FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE	REPORT DATE
Lung adenocarcinoma	08 Feb 2022

COUNTRY CODE	ORDERED TEST #
PE	ORD-1290609-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Lung adenocarcinoma
NAME Angulo Chueca de Flaherty, Maria Lucia
DATE OF BIRTH 11 March 1937
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN
ORDERING PHYSICIAN Bermudez Alfaro, Vanesa
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Pleura
SPECIMEN ID 2021 Q68135
SPECIMEN TYPE Block
DATE OF COLLECTION 20 December 2021
SPECIMEN RECEIVED 25 January 2022

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings
Microsatellite status - Cannot Be Determined ^{α}
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.

EGFR exon 19 deletion (L747_A750>P)
U2AF1 S34F

7 Disease relevant genes with no reportable alterations: *ALK, BRAF, ERBB2, KRAS, MET, RET, ROS1*

....

† See About the Test in appendix for details.
α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with NCCN categories of evidence in this tumor type: **Afatinib** (p. 6), **Dacomitinib** (p. 7), **Erlotinib** (p. 7), **Gefitinib** (p. 8), **Osimertinib** (p. 9)

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: *U2AF1* S34F (p. 5)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS

Microsatellite status - Cannot Be Determined

No therapies or clinical trials. *see Biomarker Findings section*

Tumor Mutational Burden - Cannot Be Determined

No therapies or clinical trials. *see Biomarker Findings section*

GENOMIC FINDINGS

EGFR - exon 19 deletion (L747_A750>P)

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Afatinib	1	none
Dacomitinib	1	
Erlotinib	1	
Gefitinib	1	
Osimertinib	1	

10 Trials *see p. 10*

☐ *NCCN category*

Electronically signed by Erik Williams, M.D. | 08 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531

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VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

U2AF1 - S34F .... p. 5

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

U2AF1 - S34F .... p. 5

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER
Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —
On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS
MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[12-17], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[18-21]. One study reported MSI-H in lung adenocarcinoma patients with smoking history, and 3 of 4 MSI-H patients examined also had metachronous carcinomas in other organs, although this has not been investigated in large scale studies[12]. Published data investigating the prognostic implications of MSI in NSCLC are limited (PubMed, Oct 2021).

FINDING SUMMARY
Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[22]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[22-24]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

BIOMARKER
Tumor Mutational Burden

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —
On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[25-27], anti-PD-1 therapies[25-28], and combination nivolumab and ipilimumab[29-34]. Multiple clinical trials of PD-1- or PD-L1-targeting immune checkpoint inhibitors or combination of PD-1 and CTLA-4 inhibitors in NSCLC have reported that patients with tumors harboring TMB ≥10 Muts/Mb derive greater clinical benefit from these therapies than those with TMB <10 Muts/Mb (based on this assay or others); similarly, higher efficacy of anti-PD-1 or anti-PD-L1 immunotherapy for treatment of patients with NSCLC, compared with the use of chemotherapy, has been observed more significantly in cases of TMB ≥10 Muts/Mb (based on this assay or others)[7,25-26,29-31,35-41]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[42], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[43], has been observed across all TMB levels. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS
A large-scale genomic analysis found that unspecified lung non-small cell lung carcinoma (NSCLC), lung adenocarcinoma, and lung squamous cell carcinoma (SCC) samples harbored median TMBs between 6.3 and 9 Muts/Mb, and 12% to 17% of cases had an elevated TMB of greater than 20 Muts/Mb[44]. Lower TMB is observed more commonly in NSCLCs harboring known driver mutations (EGFR, ALK, ROS1, or MET) with the exception of BRAF or KRAS mutations, which are commonly observed in elevated TMB cases[45]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[46-47], several other large studies did find a strong association with increased TMB[48-51]. TMB >10 muts/Mb was found to be more frequent in NSCLC metastases compared with primary tumors for both adenocarcinoma (38% vs. 25%) and SCC (41% vs. 35%) subtypes[52]. A large study of Chinese patients with lung adenocarcinoma reported a shorter median OS for tumors with a higher number of mutations in a limited gene set compared with a lower mutation number (48.4 vs. 61.0 months)[46]. Another study of patients with NSCLC correlated elevated TMB with poorer prognosis and significantly associated lower TMB in combination with PD-L1 negative status with longer median survival in patients with lung adenocarcinoma[53]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[53-54].

