FoundationOne®Liquid CDx

Patient Guide: Understanding the Liquid Biopsy Report with Your Doctor

This FoundationOne Liquid CDx report guide will help you understand each section of your liquid biopsy report. Use this guide after your results are ready. Once you review the results with your doctor, together you can decide the next best step in your treatment plan.

Definitions of key terms are on the last page of this guide.

FoundationOne Liquid CDx is an FDA-approved test for all solid tumors that analyzes over 300 genes from a simple blood draw, called a liquid biopsy.

report page one

1 Genomic Findings Detected

If mutations are found in your blood sample, these mutations will be listed as "genomic findings detected" in the companion diagnostic section of your report. This section includes the name of the gene where the mutation was found (e.g., "*EGFR*") along with the description of the mutation within that gene (e.g., "*exon 19 deletion*").

2 FDA-Approved Therapeutic Options

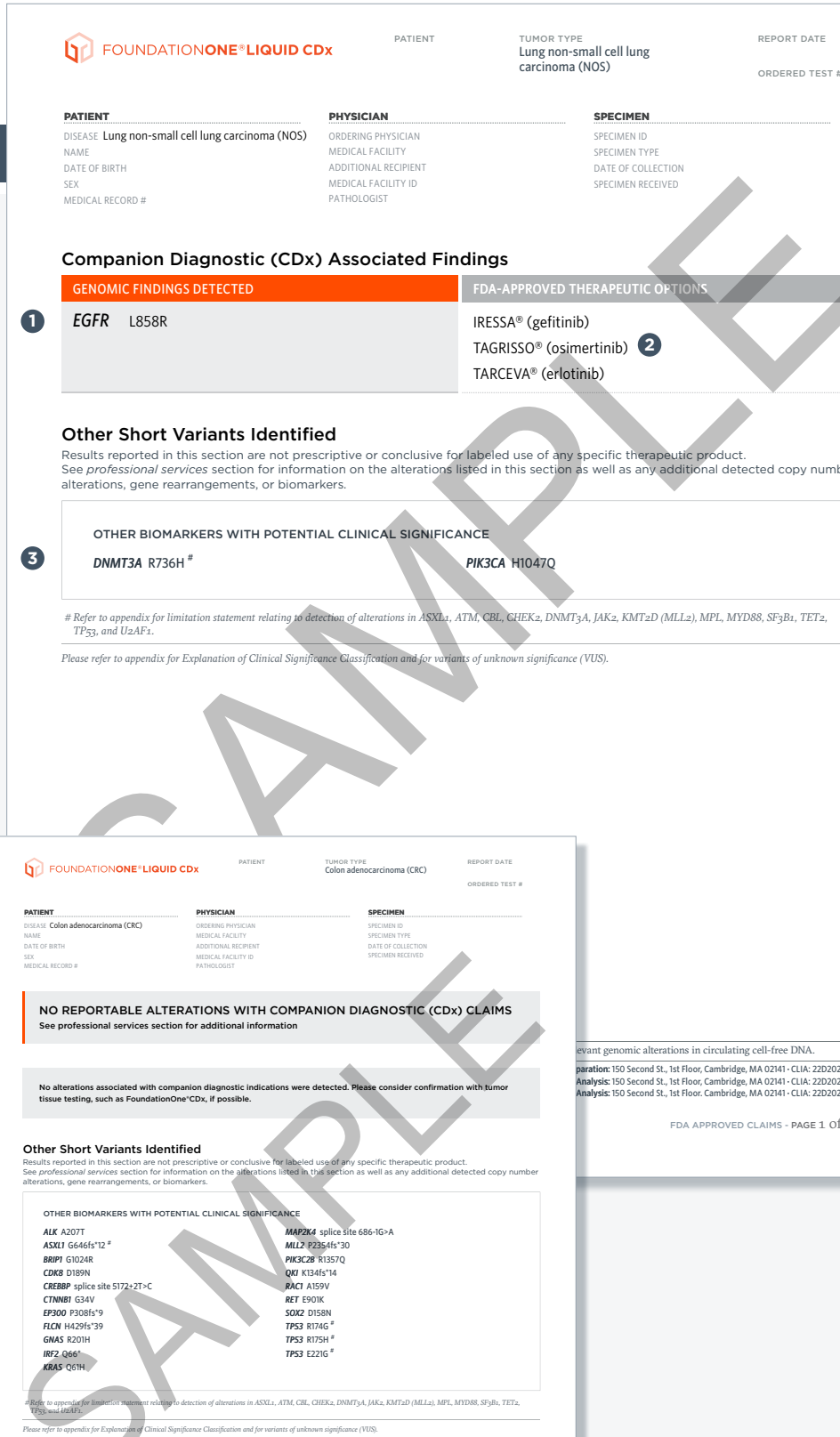
The test is an FDA-approved "companion diagnostic" (or "CDx") for certain treatments. This means that the FDA has extensively reviewed and approved the test to be used to identify patients who may benefit from these treatments. This section lists treatment options linked with specific gene mutations found in your blood sample. Your doctor will determine if any of these treatments may be right for you.

