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

DATE OF BIRTH 03 March 1951
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Oncologia Patologica
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 320946
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Pleura
SPECIMEN ID 21 1675 A (H21-12487)
SPECIMEN TYPE Block
DATE OF COLLECTION 03 March 2021
SPECIMEN RECEIVED 18 May 2021

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
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

BRAF V600E
MLL2 S166*
SETD2 T305fs*4
SMAD4 R361H

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

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

BIOMARKER FINDINGS

Microsatellite status - Cannot Be Determined

Tumor Mutational Burden - Cannot Be Determined

GENOMIC FINDINGS

***BRAF* -** V600E

10 Trials *see p. 11*

ACTIONABILITY

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)		THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)	
Dabrafenib + Trametinib	2A	Vemurafenib	2A
		Dabrafenib	
		Encorafenib + Binimetinib	
		Selumetinib	
		Trametinib	
		Vemurafenib + Cobimetinib	

☐ *NCCN category*

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

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.

MLL2 **-** S166* ..... p. 5

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

MLL2 **-** S166* ..... p. 5
SETD2 **-** T305fs*4 ..... p. 6
SMAD4 **-** R361H ..... p. 6

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.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] . 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]. The prognostic implications of MSI in NSCLC have not been extensively studied (PubMed, Oct 2020).

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.

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[22], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[25]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[25-27] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[28-30]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[31-33], anti-PD-1 therapies[31-34], and combination nivolumab and ipilimumab[35-40]. 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);[11,31-32,35-37,41-47]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[48], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[49], 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[50]. 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[51]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[52-53], several other large studies did find a strong association with increased TMB[54-57]. 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[58]. 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)[52]. 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[59]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[59-60].

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[61-62] and cigarette smoke in lung cancer[11,63], treatment with temozolomide-based chemotherapy in glioma[64-65], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[66-70], and microsatellite instability (MSI)[66,69-70]. 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[32-34,71]. However, the TMB level in this sample could not be determined with confidence.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

GENE
BRAF

ALTERATION
V600E

TRANSCRIPT ID
NM_004333

CODING SEQUENCE EFFECT
1799T>A

VARIANT ALLELE FREQUENCY (% VAF)
5.2%

POTENTIAL TREATMENT STRATEGIES
BRAF V600 mutations activate MEK-ERK signaling and are associated with sensitivity to BRAF V600 mutation-specific inhibitors such as vemurafenib[72], dabrafenib[73], and encorafenib[74]; the combination of BRAF V600 mutation-selective inhibitors with MEK inhibitors such as encorafenib plus binimetinib[75], vemurafenib plus cobimetinib[76-77], or dabrafenib plus trametinib[78-80]; MEK inhibitors such as trametinib[81-83], cobimetinib[84], binimetinib[85], and selumetinib[86-88]; pan-RAF inhibitors such as sorafenib[89-91]; and ERK inhibitors[92]. A Phase 1 trial of the ERK1/2 inhibitor ulixertinib reported PRs for 16% (3/19) of previously treated patients and 1 out of 2 newly diagnosed patients with BRAF V600E-mutant melanoma, 25% (3/12) of patients with BRAF-mutated lung cancer (2 with V600E and 1 with L597Q), and 19% (4/21) of patients with other BRAF-mutated cancers (2 with G469A, 1 with V600E, and 1 with L485W); 2 patients with BRAF V600E mutations also experienced CNS response[93]. BRAF inhibitors can induce adverse effects such as the development of cutaneous squamous cell carcinomas (SCC), keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[72-73,94]. Meta-analysis confirmed a reduced risk of developing cutaneous SCC with combined BRAF- and MEK-inhibition relative to BRAF-inhibitor monotherapy[95]. A Phase 1/2 trial of PLX8394, a next-generation BRAF inhibitor predicted to not induce paradoxical MAPK pathway activation[96-97], reported PRs in patients with BRAF V600E-mutant tumors, specifically in glioma (3/4), papillary thyroid carcinoma (1/9), colorectal cancer (1/10), and ovarian cancer (1/1)[98].