FINDING SUMMARY
Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[55-56] and cigarette smoke in lung cancer[7,57], treatment with temozolomide-based chemotherapy in glioma[58-59], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[60-64], and microsatellite instability (MSI)[60,63-64]. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[26-28,65]. However, the TMB level in this sample could not be determined with confidence.

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GENOMIC FINDINGS

ORDERED TEST # ORD-1290609-01

GENE
EGFR

ALTERATION
exon 19 deletion (L747_A750>P)

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
2239_2248TTAAGAGAAG>C

VARIANT ALLELE FREQUENCY (% VAF)
5.1%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[66], gefitinib[67], afatinib[68], dacomitinib[69], and osimertinib[70]; however, the data for patients with other tumor types are limited[71-76]. The Phase 1 CHRYSALIS study of amivantamab monotherapy or in combination with lazertinib for the treatment of EGFR-mutated non-small cell lung cancer (NSCLC) has produced encouraging preliminary results for treatment-naive patients and patients who relapsed after treatment with osimertinib with and without chemotherapy, including osimertinib-relapsed patients with biomarkers indicating EGFR/MET-based osimertinib resistance[77-80] . In a Phase 1 trial, the HER3-targeted antibody patritumab deruxtecan elicited an ORR of 39% (22/57, 1 CR) and a median PFS of 8.2 months for patients with non-small cell lung cancer previously treated with an EGFR TKI, many of whom displayed TKI resistance alterations[81]. A Phase 1 trial evaluating the EGFR inhibitor AZD3759 reported a reduction in the volume of brain metastases in 40% (8/20) of patients with previously treated non-small cell lung cancer (NSCLC) harboring either the EGFR L858R alteration or EGFR exon 19 deletion, including 3 confirmed PRs and 3 unconfirmed PRs[82-83]. In a Phase 1/2 trial for advanced NSCLC, the brain-penetrant third-generation EGFR TKI lazertinib enabled ORRs of 54% (69/127) for all evaluable patients and 44% (8/18, intracranial) for patients with brain metastases[84]. The Phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy treatment also had clinical efficacy for patients with EGFR-mutated or ALK-rearranged metastatic NSCLC[85]; therefore, the patient's clinical context should be considered.

FREQUENCY & PROGNOSIS

EGFR mutation has been reported in 12-36% of lung adenocarcinomas[50,86-87] and in 4% of lung squamous cell carcinomas[88]. EGFR protein expression/overexpression has been reported in up to 70% of NSCLC cases[89-94]. 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 patients with lung adenocarcinoma, EGFR mutation was a predictor of poor overall survival[97-98]. However, EGFR mutations have been reported to predict improved survival in patients with resected Stage 1-3 lung adenocarcinoma[99] or resected Stage 1 NSCLC[100].

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[101]. EGFR exon 19 deletion mutations, such as seen here, have been shown to activate the tyrosine kinase activity of EGFR and to confer sensitivity to EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib[102-104], afatinib[105], osimertinib[106], and dacomitinib[69,107], although limited preclinical data suggest reduced sensitivity to lapatinib[108-109].

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GENE
U2AF1

ALTERATION
S34F

TRANSCRIPT ID
NM_006758

CODING SEQUENCE EFFECT
101C>T

VARIANT ALLELE FREQUENCY (% VAF)
3.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies approved or in clinical trials that directly address genomic alterations in U2AF1; however, preclinical studies suggest that mutations in genes encoding spliceosome components, including U2AF1, may confer sensitivity to spliceosome inhibitors[110-114]. In preclinical models, U2AF1 mutation leads to DNA damage and ATR pathway activation, rendering cells sensitive to ATR inhibitors both alone and in combination with spliceosome inhibitors[115-116].

FREQUENCY & PROGNOSIS

Mutations in U2AF1 have been reported in 3% of endometrial, 2% of urinary tract, 2% of small intestine, 2% of lung, 2% of large intestine, and less than 2% of other solid tumor types (COSMIC, Aug 2021)[117]. U2AF1 mutations have been associated with significantly shorter survival for patients with lung adenocarcinoma[50].

FINDING SUMMARY

U2AF1 encodes a pre-mRNA splicing factor required for accurate 3' splice site selection[118-119]. The S34F mutation is commonly found in patients with myelodysplastic syndrome (MDS), and is located in the first zinc finger domain of the protein; this alteration has been shown to affect splicing in preclinical cell-based assays[119-120]. This mutation has been reported to be a common mutation in acute myeloid leukemia (AML), accounting for 47% of U2AF1 mutations in AML in one study[121], as well as accounting for 42% of U2AF1 mutations in the cBioPortal curated set of non-redundant studies across tumor types (cBioPortal, Mar 2021)[122-123].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[124-129]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[124-125]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[130]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[128,131-132]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Afatinib

Assay findings association

EGFR
exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Afatinib is an irreversible kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) and nonresistant EGFR mutations and for the treatment of patients with metastatic, squamous NSCLC after progression on platinum-based chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[68-69,133-134], whereas data for patients with other tumor types are limited[71-76,135].

