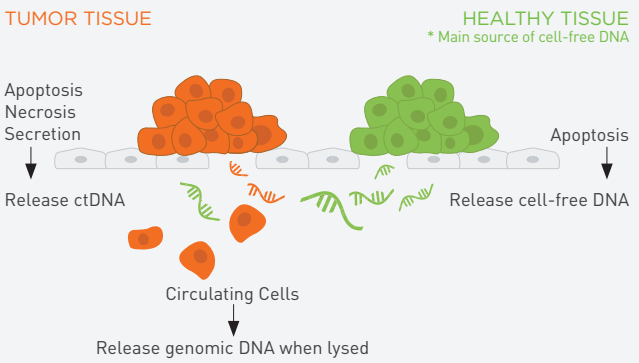
FOUNDATIONACT™

Technical Information

Clinical Background

Cell-free DNA is DNA that circulates freely in the bloodstream. In a cancer patient, tumor cells that undergo apoptosis or necrosis also shed cell-free DNA. The tumor derived cell-free DNA is called circulating tumor DNA or ctDNA.

By analyzing cell-free DNA isolated from a patient's blood, we can now identify clinically relevant genomic alterations in ctDNA and match these alterations to targeted therapies and clinical trials.



Blood contains circulating cell-free DNA released from healthy tissue and tumor tissue (ctDNA)

About FoundationACT™

FoundationACT (Assay for Circulating Tumor DNA) is a hybrid capture based next-generation sequencing assay designed to interrogate 62 genes. This assay identifies all classes of alterations including base substitutions, insertions and deletions, copy number variations, and rearrangements/fusions.

FoundationACT Approach

Circulating cell-free DNA is highly fragmented, presents at very low concentrations, and contains only a small fraction of tumor-derived ctDNA. These factors make the isolation and identification of ctDNA extremely challenging. Assay sensitivity and specificity are directly dependent on cell-free DNA extraction, high efficiency sample preparation, and capture efficiency combined with custom low frequency variant calling algorithms.

Foundation Medicine has optimized the process to achieve greater sensitivity and specificity:

- Enhanced extraction methodology to generate a high quantity of quality ctDNA.
- Proprietary FragTag™ technology to accurately identify unique ctDNA fragments from plasma.
- Hybrid capture-based NGS combined with proprietary computational algorithms enable us to accurately call variants by discriminating sequencing artifacts from bona-fide mutations.

		MAF/Tumor Fraction	Sensitivity	Positive Predictive Value (PPV)
Performance Specifications	Base Substitutions	≥0.5%	>98.9%	>99.9%
	Insertions/Deletions (1-40 bp)	≥1%	>99%	98.8%
	Rearrangements/Fusions	≥1%	>99%	98.0%
	Copy Number Variations (CNV)*	≥20%	95.3%	97.6%
		<20%	Will vary depending on CNV level and tumor fraction.	
Turn Around Time	Less than 14 days			
Sample Requirements	Two 10 ml tubes of peripheral whole blood			

* Copy-number ≥ 8 in genes with at least 4 targets.

Reporting

Clinically relevant alterations detected by FoundationACT are matched to targeted therapies and clinical trials and reported on the front page of the report.

Mutant Allele Fraction (MAF)

The mutant allele fraction is the frequency of the mutant allele identified in the sample and is reported for base substitutions, insertions and deletions and rearrangements/fusions.

Connectivity with Prior Tissue-Based Testing

Compare the results of prior FoundationOne tissue-based testing to current FoundationACT results in a single report.

Variants of Unknown Significance (VUS)

Often an alteration is detected in one of the genes included in FoundationACT, but that specific alteration has not yet been adequately characterized in the scientific literature. These variants are included so that they may be acted upon in the future should clinical evidence emerge.

FOUNDATION MEDICINE®

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Current Gene List

FoundationACT identifies all clinically relevant genomic alterations in each of the genes listed below.

ABL1	CDK4	FGFR1	JAK2	MYCN	RAF1
AKT1	CDK6	FGFR2	JAK3	MYD88	RET
ALK	CDKN2A	FGFR3	KIT	NF1	SMO
ARAF	CRKL	FLT3	KRAS	NPM1	TERT
BRAF	CTNNB1	FOXL2	MAP2K1	NRAS	TP53
BRCA1	DDR2	GNA11	MAP2K2	PDCD1LG2	VEGFA
BRCA2	EGFR	GNAQ	MDM2	PDGFRA	
BTK	ERBB2	GNAS	MET	PDGFRB	
CCND1	ERRFI1	HRAS	MPL	PIK3CA	
CD274	ESR1	IDH1	MTOR	PTEN	
CDH1	EZH2	IDH2	MYC	PTPN11	

Rearrangements/Fusions (6 genes)

ALK	EGFR	FGFR3	PDGFRA	RET	ROS1

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