3 Other Alterations & Biomarkers Identified

A list of additional genomic findings in the report are listed in this section. These findings, along with associated treatments, are described in the following pages of the report.

4 No Reportable Alterations with CDx Claims

It is possible that there are no treatment options listed in this CDx section—this is not uncommon and there may be other options on the following pages of your report. Talk to your doctor about the treatment options in your full report.



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Companion Diagnostic (CDx) Associated Findings

1 GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
EGFR L858R	IRESSA® (gefitinib) TAGRISSO® (osimertinib) 2 TARCEVA® (erlotinib)

Other Short Variants Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy numb
alterations, gene rearrangements, or biomarkers.

3 OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

DNMT3A R736H #
PIK3CA H1047Q

 # Refer to appendix for limitation statement relating to detection of alterations in ASXL1, ATM, CBL, CHEK2, DNMT3A, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Colon adenocarcinoma (CRC)

REPORT DATE

ORDERED TEST #

PATIENT
DISEASE Colon adenocarcinoma (CRC)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

4 **NO REPORTABLE ALTERATIONS WITH COMPANION DIAGNOSTIC (CDx) CLAIMS**
See professional services section for additional information

No alterations associated with companion diagnostic indications were detected. Please consider confirmation with tumor tissue testing, such as FoundationOne®CDx, if possible.

Other Short Variants Identified

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product.
See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

ALK A207T
ASXL1 G646fs*12 #
BRIP1 G1024R
CDK8 D189N
CREBBP splice site 5172+2T>C
CTNNB1 G34V
EP300 P308fs*9
FLCN H429fs*39
GNAS R201H
IRF2 Q66*
KRAS Q61H
MAP2K4 splice site 686-1G>A
MLL2 P2354fs*30
PIK3C2B R1357Q
QKI K134fs*14
RAC1 A159V
RET E901K
SOX2 D158N
TP53 R174G #
TP53 R175H #
TP53 E221G #

 # Refer to appendix for limitation statement relating to detection of alterations in ASXL1, ATM, CBL, CHEK2, DNMT3A, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

evant genomic alterations in circulating cell-free DNA.

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FDA APPROVED CLAIMS - PAGE 1 of

Page two of your report contains additional biomarker and genomic findings and associated treatments that may be options for your doctor to consider for your treatment plan.

report page two

5

Biomarker Findings

This section contains information about two biomarkers that may be linked to immunotherapy treatment options — microsatellite instability (MSI) and blood tumor mutational burden (bTMB). It also contains a measure of tumor fraction to show the concentration of tumor DNA that we found circulating in your blood sample.

6

Genomic Findings

This section shows the gene mutations found in your circulating-tumor DNA (ctDNA) that may be linked with treatment options.

7

Therapies with Clinical Benefit

These are potential treatment options that may be relevant for you based on your genomic findings.

The therapies listed in the middle column are FDA-approved for your cancer type. The therapies in the right column are FDA-approved for another cancer type. Your doctor will determine if any of these treatments may be right for you.

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)
COUNTRY CODE

REPORT DATE

ORDERED TEST #

ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

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Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT
DISEASE Lung non-small cell lung carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

Biomarker Findings
Blood Tumor Mutational Burden - 8 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - 15%
6

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.
EGFR amplification, L858R
PIK3CA H1047Q
DNMT3A R736H

10 Therapies with Clinical Benefit
0 Therapies with Lack of Response
19 Clinical Trials

BIOMARKER FINDINGS
Blood Tumor Mutational Burden - 8 Muts/Mb
Microsatellite status - Cannot Be Determined
Tumor Fraction - 15%

GENOMIC FINDINGS		VAF %
EGFR -	amplification	-
	L858R	47.5%

10 Trials see p. 14

THERAPY AND CLINICAL TRIAL IMPLICATIONS
No therapies or clinical trials. See Biomarker Findings section
Unable to determine Microsatellite status due to insufficient evidence of genomic instability.
Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instabili