SUPPORTING DATA

Afatinib has shown significant clinical activity for patients with NSCLC and the EGFR common sensitizing mutations L858R or exon 19 deletions, based on extensive clinical evidence[68,133,136-139]. Two randomized Phase 3 trials reported significantly improved median PFS from afatinib compared with chemotherapy for patients with EGFR common sensitizing mutations (LUX-Lung 3, 13.6 vs. 6.9 months, HR 0.47, p<0.001; LUX-Lung 6, 11.0 vs. 5.6 months, HR 0.28, p<0.0001)[68,133]. However, while afatinib significantly increased OS relative to chemotherapy for patients with EGFR exon 19 alterations in these two trials (LUX-Lung 3, 33.3 vs. 21.1 months, HR=0.54; LUX-Lung 6, 31.4 vs. 18.4 months, HR=0.64), no significant OS differences were observed in treatment for patients with L858R mutation[105]. A similar alteration-specific difference was observed for EGFR-mutated treatment-naive NSCLC in a retrospective analysis, which reported numerically longer median OS from second- versus first-generation EGFR TKIs (48.8 vs. 26.4 months, HR=0.59) for patients with exon 19 deletions, but no substantial difference for patients with L858R (25.4 vs. 20.6 months, HR=0.90)[136]. A Phase 2b study of first-line afatinib compared with gefitinib, also for NSCLC with exon 19 deletions or L858R, reported similar median OS for the two therapies (27.9 vs. 24.5 months, HR=0.86) but significantly longer time-to-treatment-failure (13.7 vs. 11.5 months, HR=0.75) and higher ORR (73% vs. 56%, p=0.0018) with afatinib[137].

Patients with metastatic NSCLC and common EGFR mutations who progressed on prior chemotherapy experienced an ORR of 50.0% (30/60) from afatinib in a Phase 4 trial[138]. As first-line therapy for NSCLC with EGFR exon 19 deletions or L858R, prospective or randomized Phase 2 trials have reported a median PFS of 10.2 months and OS of 24.8 months for patients unfit for chemotherapy[139] and an ORR of 72.5% (n=40, 1 CR), DCR of 100% (40/40), and median PFS and OS of 15.2 and 30.0 months, respectively, for elderly patients ≥70 years old[140]. A retrospective study of afatinib administered to Asian patients with NSCLC, 99% of whom were previously treated with erlotinib and/or gefitinib, reported an ORR of 27.4% (63/230) for patients with common sensitizing EGFR mutations and an ORR of 24.4% (105/431) for the entire cohort[141]. In a case report, a patient with NSCLC with exon 19 deletion and leptomeningeal metastases experienced an ongoing 16-month PR from afatinib in extracranial, brain, and leptomeningeal lesions[142]. For patients with erlotinib- or gefitinib-resistant NSCLC and EGFR mutations, Phase 2/3 studies of afatinib treatment have generally reported ORRs of only 7 to 9%[143-148]; however, DCRs of more than 50% have been observed[147]. In a Phase 1b or observational study, patients with EGFR-mutated NSCLC who progressed on afatinib experienced further clinical benefit from subsequent treatment with afatinib and cetuximab[149] or osimertinib[150], respectively. Extensive clinical data have demonstrated that afatinib is effective for patients with EGFR-mutated advanced NSCLC, including exon 19 deletions and L858 mutations, as well as uncommon sensitizing mutations in exons 18 or 20[68,105,133,137,139,141,151]. Afatinib has also shown activity for patients with advanced NSCLC and ERBB2 mutations, most of which were exon 20 insertions[147,152-162]. The randomized Phase 3 LUX-Lung 8 trial comparing afatinib with erlotinib as second-line therapy for advanced lung squamous cell carcinoma (SCC) reported significantly longer median OS (7.9 vs. 6.8 months, HR=0.81), significantly longer median PFS (2.6 vs. 1.9 months, HR=0.81), and higher DCR (51% vs. 40%, p=0.002) for patients treated with afatinib[151]. For patients who progressed on afatinib monotherapy, additional clinical benefit has been reported from afatinib combined with paclitaxel[163].

