characteristics at 114 homopolymer repeat loci, in or near the targeted gene regions of the FoundationOne® profile.[4]

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FOUNDATIONONE® TECHNICAL INFORMATION	BASE SUBSTITUTIONS[5]	INSERTIONS AND DELETIONS[5]	COPY NUMBER ALTERATIONS – AMPLIFICATIONS[5]	COPY NUMBER ALTERATIONS – DELETIONS[5]	REARRANGEMENTS[6,7]
Sensitivity	>99% (MAF ≥5%)	>97% (MAF ≥10%; 1–40bp)	>99% (CNA ≥8; ≥30% tumour nuclei)	>97% (homozygous deletions; ≥30% tumour nuclei)	>90%* >99% for ALK fusion (95% CI 89%–100%)† (≥20% tumour nuclei)
Specificity (PPV)	>99%	>99%	>99%	>99%	>99%*
Concordance MSI	97%‡[8]				
Concordance TMB	>90%§[4,9]				
Typical median depth of coverage	500[5]				
Sample requirements	≥40 µm tissue, of which a minimum of 20% is of malignant origin,‖ on 10 unstained slides or in an FFPE block. Needle biopsy is also acceptable.[10]				
Turn-around time	14-day average¶				

REPORTING

The FoundationOne® report can reveal alterations that may lead to additional treatment options for physicians and their patients to consider. Results are provided in a report available via a link sent in a secure email and via Foundation Medicine Online.#

When a clinically relevant alteration is found, the first page of the report identifies the specific gene and alteration(s) and for each alteration, provides a list of targeted therapies or clinical trials relevant to the patient's cancer.

The report offers a curation of peer-reviewed studies and other publicly available evidence compiled by Foundation Medicine's computational bioinformatics scientists, molecular biologists, cancer genomic scientists and pathologists. This may include associations between the presence of a specific genomic alteration (or wild-type status) and one or more therapies which may have clinical benefit (or may lack of clinical benefit). Alterations designated to be variants of unknown significance (VUS) are listed at the back of the report in the VUS section.

In some cases, pertinent negatives are displayed on the front of the report; these are genes that have no alterations but are particularly relevant to the specific tumour type (e.g. *KRAS* in colon cancer, *EGFR* in lung cancer).

MSI status is reported on the front page as MSI-High, MSI-Intermediate or MSI-Stable (MSS). If the report is affected by certain quality metrics (e.g. poor sample quality due to low tumour purity or contamination), the MSI status may be listed as 'Cannot Be Determined'.

TMB status is reported on the front page for all cancer types. TMB status may be reported as TMB-High (≥20 Muts/Mb), TMB-Intermediate (6–19 Muts/Mb) or TMB-Low (≤5 Muts/Mb). If the report is affected by certain quality metrics (e.g. poor sample quality due to low tumour purity or contamination), the TMB status may be listed as 'Cannot Be Determined'.

VARIANTS OF UNKNOWN SIGNIFICANCE (VUS)

Sometimes an alteration may be detected that has not yet been adequately characterised in the scientific literature at the time the report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include these variants in the FoundationOne® report in the event they may become clinically meaningful in the future.

EQUIVOCAL

A copy number alteration denoted as 'amplification – equivocal' implies that the sequencing data provide some, but not unambiguous, signal that the copy number exceeds the threshold for copy number events assigned to the relevant gene. The threshold used in FoundationOne® for identifying copy number amplification is 5 for *ERBB2* and 6 for all other genes.

An alteration denoted as 'loss – equivocal' implies that the sequencing data provide some, but not unambiguous, signal of homozygous deletion of the gene in question.

SUBCLONAL

An alteration designated as subclonal signifies that the FoundationOne® analytical methodology has identified the presence of the alteration in <10% of the assayed tumour DNA.

* Based on cell line titration experiments in 5 solid-tumour, fusion-bearing cell lines representing 32 gene-fusion cases in *ALK*, *RET*, *ROS1* and *TMPRSS2*.
† Based on concordance analysis of detection of *ALK* fusions based on standard clinical FISH assay. 18/20 *ALK* fusion FISH-positive specimen detected plus two specimens showing sub-threshold events.
‡ Based on concordance analysis of MSI status based on standard clinical testing with PCR or IHC (65/67).
§ Based on concordance with WES analysis (26/29).
‖ For liver specimens, a minimum of 40% of tumour nuclei is required. Since polyploidy is a common characteristic of hepatocytes, twice as many tumour cells would be needed to obtain enough tumour DNA for analysis.[10]
¶ As measured from the date the Foundation Medicine laboratory receives a sample that meets requirements.
# Please contact your local customer services team to set up an account on Foundation Medicine Online.

CNA: copy number alterations; **FFPE**: formalin fixed, paraffin embedded; **FISH**: fluorescence *in situ* hybridisation; **IHC**: immunohistochemistry; **MAF**: mutant allele frequency; **PCR**: polymerase chain reaction; **PPV**: positive predictive value.

FOUNDATION**ONE**® **CURRENT GENE LIST****

FoundationOne® is a pan-cancer comprehensive genomic profile, which interrogates the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer.

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	

** Current as of August 18th, 2014.

The analytic validation of FoundationOne®, based on a prior version of the FoundationOne® assay (236 genes, 19 select rearrangements), was published in *Nature Biotechnology*[5] and established the performance specifications required to deliver the high level of accuracy routinely obtained by FoundationOne® for major classes of genomic alteration. This updated version of FoundationOne® met these performance specifications by demonstrating high concordance with genomic profiles of 94 clinical specimens previously profiled on the validated version of FoundationOne®.

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