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFI (IN OTHER TUMOR TYPE)	
Afatinib	1	Cetuximab	2A
Dacomitinib	1	Panitumumab	
Erlotinib	1		
Gefitinib	1		
Osimertinib	1		

7

NCCN category

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PROFESSIONAL SERVICES - PAGE 1 of

Your report contains additional pages with supporting information that your doctor can use to better understand your findings and their relevance to your cancer.

the rest of the report

8

Clinical Trial Options

When applicable, your results are matched with potential treatments that are currently being tested in clinical trials. Participating in a clinical trial could help you access some of the newest treatments in development. Talk to your doctor about which clinical trials may be available and if you qualify for them.

Even if the results do not identify a specific therapy or clinical trial that may be right for you, they can still provide valuable information to you and your doctor. They may show what treatments may not be appropriate for you based on your genomic findings, they may confirm your current treatment, or point to new treatments that may become available in the future.

FOUNDATIONONE® LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

8 GENOMIC FINDINGS

GENE
EGFR

ALTERATION
amplification, L858R

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2573T>G

POTENTIAL TREATMENT STRATEGIES

EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[36], gefitinib[37], afatinib[38], dacomitinib[39], and osimertinib[40]. Third-generation EGFR inhibitors, such as osimertinib, selectively target mutated EGFR, including EGFR T790M[40-41]. Osimertinib achieved an ORR of 61% in T790M-positive cases and 21% in T790M-negative cases[40]. Resistance to EGFR inhibition may arise by reactivation of the MAPK pathway, and preclinical evidence suggests that co-targeting EGFR and MAPK signaling may retard the development of acquired resistance to third-generation EGFR inhibitors[42-44]. EGFR amplification or expression may be associated with benefit from anti-EGFR antibodies, such as cetuximab[45-48], panitumumab[46], or necitumumab[49], or EGFR TKIs that target wild-type EGFR[50-54]. Necitumumab is an anti-EGFR antibody that is approved to treat metastatic squamous NSCLC in combination with gemcitabine and cisplatin[55-56] that has also shown benefit in patients with CRC and melanoma[57-58]. Irreversible EGFR inhibitors, as well as HSP90 inhibitors, may be appropriate for patients with de novo or acquired resistance to EGFR-targeted therapy[59-62]. Preclinical studies have reported that EGFR-mutant cells[59-61], including cells with exon 20 insertions[63], are sensitive to HSP90 inhibitors. For patients with EGFR exon 19 deletion/ L858R-positive and T790M- negative NSCLC who had previously progressed on first or second generation EGFR TKIs, a Phase 1 study evaluating the HER3-targeted antibody U3-1402 reported tumor reduction in 12 patients with 2 confirmed PRs (2/13)[64]. Consistent with preclinical data demonstrating that the EGFR inhibitor AZD3759 is capable of penetrating the blood-brain barrier and reducing the volume of brain and leptomeningeal metastases, preliminary results from a Phase 1 trial evaluating single-agent AZD3759 reported a reduction in the volume of brain metastases in 40.0% (8/20) of patients with previously treated NSCLC harboring either EGFR L858R or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[65-66]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54.3% (69/127) for all evaluable patients and 44.4% (8/18, intracranial) for patients with brain metastases[67]. The reovirus Reolysin targets cells with activated RAS signaling[68-70] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[71-79]. The role of EGFR or KRAS mutations as biomarkers for response to Reolysin in NSCLC is unclear[80]. For patients with NSCLC treated with EGFR tyrosine kinase inhibitors, PIK3CA mutation is associated with shorter OS in a meta-analysis (pooled HR of 1.83)[81]. Clinical studies of lung cancer have shown that acquired PIK3CA mutation may confer resistance to EGFR inhibitors like osimertinib[82-83] . The Phase 3 IMpower study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy in patients with untreated EGFR-mutated or ALK-rearranged metastatic NSCLC[84]; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

Amplification of EGFR has been variously reported in 4-42% of non-small cell lung carcinoma (NSCLC) samples[85-89]. EGFR mutation has been reported in 12-36% of lung adenocarcinomas[85,90-91] and in 4% of lung squamous cell carcinomas[86]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[87-89,92-94]. In addition, expression of EGFR protein has been shown to be higher in lung squamous cell carcinoma samples as compared to lung adenocarcinoma[95-96]. In lung adenocarcinoma, EGFR gene amplification was a predictor of poor disease-free survival in all patients and of poor overall survival in patients with EGFR mutations[97-98]. Nuclear expression of EGFR in NSCLC has been reported to associate with higher disease stage, shorter progression-free survival, and shorter overall survival[99]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[100] or resected Stage 1 NSCLC[101].