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THERAPIES WITH CLINICAL BENEFIT   IN PATIENT'S TUMOR TYPE

Dacomitinib

Assay findings association

EGFR
exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[68-69,133-134], whereas data for patients with other tumor types are limited[71-76,135]. Patients with untreated advanced NSCLC and EGFR exon 19 deletions achieved an ORR of 76%[107] and a median OS of 34.1 months with dacomitinib[69].

SUPPORTING DATA

A randomized Phase 3 trial in patients with NSCLC with activating EGFR mutations (primarily L858R or exon 19 deletions) reported improved clinical benefit with first-line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[107,164]; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[165]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs 9.6 months, HR=0.717; median OS, 26.6 vs 23.2 months, HR=0.737)[166]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[167-169]. A Phase 1 trial of combination dacomitinib and a MEK1/2 inhibitor for patients with KRAS-mutated CRC, NSCLC, or pancreatic cancer reported 20/36 SDs and 16 PDs, however toxicity from this combination prevented long-term treatment in this patient population[170]. A Phase 2 study of dacomitinib in patients with NSCLC who had been previously treated with chemotherapy or erlotinib and were not selected for EGFR mutations reported an ORR of 4.5% (3/66)[168]. In one study, the combination of dacomitinib and crizotinib was ineffective and associated with high toxicity in patients with NSCLC[171].

Erlotinib

Assay findings association

EGFR
exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[66,172-174].

SUPPORTING DATA

For patients with EGFR-mutated NSCLC, the Phase 3 EURTAC trial reported improved PFS with first-line erlotinib relative to platinum-based chemotherapy (9.7 vs. 5.2 months, HR=0.37)[66]. A Phase 3 study reported similar efficacy of erlotinib and gefitinib for patients with EGFR-mutated NSCLC[175]. Meta-analysis of studies comparing erlotinib or gefitinib versus chemotherapy in the first-line setting reported no significant improvement in OS for patients with EGFR-mutated NSCLC; however, the lack of improved OS was attributed to the effectiveness of postprogression salvage therapy[176]. In the maintenance setting, the placebo-controlled Phase 3 SATURN trial reported significantly improved PFS with maintenance erlotinib following first-line platinum-based chemotherapy irrespective of EGFR status; however, the largest effect was seen for patients with EGFR mutations (HR=0.10)[172]. In the neoadjuvant setting, a Phase 2 trial reported a numerically improved ORR and significantly longer PFS with erlotinib compared with chemotherapy for patients with advanced EGFR-mutated NSCLC[173]. In the placebo-controlled Phase 3 RELAY trial, the addition of ramucirumab to erlotinib improved PFS for previously untreated patients with NSCLC harboring EGFR L858R or exon 19 deletion (19.4 vs. 12.4 months, HR=0.59)[177]. In a Phase 2 trial, no clinical benefit was observed from the addition of bevacizumab to erlotinib for patients with NSCLC harboring EGFR exon 19 deletion or L858R mutation[178]. In one study, median PFS (4.1 vs. 11.7 months, HR=9.7) and median OS (14.1 vs. 47.0 months, HR=10.2) were significantly shorter for patients with NSCLC harboring EGFR L747_A750>P (n=6) relative to those with deletions affecting EGFR E746_A750 (n=24) treated with first-line erlotinib[179]. The Phase 3 BR.21 trial demonstrated prolonged OS for genomically unselected patients with NSCLC treated with erlotinib compared with those treated with standard chemotherapy[180].

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THERAPIES WITH CLINICAL BENEFIT   IN PATIENT'S TUMOR TYPE

Gefitinib

Assay findings association

EGFR
exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[174,181-186], and responses have been reported for patients with EGFR-rearranged NSCLC[187-188].

