

Analytical Validation¹ of the FoundationACT® Liquid Biopsy Test

Why is Analytical Validation Important?

An assay's validation offers insight into the quality of its laboratory performance and its ability to confidently detect genomic variants at various frequency levels.

Due to the complexity of liquid biopsies, a robust analytical validation should demonstrate that the test has a high degree of sensitivity and specificity in identifying variants at very low levels, in order to be trusted to help guide clinical decisions.

Key Findings from the Analytical Validation of FoundationACT

In the validation study, 2,666 reference alterations were utilized to evaluate the FoundationACT liquid biopsy assay against multiple orthogonal methods, including matched tissue with FoundationOne®, achieving high sensitivity in detecting genomic alterations even at low mutant allele frequencies (MAF>0.25%) often observed in clinical samples.

Analytical Performance Table

FoundationACT analytical performance demonstrates sensitive detection of genomic alterations down to very low mutant allele frequency (MAF) levels with a high degree of certainty (PPV).

	MUTANT ALLELE FREQUENCY (MAF)*	SENSITIVITY [†]	POSITIVE PREDICTIVE VALUE (PPV) [‡]
BASE SUBSTITUTIONS	≥ 0.5%	99.3% (CI 99.1% - 99.4%)	100% (CI >99.9% - 100%)
	0.25% - 0.5%	95.7% (CI 94.9% - 96.4%)	100% (CI 99.8% - 100%)
	0.125% - 0.25%	70.0% (CI 68.3% - 71.6%)	99.9% (CI 99.8% - 100%)
INSERTIONS/DELETIONS (INDELS)	≥ 0.5%	98.5% (CI 97.3% - 99.2%)	100% (CI 99.4% - 100%)
	0.25% - 0.5%	86.6% (CI 81.4% - 90.5%)	100% (CI 97.8% - 100%)
	0.125% - 0.25%	68.5% (CI 62.1% - 74.3%)	100% (CI 97.1% - 100%)
REARRANGEMENTS	≥0.5%	100% (CI 77.1% - 100%)	100% (CI 77.1% - 100%)
	0.25% - 0.5%	100% (CI 56.1% - 100%)	100% (CI 56.1% - 100%)
	0.125% - 0.25%	80% (CI 29.9% - 99.0%)	100% (CI 39.6% - 100%)
COPY NUMBER AMPLIFICATIONS[‡] (CNA)	≥ 20% ctDNA fraction	95.3% (CI 82.9%-99.2%)	97.6% (CI 85.9%-99.9%)
	< 20% ctDNA fraction	Varies depending on amplitude of CNA and ctDNA fraction	

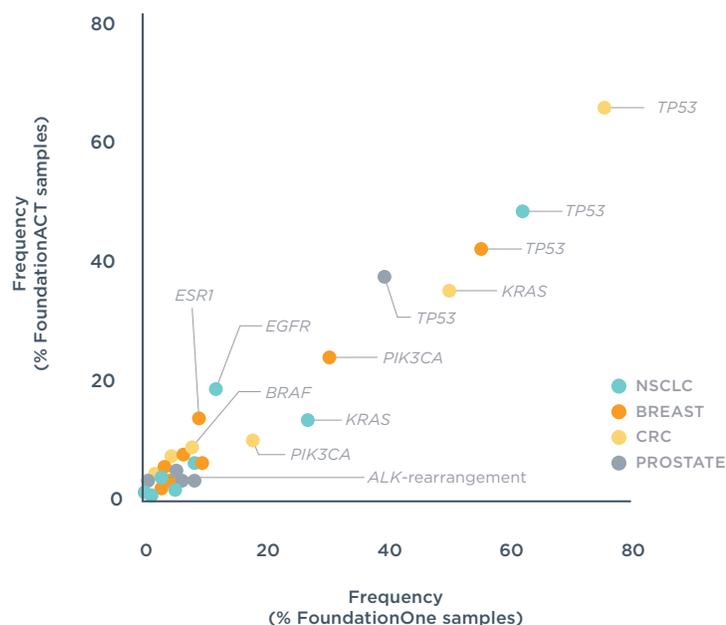
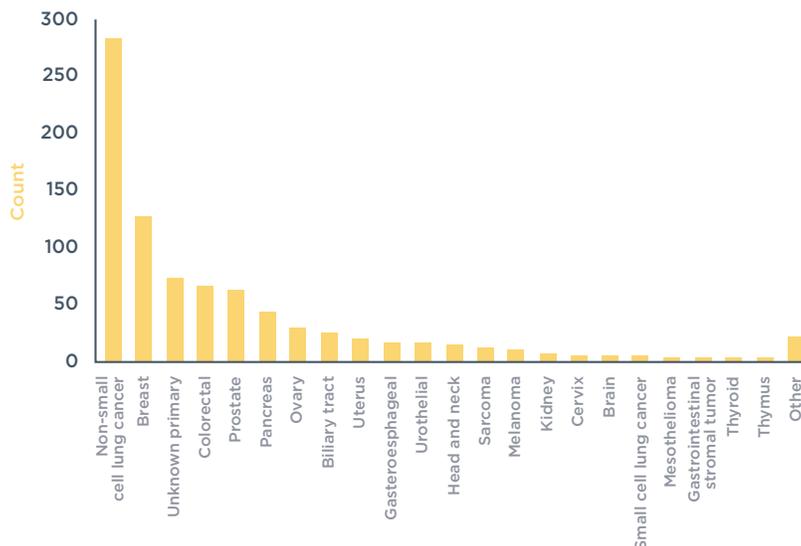
* Copy number amplifications were calculated using tumor fraction

† 95% confidence interval (CI)

‡ for genes with ≥4 targets

Clinical Validation Across a Variety of Cancers

In addition to providing a robust assessment of analytical concordance, the paper describes FoundationACT's clinical performance across a wide range of cancers. In the subset of clinical samples analyzed, 97.3% (860/884) were successfully reported with a median unique coverage of 8,296x.



Strong Correlation Between Blood and Tissue

The frequency of common alterations by tumor type was also investigated to uncover the correlation between identifying certain disease-specific mutations in FoundationACT (blood) versus FoundationOne (tissue). Overall, the observed frequencies of alterations from FoundationACT was highly consistent with frequencies observed in FoundationOne (tissue) samples (Pearson correlation $r=0.98$, $P<0.0001$).

Conclusion

This study is one of the largest and most extensive analytical validation studies completed in liquid biopsy. FoundationACT also demonstrated strong analytical performance and high concordance with FoundationOne; these results support that FoundationACT can detect alterations that may provide valuable clinical insight when tissue profiling is infeasible.

FoundationACT is a blood-based circulating tumor DNA (ctDNA) assay for solid tumors that is performed in Foundation Medicine's Clinical Laboratory Improvement Amendments (CLIA) certified, College of American Pathologists (CAP) accredited laboratory. It is also approved by the New York State Clinical Laboratory Evaluation Program (CLEP).

¹ This fact sheet provides a summary of the FoundationACT validation study. The full results including charts, figures, and tables depicted here can be found in: Clark TA, et al. Analytical validation of FoundationACT: a hybrid capture-based next-generation sequencing clinical assay for genomic profiling of cell-free circulating tumor DNA. *Journal of Molecular Diagnostics*. 2018; published online ahead of print.

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