FINDING SUMMARY

EGFR encodes the epidermal growth factor receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[102]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[88,103-104]. EGFR L858 is located in the kinase domain and is encoded by exon 21; mutations at this position including L858R[105-107] and L858Q[108] have been characterized as activating. Patients with the L858R mutation have been shown to be sensitive to EGFR tyrosine kinase inhibitors, such as erlotinib, gefitinib[105-107], and afatinib[109]. Other mutations at this position are predicted to be activating.

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Key Terms

Alterations
Changes in the DNA that can influence cancer growth (also referred to as "mutations").

Biomarker
A measurable characteristic within a cancer cell. The status of a biomarker may provide your doctor with information about potential treatment options.

Biomarker Findings
On your FoundationOne CDx report, the "Biomarker Findings" section includes the genomic signatures microsatellite instability (MSI) and tumor mutational burden (TMB). A high level of either of these two biomarkers may indicate that you could benefit from immunotherapy. Please note, however, that in other contexts, "biomarkers" may also include gene mutations.

Biomarker Testing
You may also hear the testing referred to as genomic testing, tumor testing, molecular testing, next-generation sequencing (NGS), and genomic profiling. Biomarker testing is a general category of testing that looks for mutations in cancer genes to identify potential treatment options.

Blood Tumor Mutational Burden (bTMB)
A biomarker that can be detected from your blood sample and that may help predict response to immunotherapy. bTMB is a measure of the frequency of mutations in your circulating-tumor DNA (ctDNA).

Cells
Basic units that make up your body.

Circulating-tumor DNA (ctDNA)
DNA that has come from your tumor and can be found in your blood.

Clinical Trial
Process by which new potential treatments are studied and compared to existing treatment options.

Companion Diagnostic (CDx)
A diagnostic test required to determine the eligibility of a patient for the intended use of a corresponding treatment.

Comprehensive Genomic Profiling
A type of biomarker/genomic testing performed at Foundation Medicine.

DNA
Instructs cells how to grow and divide; DNA mutations may lead to cancer growth.

Food and Drug Administration (FDA)
The official US government agency responsible for review and approval of drugs and diagnostic tests to determine their safety and effectiveness for the intended use in patients.

Foundation Medicine
Company that performs biomarker/genomic testing called comprehensive genomic profiling.

FoundationOne Liquid CDx
An FDA-approved companion diagnostic test developed by Foundation Medicine that analyzes genes and biomarkers detected in your blood to identify potential treatment options for advanced cancer patients with solid tumors.

Genes
Segments of DNA where mutations may be found with genomic testing.

Genomic Findings
Mutations identified in your cancer's DNA that may be matched with targeted treatment options.

Genomic Testing
You may also hear the testing referred to as biomarker testing, tumor testing, molecular testing, next-generation sequencing (NGS), and genomic profiling. Genomic testing is a general category of testing that looks for mutations in cancer genes to identify potential treatment options.

Immunotherapy
A type of cancer treatment that helps the body's immune system attack cancer cells.

Liquid biopsy
This type of testing is performed on a blood sample instead of a tissue sample. It looks at DNA from your tumor that is circulating in your blood.

Microsatellite Instability (MSI)
A biomarker that may help predict benefit from immunotherapy. MSI refers to a type of instability in a tumor's DNA.

Mutations
Changes in the DNA that can influence cancer growth (also referred to as "alterations").

NCCN category
A designation from the National Comprehensive Cancer Network that helps your doctor decide if the treatment might be appropriate for you.

Targeted Therapy
A type of cancer treatment that attacks cancer cells with specific gene mutations.

Tumor
A mass within the body caused by abnormal growth of cells.

Tumor Fraction
An estimate of the percentage of DNA found in your blood sample that is tumor DNA.

Tumor type
The type of cancer (e.g., lung cancer, breast cancer, etc.).

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. It is intended to help identify patients who may benefit from treatments with certain therapies. Use does not guarantee a match to treatment or that all relevant alterations will be found. 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 full use and risk information: www.foundationmedicine.com/patients

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