Foundation Findings: Publication Summary

Clinical and Analytical Validation of FoundationOne®Liquid CDx

"Study results demonstrate that FoundationOne Liquid CDx accurately and reproducibly detects major types of genomic alterations, in addition to complex biomarkers such as blood tumor mutational burden (bTMB), microsatellite instability high (MSI-H), and tumor fraction." — Woodhouse et al., PLOS One, 2020.

Comprehensive Test Requires Comprehensive Validation

Over 7,500 validation samples

were run covering over **30,000 unique variants** in over 300 genes across **more than 30 cancer types**.

Summary of Analytical Sensitivity and Specificity

ALTERATION TYPE	BAIT SET REGION	MEDIAN LIMIT OF DETECTION (LOD)
Short Variants	Enhanced Sensitivity	0.40% VAF
	Standard Sensitivity	0.82% VAF
Rearrangements	Enhanced Sensitivity	0.37% VAF
	Standard Sensitivity	0.90% VAF
Copy Number Amplifications	NA	21.7% TF
Copy Number Loss	NA	30.4% TF
MSI	NA	0.8% unstable loci
bTMB (component indels)	NA	1.0% VAF
bTMB (component subs)	NA	1.0% VAF

VAF = variant allele frequency; TF = tumor fraction
The accuracy of %VAF / %TF have not been analytically validated

In our Limit of Blank study, which evaluated variant calling in healthy donors, 1,735 unique variants were included in the analysis for a total of 137,065 data points. A total of 18 false positive calls were observed across 4 unique short variants. The LoB was determined to be ideal value of zero for short variants, rearrangements and CNAs. The false positive rate was shown to be 0% for rearrangements and CNAs and 0.013% (~1 in 8,000) for short variants (substitutions and indels).

Concordance of FoundationOne Liquid CDx to an Externally Validated cfDNA NGS Assay

Across >900 positive variants and >150,000 negative variants, an overall PPA of 96.3% and NPA of ≥99.9% was observed when comparing to an orthogonal cfDNA-based NGS method.

ALTERATION	PPA	NPA
EGFR L858R	100%	100%
EGFR Exon 19 non-frameshift deletions	100%	100%
PIK3CA base substitutions	100%	100%
ALK rearrangements	100%	99.9%
NTRK1 rearrangements	100%	100%
ROS1 rearrangements	100%	100%
BRCA1 short variants	100%	100%
BRCA2 short variants	100%	100%

Demonstrated Clinical Validation

In a retrospective clinical validation study of 572 breast cancer patients enrolled in the SOLAR-1 trial, patients who tested positive for *PIK3CA* alterations using FoundationOne Liquid CDx showed an estimated 54% risk reduction in disease progression or death in the alpelisib + fulvestrant arm compared to the placebo + fulvestrant arm (hazard ratio: 0.46).

Through clinical validation study of 177 samples from NSCLC patients, FoundationOne Liquid CDx demonstrated non-inferiority to plasma testing with cobas *EGFR* Mutation Test v2 for the identification of non-small cell lung cancer patients eligible for treatment with erlotinib, gefitinib, and osimertinib.

More About FoundationOne Liquid CDx

FoundationOne Liquid CDx is the broadest FDA-approved liquid-based comprehensive genomic profiling test, analyzing over 300 genes to help identify patients who may benefit from treatment with specific targeted therapies in multiple cancer indications. FoundationOneLiquid CDx also analyzes bTMB, MSI-H status, and tumor fraction as a laboratory professional service not reviewed or approved by the FDA.

To learn more about FoundationOne Liquid CDx go to www.foundationmedicine.com/F1LCDx

FoundationOne®Liquid CDx is for prescription use only and is a qualitative next-generation sequencing based *in vitro* diagnostic test for advanced cancer patients with solid tumors. The test analyzes 324 genes utilizing circulating cell-free DNA and is FDA-approved to report short variants in 311 genes and as a companion diagnostic to identify patients who may benefit from treatment with specific therapies (listed in Table 1 of the Intended Use) in accordance with the approved therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the test does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Patients who are negative for companion diagnostic mutations should be reflexed to tumor tissue testing and mutation status confirmed using an FDA-approved tumor tissue test, if feasible. For the complete label, including companion diagnostic indications and complete risk information, please visit *www.F1LCDxLabel.com*.

Reference

Woodhouse, et al. Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. *PLOS One*. September 25, 2020. doi: https://doi.org/10.1371/journal.pone.0237802.

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