FREQUENCY & PROGNOSIS
BRAF mutations have been reported in up to 4% of non-small cell lung cancer (NSCLC) cases in various studies[99-103], with a large-scale meta-analysis suggesting a frequency of 3%[104]. BRAF mutations are significantly more prevalent in lung adenocarcinoma than non-adenocarcinoma NSCLC[101,104]. BRAF mutations can co-occur with alterations in other known oncogenic drivers of NSCLC, including EGFR, KRAS, and ALK[101,103]. Studies have reported a lack of association between BRAF mutation and tumor stage or prognosis in NSCLC[99,104].

FINDING SUMMARY
BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[105-106]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[107-108]. Among the V600 mutations, V600E accounts for 70-80% of observations, V600K for 10-30%, and V600R for 5-7%, with V600D comprising the majority of the rest[107,109-110]. Mutations at V600 have been shown to constitutively activate BRAF kinase and hyperactivate the downstream MEK-ERK signaling, promoting oncogenic transformation[107,111]. In multiple cancer types, multiple mutations at V600, including V600E, V600K, V600R, V600D, and V600M exhibited sensitivity to V600-targeted therapies[72-73,110,112-120]; other mutations at this position are predicted to behave similarly.

GENE
MLL2

ALTERATION
S166*

TRANSCRIPT ID
NM_003482

CODING SEQUENCE EFFECT
497C>G

VARIANT ALLELE FREQUENCY (% VAF)
5.8%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS
MLL2 alterations are observed in a number of solid tumor contexts (COSMIC, 2021)[121], and are especially prevalent in lung squamous cell carcinoma (SCC)[122] and small cell lung carcinoma (SCLC)[123]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[124]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[125]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[126].

FINDING SUMMARY
MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[127]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[128]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[129].

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[130-135]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[134,136-137]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

GENE
SETD2

ALTERATION
T305fs*4

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
913_914insA

VARIANT ALLELE FREQUENCY (% VAF)
7.3%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS
Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[138]. SETD2 mutations have been detected in 6-12% of acute lymphoblastic leukemias (ALL) and reportedly increase chromosomal abnormalities and contribute to leukemia development[139-141].

FINDING SUMMARY
SETD2 encodes a histone lysine-36 methyltransferase[142] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[143]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[144].

GENE
SMAD4

ALTERATION
R361H

TRANSCRIPT ID
NM_005359

CODING SEQUENCE EFFECT
1082G>A

VARIANT ALLELE FREQUENCY (% VAF)
5.6%

POTENTIAL TREATMENT STRATEGIES
There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[145-146] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[147].

FREQUENCY & PROGNOSIS
SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[148], pancreatic acinar cell carcinoma[149], cholangiocarcinoma (25%)[150], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[151-152], colorectal adenocarcinoma (CRC; 14%)[69], esophageal adenocarcinoma (14%)[153], and stomach adenocarcinoma (13%)[154]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[155] and intraductal papillary mucinous neoplasms (IPMN)[156]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[157]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[158]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[159-161], appendiceal mucinous neoplasm[162], gastric adenocarcinoma[163-164], esophageal adenocarcinoma[165], esophageal squamous cell carcinoma[166], breast cancer[167], and prostate cancer[168].

FINDING SUMMARY
SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[169-170]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[171-184].

POTENTIAL GERMLINE IMPLICATIONS
One or more of the SMAD4 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with juvenile polyposis syndrome (ClinVar, Mar 2021)[185]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[186-188], which is associated with an increased risk of gastrointestinal cancers[189]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[190]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

Dabrafenib + Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor and trametinib is a MEK inhibitor. These two therapies are FDA approved in combination to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. This combination is also approved to treat patients with non-small cell lung cancer (NSCLC) with a BRAF V600E mutation, and to treat patients with BRAF V600E-positive anaplastic thyroid cancer (ATC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in various solid tumors and hematologic malignancies, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as dabrafenib and trametinib[78-80,191-197] .