SUPPORTING DATA

A Phase 3 trial of first-line gefitinib therapy for patients with NSCLC and EGFR exon 19 deletions or L858R mutations reported a longer PFS (9.2 months vs. 6.3 months)[183] but no change in median OS (34.9 months vs. 37.2 months) compared with patients treated with cisplatin plus docetaxel (median OS of 37.2 months)[189]. Gefitinib achieved an ORR of 69.8% and an OS of 19.2 months as first-line treatment for Caucasian patients with non-small cell lung carcinoma (NSCLC) and EGFR sensitizing mutations[67]. In the retrospective analysis of a Phase 3 study for East Asian patients, gefitinib was reported to have a longer PFS for patients with EGFR mutation-positive NSCLC compared with carboplatin/ paclitaxel doublet chemotherapy[184,190]. Two Phase 3 trials of gefitinib plus pemetrexed and carboplatin compared with gefitinib alone for patients with advanced NSCLC harboring EGFR activating mutations reported significantly higher ORRs (75.3% and 84% vs. 62.5% and 67%), longer median PFSs (16 and 20.9 months vs. 8 and 11.9 months), and longer median OSs (50.9 months and not reached vs. 17 and 38.8 months) with combination treatment; however, combination treatment was associated with increased Grade 3 or higher adverse events[191-192]. Retrospective analysis of East Asian patients with advanced NSCLC receiving first-line gefitinib therapy reported that patients with EGFR exon 19 mutations experienced a longer median PFS (10.9 months) compared with patients with EGFR mutations in exon 18 (7.9 months), exon 20 (1.2 months), exon 21 (7.7 months), or double mutations (5.7 months); however, no differences in OS were seen between EGFR mutations[193]. In a Phase 1 study for treatment-naive patients with NSCLC, best ORRs of 78% (7/9) were observed in patients treated with combination gefitinib and the PD-L1 inhibitor durvalumab as first-line treatment and of 80% (8/10) in those treated with the combination after gefitinib monotherapy[194].

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THERAPIES WITH CLINICAL BENEFIT	IN PATIENT'S TUMOR TYPE

Osimertinib

Assay findings association

EGFR
exon 19 deletion (L747_A750>P)

AREAS OF THERAPEUTIC USE

Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, exon 21 L858R mutations, or T790M mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

EGFR TKI-sensitizing mutations or rearrangements and/or the EGFR T790M mutation may predict sensitivity to osimertinib in non-small cell lung cancer[70,106,187,195-196]. Patients with untreated advanced NSCLC and EGFR exon 19 deletions or L858R mutations achieved an ORR of 80% and a median PFS of 21.4 and 14.4 months, respectively[106].

SUPPORTING DATA

The Phase 3 FLAURA study reported that, relative to erlotinib or gefitinib, first-line osimertinib significantly increased both median PFS (18.9 vs. 10.2 months, HR=0.46) and median OS (38.6 vs. 31.8 months; HR=0.80) for patients with advanced NSCLC and activating, sensitizing EGFR mutations (specifically, exon 19 deletion or L858)[106,197]. In the Phase 3 ADAURA study, patients with early Stage (IB/II/IIIA) EGFR-mutated NSCLC experienced longer PFSs on osimertinib compared to placebo in the adjuvant setting (not reached vs. 28.1 months; HR=0.21)[198]. A Phase 1 study reported that

T790M-negative patients with acquired EGFR TKI resistance experienced an ORR of 21% and a median PFS of 2.8 months[70]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 AACR Abstract CT163). A Phase 2 trial of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with untreated advanced non-small cell lung cancer (NSCLC) harboring EGFR del19 or L858R reported no difference in ORR (82% vs 86%) and median PFS (22.1 vs 20.2 months, HR 0.862 p=0.213)[199]. The Phase 2 BOOSTER study of osimertinib in combination with bevacizumab versus osimertinib monotherapy for patients with advanced NSCLC with EGFR-sensitizing mutations (exon 19 del or L858R) and L790M at progression on prior EGFR TKI reported no difference in ORR (55% vs 55%), median OS (24.0 vs 24.3 months, HR 1.03 p=0.91), or median PFS (15.4 vs 12.3 months, HR 0.96 p=0.83), although improved PFS was observed for the combination in the subgroup of current or former smokers (16.5 vs 8.4, HR 0.52) while nonsmokers had no benefit (HR 1.47)[200]. The Phase 1b TATTON study of osimertinib in combination with selumetinib, savolitinib, or durvalumab for patients with previously treated EGFR-mutated NSCLC reported ORRs of 42% (15/36), 44% (8/18), and 44% (10/23), respectively[201].