SUPPORTING DATA

In a Phase 2 trial for patients with previously treated BRAF V600E-mutated metastatic non-small cell lung cancer (mNSCLC), dabrafenib in combination with trametinib achieved an ORR of 63.2% (36/57, 2 CRs), a DCR (CRs, PRs, and SD) of 78.9% (45/57), and median PFS (mPFS) of 9.7 months[192]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy in this trial for BRAF V600E-mutated mNSCLC, with an ORR of 63.9% (23/36) and mPFS of 10.9 months[191]. A retrospective analysis of patients with BRAF-mutated NSCLC reported that 100% (9/9, including 5 newly diagnosed) achieved disease control and 6-month mPFS on dabrafenib plus trametinib[198]. In case studies of trametinib plus dabrafenib for BRAF V600E-mutated mNSCLC, 2 patients experienced a CR and PR by RECIST[199], and another patient achieved a dramatic response including significant symptomatic improvement and rapid tumor shrinkage[200]. Other case studies reported on a heavily pre-treated patient with BRAF V600E-positive lung adenocarcinoma who experienced tumor regression ongoing for 8 months on the combination of dabrafenib and trametinib[201], and another patient who experienced tumor shrinkage in both primary and metastatic lesions from the combination treatment[202]. Dabrafenib plus trametinib enabled a complete intracranial response, ongoing for 14 months, for a patient with newly diagnosed BRAF V600E-mutated NSCLC and multiple brain metastases[203]; another patient also experienced complete resolution of brain metastases from the therapy combination, but this patient's concurrent leptomeningeal disease was unresponsive[204].

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

Dabrafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Dabrafenib is a BRAF V600-selective inhibitor that is FDA approved as a monotherapy to treat melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Mutations at BRAF V600, including V600E, V600K, V600R, V600D, and V600M, have been reported to exhibit clinical sensitivity to V600-targeted therapies[72-73,110,112-119,205] ; therefore, this tumor may be sensitive to V600-targeted therapy such as dabrafenib.

SUPPORTING DATA

For patients with previously treated BRAF V600E-mutated metastatic NSCLC, dabrafenib in combination with trametinib achieved an objective response rate (ORR) of 63% (36/57), including 2 complete responses (CRs) and 34 partial responses (PRs), a disease control rate (CRs, PRs, and stable disease) of 79% (45/57), and a median progression-free survival (PFS) of 9.7 months[192]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy for BRAF V600E-mutated metastatic NSCLC, with an ORR of 64% (23/36) and a median PFS of 10.9 months[191]. In a Phase 2 trial for BRAF V600E-mutated metastatic NSCLC, dabrafenib monotherapy resulted in PRs for 33% (26/78) and disease control for 58% (45/78) of previously treated patients; 4/6 treatment-naive patients achieved PRs[206]. The median PFS and overall survival (OS) were 5.5 months and 12.7 months, respectively[206]. Similar median PFS (5.0 months) and OS (10.8 months) were reported in a retrospective study of BRAF-targeted therapy outcomes for BRAF-mutated metastatic NSCLC; 44% (4/9) of patients responded to dabrafenib in this study[91]. A patient with BRAF V600E-mutated lung adenocarcinoma experienced a PR to dabrafenib of 8 months and subsequently had progressive disease that coincided with the acquisition of a secondary KRAS mutation[207]. Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[72-73,110,112-119,205] . Dabrafenib can induce adverse effects such as the development of cutaneous squamous cell carcinomas and keratoacanthomas caused by inactivation of wild-type BRAF that leads to paradoxical activation of the MAPK pathway, but it has been reported to be well tolerated in patients with BRAF V600E-mutant thyroid cancer[73,94,208] . Patients with melanoma harboring BRAF V600E or V600K mutation treated with a combination of dabrafenib and trametinib experienced significantly lower rates of cutaneous squamous cell carcinoma and regression of established BRAF inhibitor-induced skin lesions[78,80,209-211] .

Encorafenib + Binimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

The combination of the BRAF inhibitor encorafenib and MEK inhibitor binimetinib is FDA approved to treat patients with melanoma with BRAF V600E or BRAF V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical efficacy in the treatment of patients with BRAF V600-mutated melanoma[75,212-214] , and activity in colorectal, thyroid, and lung cancer[214-216] , activating alterations affecting BRAF predict sensitivity to the combination of encorafenib and binimetinib.

SUPPORTING DATA

A case study observed improved responses in leptomeningeal and brain metastases for a patient with BRAF V600E-mutated lung adenocarcinoma following combination treatment with encorafenib and binimetinib[216]. The combination of encorafenib and binimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[75,214-216] , and has been studied primarily in the context of BRAF V600-mutated melanoma where patients treated with this combination achieved greater PFS and OS compared with encorafenib or vemurafenib monotherapy[75,212,217] . A combination of encorafenib, binimetinib, and the CDK4/6 inhibitor ribociclib in a Phase 1b trial for patients with BRAF V600-mutant cancers elicited responses in melanoma, astrocytoma, unknown carcinoma, and in 1 of 3 patients with colorectal cancer; a Phase 2 study of this combination in V600-mutant melanoma reported an ORR of 52.4% (22/42), including 5 CRs, median PFS of 9.2 months, and median OS of 19.4 months[218].

Selumetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence demonstrating the efficacy of selumetinib in patients with BRAF V600-mutated papillary thyroid cancer[219], melanoma,[88,220-223] and low grade glioma[87], as well as in patients with BRAF fusion-positive glioma[86-87] , BRAF activating alterations may predict sensitivity to selumetinib.

SUPPORTING DATA

In a Phase 2 study of selumetinib monotherapy to treat patients with lung cancer who were selected for mutation in KRAS, HRAS, NRAS, or BRAF, a mPFS of 2.3 months and mOS of 6.5 months was observed[224]. In a Phase 2 study of patients with NSCLC who had failed on at least 2 prior chemotherapeutic regimes, selumetinib as a monotherapy did not improve survival as compared to pemetrexed (67 vs 90 days, HR= 1.08); however, 2 PRs were reported[225]. A Phase 2 study of selumetinib combined with docetaxel in patients with advanced or metastatic KRAS wild-type NSCLC who were previously treated did not report improved survival benefit compared to docetaxel alone[226]. A Phase 2 study of selumetinib combined with pemetrexed and platinum based chemotherapy for treatment of patients with advanced non-squamous NSCLC showed improved ORR (35% with intermittent dosing and 62% for continuous dosing) compared to chemotherapy alone (24%) but did not report a statistically significant improvement in mPFS[227]. The combination of selumetinib with platinum doublet chemotherapy has been studied in a Phase 1 trial for patients with advanced NSCLC in the first line setting and has reported 4/21 PRs in the selumetinib + pemetrexed/carboplatin cohort and 2/15 PRs in the pemetrexed/cisplatin cohort; selumetinib in combination with gemcitabine regimens was not tolerated[228]. A Phase 1b study of selumetinib in combination with osimertinib for patients with EGFR-mutated lung cancer who had progressed on previous TKI treatment reported an ORR of 41.7% (15/36)[229].

Trametinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating BRAF alterations may predict sensitivity to MEK inhibitors such as trametinib. Significant clinical responses to trametinib have been achieved by patients with melanoma harboring BRAF V600E[82-83] , V600K[82], V600R[83], K601E[83,230] , L597V[82], L597Q[230-231] , or L597S[232] mutations; by a patient with histiocytosis harboring an activating N486_P490del alteration[120]; as well as by patients with tumors harboring BRAF fusions[233-238] .

SUPPORTING DATA

For patients with previously treated BRAF V600E-mutated metastatic NSCLC, trametinib in combination with the BRAF inhibitor dabrafenib achieved an ORR of 63% (36/57), including 2 CRs and 34 PRs, a DCR (CRs, PRs, and SD) of 79% (45/57), and a median PFS of 9.7 months[192]. Dabrafenib plus trametinib demonstrated similar activity as first-line therapy for BRAF V600E-mutated metastatic NSCLC, with an ORR of 64% (23/36) and a median PFS of 10.9 months[191]. Phase 1 and 2 monotherapy trials of MEK inhibitors such as trametinib and RO4987655 have shown low response rates in patients with NSCLC, irrespective of KRAS mutation status, and no improvement in PFS compared to docetaxel[239-241] . However, Phase 1 and 2 trials of MEK inhibitors in combination with docetaxel or pemetrexed in NSCLC have shown improved clinical activity and patient survival compared to chemotherapeutics alone, although no association was observed between response and KRAS mutation status[242-244] . In contrast, although 3 objective responses were observed in patients with NSCLC treated with the MEK inhibitor selumetinib in combination with erlotinib in a Phase 2 trial, there was no significant increase in either PFS or OS relative to patients treated with selumetinib alone; further, the combination increased toxicity relative to monotherapy[245]. Preclinical and early clinical studies have shown synergistic antitumorigenic effects when the combination of MEK and PI3K inhibitors was used to treat KRAS-driven NSCLC[246-248] . A Phase 1b combination trial of trametinib and the pan-PI3K inhibitor BKM120 reported a DCR of 59% in patients with NSCLC, including 1 confirmed PR in 17 patients; although the reported adverse effects were prevalent and often severe, the study recommended a Phase 2 dose[249]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[250], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[251].

Vemurafenib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and is FDA approved to treat melanoma as monotherapy for patients with the BRAF V600E mutation. It is also approved to treat patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of strong clinical data, BRAF V600E mutations may confer sensitivity to V600-targeted therapies such as vemurafenib[72,112,117,252-258] .

SUPPORTING DATA

Dabrafenib and vemurafenib have primarily been studied in the context of BRAF V600E-positive melanoma and NSCLC[72-73,110,112-119,205] . Single-agent vemurafenib has been examined in Phase 2 basket trials including cohorts with BRAF-mutated NSCLC. In the VE-BASKET study for patients with BRAF V600 mutation, vemurafenib elicited an ORR of 37% (23/62 PRs), a median PFS of 6.5 months, a median OS of 15.4 months, and a median response duration of 7.2 months in the overall NSCLC cohort; similar ORRs were achieved by treatment-naïve and previously-treated patients[255,259] . In the AcSé study, patients with BRAF V600-mutated NSCLC and progression on 1 or more standard treatments achieved an ORR of 44.8% (43/96), with a median PFS, OS, and duration of response of 5.2, 10, and 6.4 months, respectively; patients with BRAF non-V600 mutations did not experience a response (0/15) and achieved a median PFS of 1.8 months and a median OS of 5.2 months[256]. Similarly, in the MyPathway study, patients with advanced BRAF V600E-mutated NSCLC experienced an ORR of 43% (6/14, 1 CR), while the response rate was low for diverse tumor types with BRAF non-V600 mutation (4%, 1/23)[260]. A retrospective study reported an ORR of 54% (13/24, 2 CR) and a DCR of 96% (23/24) for patients with V600E-mutated advanced NSCLC treated with vemurafenib following prior BRAF inhibitor therapy[91]. Case reports support the activity of vemurafenib against BRAF V600E-mutated metastatic NSCLC[261-262] , including patients with intracranial disease[263] or pulmonary sarcomatoid carcinoma[264]. One patient with NSCLC, low TMB, and TRIM24-BRAF fusion experienced a PR with vemurafenib treatment[265]. Vemurafenib can induce adverse effects, such as the development of cutaneous squamous cell carcinomas, keratoacanthomas, and new primary melanomas caused by inactivation of wild-type BRAF and leading to paradoxical activation of the MAPK pathway[72,94] . In a Phase 1b trial, patients with BRAF V600E-mutant melanoma treated with a combination of vemurafenib and cobimetinib had increased RR (87%) and PFS (13.7 months) compared to the RR and PFS values previously reported for vemurafenib or MEK inhibitor monotherapy; this combination also resulted in lower rates of cutaneous SCC[266].

Vemurafenib + Cobimetinib

Assay findings association

BRAF
V600E

AREAS OF THERAPEUTIC USE

Vemurafenib is a selective inhibitor of BRAF with V600 mutations and cobimetinib is a MEK inhibitor. The combination is FDA approved to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence in melanoma and colorectal carcinoma, BRAF activating alterations may confer sensitivity to the combination of BRAF V600-targeted therapies and MEK inhibitors such as vemurafenib and cobimetinib[76-77,267] .

SUPPORTING DATA

One patient with BRAF V600E-positive NSCLC experienced a15-month SD on vemurafenib plus cobimetinib after switching from dabrafenib plus trametinib due to toxicity[268]. The combination of vemurafenib and cobimetinib has been reported to provide clinical benefit for patients with various solid tumors harboring BRAF V600 activating alterations[267-269] and has been studied primarily in the context of BRAF V600-mutated melanoma, where patients treated with this combination achieved greater PFS and OS compared with vemurafenib alone[76-77,270] .

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.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, 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

ORDERED TEST # ORD-1098581-01

CLINICAL TRIALS

NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
BRAF

ALTERATION
V600E

RATIONALE
BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK.