NOTE Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

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CLINICAL TRIALS

ORDERED TEST # ORD-1290609-01

GENE
EGFR

ALTERATION
exon 19 deletion (L747_A750>P)

RATIONALE
EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03521154
PHASE 3

A Global Study to Assess the Effects of Osimertinib Following Chemoradiation in Patients With Stage III Unresectable Non-small Cell Lung Cancer (LAURA)

TARGETS
EGFR

LOCATIONS: San Isidro (Peru), Lima (Peru), San Salvador de Jujuy (Argentina), Rosario (Argentina), São José do Rio Preto (Brazil), Mar del Plata (Argentina), Ciudad Autónoma de Bs. As. (Argentina), Barretos (Brazil), Ribeirão Preto (Brazil), Curitiba (Brazil)

NCT04035486
PHASE 3

A Study of Osimertinib With or Without Chemotherapy as 1st Line Treatment in Patients With Mutated Epidermal Growth Factor Receptor Non-Small Cell Lung Cancer (FLAURA2)

TARGETS
EGFR

LOCATIONS: San Isidro (Peru), Lima (Peru), La Libertad (Peru), Viña del Mar (Chile), Santiago (Chile), Cordoba (Argentina), Santa Fe (Argentina), Londrina (Brazil), São José do Rio Preto (Brazil), Ciudad Autonoma De Buenos Aire (Argentina)

NCT04487080
PHASE 3

A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer

TARGETS
MET, EGFR

LOCATIONS: La Rioja (Argentina), Cordoba (Argentina), Ijuí (Brazil), Capital Federal (Argentina), Buenos Aires (Argentina), Barretos (Brazil), Porto Alegre (Brazil), Pelotas (Brazil), Sorocaba (Brazil), Florianopolis (Brazil)

NCT04181060
PHASE 3

Osimertinib With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer

TARGETS
EGFR, VEGFA

LOCATIONS: Florida, Georgia, South Carolina, Texas, North Carolina

NCT03137771
PHASE 2

Maintenance Chemotherapy With or Without Stereotactic Body Radiation Therapy in Treating Patients With Stage IV Non-small Cell Lung Cancer

TARGETS
EGFR, PD-1

LOCATIONS: Florida, Georgia, South Carolina, Louisiana

ORDERED TEST # ORD-1290609-01

CLINICAL TRIALS

NCT02795156

PHASE 2

Study to Assess the Activity of Molecularly Matched Targeted Therapies in Select Tumor Types Based on Genomic Alterations

TARGETS
BRAF, VEGFRs, RET, KIT, EGFR, ERBB4, ERBB2, MET, ROS1

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT03909334

PHASE 2

Study of Osimertinib With and Without Ramucirumab in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

TARGETS
VEGFRs, EGFR

LOCATIONS: Florida, Texas, Virginia, District of Columbia, Indiana, New Jersey, New York, Illinois, Oregon, Washington

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NCT02716116

PHASE 1/2

A Trial of AP32788 in Non-Small Cell Lung Cancer

TARGETS
EGFR, ERBB2

LOCATIONS: Florida, Georgia, North Carolina, Virginia, Arizona, California

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NCT04619004

PHASE 2

HERTHENA-Lung01: Patritumab Deruxtecan in Subjects With Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer

TARGETS
ERBB3

LOCATIONS: Florida, Georgia, North Carolina, Tennessee, Virginia, New York, Ohio, Massachusetts

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NCT04077463

PHASE 1

A Study of Lazertinib as Monotherapy or in Combination With JNJ-61186372 in Japanese Participants With Advanced Non-small Cell Lung Cancer

TARGETS
EGFR, MET

LOCATIONS: Rio Piedras (Puerto Rico), Florida, Virginia, Pennsylvania, Missouri, New York, Massachusetts, Michigan, California

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	PATIENT	TUMOR TYPE	REPORT DATE
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APPENDIX   Variants of Unknown Significance

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

APC	KMT2A (MLL)	PMS2
S1971C	A53V	D60E

Electronically signed by Erik Williams, M.D. | 08 February 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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PATIENT

TUMOR TYPE
Lung adenocarcinoma

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APPENDIX   Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B)	APC
AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2
BTK	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL	CCND1
CCND2	CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73
CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R
CTCF	CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2	DIS3	DNMT3A	DOT1L	EED	EGFR	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRFI1	ESR1	EZH2
FAM46C	FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12
FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3
FGFR4	FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3
GATA4	GATA6	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11A	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI	PTCH1
PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	REL	RET
RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC	SDHD	SETD2
SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOCS1
SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	WT1	XPO1
XRCC2	ZNF217	ZNF703						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSPO2	SDC4	SLC34A2	TERC*	TERT**	TMPRSS2

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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PATIENT

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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium.

CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table
Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials
Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.

4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.

5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.

6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

*Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL,* and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear

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cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

MR Suite Version 5.2.0

The median exon coverage for this sample is 412x

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Lung adenocarcinoma

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APPENDIX   References

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FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma

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APPENDIX   References

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