NCT02974725

PHASE 1

Study of LXH254 and LTT462 in NSCLC

TARGETS
CDK6, CDK4, ERK1, ERK2, ARAF, BRAF, MEK

LOCATIONS: Verona (Italy), Milano (Italy), Aviano (Italy), Rozzano (Italy), Paris Cedex 10 (France), Heidelberg (Germany), Lyon Cedex (France), Frankfurt (Germany), Napoli (Italy), Dresden (Germany)

NCT03178552

PHASE 2/3

A Study to Evaluate Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)

TARGETS
ALK, RET, BRAF, MEK, PD-L1, ROS1, TRKA, TRKB, TRKC

LOCATIONS: Cremona (Italy), Bergamo (Italy), Monza (Italy), Milano (Italy), Aviano (Italy), Meldola (Italy), Orbassano (TO) (Italy), Gauting (Germany), Esslingen (Germany), Gerlingen (Germany)

NCT03915951

PHASE 2

An Open-label Study of Encorafenib + Binimetinib in Patients With BRAFV600E-mutant Non-small Cell Lung Cancer

TARGETS
BRAF, MEK

LOCATIONS: Bologna (Italy), Milan (Italy), Torino (Italy), Orbassano (Italy), Napoli (Italy), Napli (Italy), Barcelona (Spain), Esplugues de Llobregat (Spain), L'Hospitalet (Spain), Amsterdam (Netherlands)

NCT02664935

PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS
FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, AXL, MET, ROS1, TRKA, TRKC, MEK, AKTs, EGFR, PD-L1, DDR2, FLT3, KIT, PDGFRA, RET, TRKB, VEGFRs

LOCATIONS: Maidstone (United Kingdom), Colchester (United Kingdom), London (United Kingdom), Cambridge (United Kingdom), Southampton (United Kingdom), Oxford (United Kingdom), Leicester (United Kingdom), Bristol (United Kingdom), Birmingham (United Kingdom), Exeter (United Kingdom)

NCT02314481

PHASE 2

Deciphering Antitumour Response and Resistance With Intratumour Heterogeneity - DARWIN II

TARGETS
PD-L1, BRAF, ALK, RET, ERBB2

LOCATIONS: London (United Kingdom)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT02693535

PHASE 2

TAPUR: Testing the Use of Food and Drug Administration (FDA) Approved Drugs That Target a Specific Abnormality in a Tumor Gene in People With Advanced Stage Cancer

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, CDK4, CDK6, CSF1R, FLT3, KIT, RET, mTOR, EGFR, ERBB2, ERBB3, MEK, BRAF, SMO, DDR2, PARP, PD-1, CTLA-4, ERBB4

LOCATIONS: Maine, New Hampshire, Pennsylvania, Virginia, Michigan

NCT01989585

PHASE 1/2

Dabrafenib, Trametinib, and Navitoclax in Treating Patients With BRAF Mutant Melanoma or Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
BCL-W, BCL-XL, BCL2, BRAF, MEK

LOCATIONS: Massachusetts, North Carolina, Illinois, Missouri, Florida, Kansas

NCT03600701

PHASE 2

Atezolizumab and Cobimetinib in Treating Patients With Metastatic, Recurrent, or Refractory Non-small Cell Lung Cancer

TARGETS
PD-L1, MEK

LOCATIONS: New Hampshire, District of Columbia, Virginia, Michigan, Ohio, North Carolina, Alabama, Florida, Oklahoma

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, AXL, MET, ROS1, TRKA, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, CSF1R, FLT3, RET, mTOR, ERBB2, ERBB3, MEK, BRAF, SMO

LOCATIONS: Montreal (Canada), Ottawa (Canada), Kingston (Canada), Toronto (Canada), London (Canada), Saskatoon (Canada), Regina (Canada), Edmonton (Canada), Vancouver (Canada)

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.

HNF1A
G292fs*25

IKZF1
D447E

KMT2A (MLL)
A53V

MLL2
A200V

ZNF217
L864F

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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)

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

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. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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.

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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%.

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 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

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

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 4.1.0

The median exon coverage for this sample is 991x

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Hochster et al., 2017; ASCO Abstract 673
4. Fleming et al., 2018; ASCO Abstract 5585
5. Bang et al., 2018; ASCO Abstract 92
6. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
7. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
8. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
9. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
10. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
11. Rizvi NA, et al. Science (2015) pmid: 25765070
12. Warth A, et al. Virchows Arch. (2016) pmid: 26637197
13. Ninomiya H, et al. Br. J. Cancer (2006) pmid: 16641899
14. Vanderwalde A, et al. Cancer Med (2018) pmid: 29436178
15. Zang YS, et al. Cancer Med (2019) pmid: 31270941
16. Dudley JC, et al. Clin. Cancer Res. (2016) pmid: 26880610
17. Takamochi K, et al. Lung Cancer (2017) pmid: 28676214
18. Pylkkänen L, et al. Environ. Mol. Mutagen. (1997) pmid: 9329646
19. Gonzalez R, et al. Ann. Oncol. (2000) pmid: 11061602
20. Chen XQ, et al. Nat. Med. (1996) pmid: 8782463
21. Merlo A, et al. Cancer Res. (1994) pmid: 8174113
22. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
23. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
24. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
25. Lynch HT, et al. Clin. Genet. (2009) pmid: 19659756
26. Pande M, et al. Fam. Cancer (2012) pmid: 22714864
27. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
28. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
29. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
30. Fam. Cancer (2005) pmid: 16136383
31. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
32. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
33. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
34. Cristescu R, et al. Science (2018) pmid: 30309915
35. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
36. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
37. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
38. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
39. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
40. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
41. Colli LM, et al. Cancer Res. (2016) pmid: 27197178
42. Wang VE, et al. J Immunother Cancer (2017) pmid: 28923100
43. Carbone DP, et al. N. Engl. J. Med. (2017) pmid: 28636851
44. Rizvi H, et al. J. Clin. Oncol. (2018) pmid: 29337640
45. Forde PM, et al. N. Engl. J. Med. (2018) pmid: 29658848
46. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
47. Chae YK, et al. Clin Lung Cancer (2019) pmid: 30425022
48. Paz-Ares et al., 2019; ESMO Abstract LBA80
49. Hellmann MD, et al. N. Engl. J. Med. (2019) pmid: 31562796
50. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
51. Spigel et al., 2016; ASCO Abstract 9017
52. Xiao D, et al. Oncotarget (2016) pmid: 27009843
53. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
54. Govindan R, et al. Cell (2012) pmid: 22980976
55. Ding L, et al. Nature (2008) pmid: 18948947
56. Imielinski M, et al. Cell (2012) pmid: 22980975
57. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
58. Stein et al., 2019; DOI: 10.1200/PO.18.00376
59. Chen Y, et al. J. Exp. Clin. Cancer Res. (2019) pmid: 31088500
60. Yu H, et al. J Thorac Oncol (2019) pmid: 30253973
61. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
62. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
63. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
64. Johnson BE, et al. Science (2014) pmid: 24336570
65. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
66. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
67. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
68. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
69. Nature (2012) pmid: 22810696
70. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
71. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
72. McArthur GA, et al. Lancet Oncol. (2014) pmid: 24508103
73. Hauschild A, et al. Lancet (2012) pmid: 22735384
74. Delord JP, et al. Clin. Cancer Res. (2017) pmid: 28611198
75. Dummer R, et al. Lancet Oncol. (2018) pmid: 29573941
76. Ascierto PA, et al. Lancet Oncol. (2016) pmid: 27480103
77. Ribas A, et al. Clin. Cancer Res. (2020) pmid: 31732523
78. Long GV, et al. Lancet (2015) pmid: 26037941
79. Long GV, et al. Ann. Oncol. (2017) pmid: 28475671
80. Robert C, et al. N. Engl. J. Med. (2015) pmid: 25399551
81. Flaherty KT, et al. N. Engl. J. Med. (2012) pmid: 22663011
82. Falchook GS, et al. Lancet Oncol. (2012) pmid: 22805292
83. Kim KB, et al. J. Clin. Oncol. (2013) pmid: 23248257
84. Larkin J, et al. N. Engl. J. Med. (2014) pmid: 25265494
85. Ascierto PA, et al. Lancet Oncol. (2013) pmid: 23414587
86. Banerjee A, et al. Neuro-oncology (2017) pmid: 28339824
87. Fangusaro J, et al. Lancet Oncol. (2019) pmid: 31151904
88. Robert C, et al. Lancet Oncol. (2013) pmid: 23735514
89. Ahmed M, et al. Eur. J. Endocrinol. (2011) pmid: 21566072
90. Schneider TC, et al. BMC Cancer (2016) pmid: 26786320
91. Gautschi O, et al. J Thorac Oncol (2015) pmid: 26200454
92. Morris EJ, et al. Cancer Discov (2013) pmid: 23614898
93. Sullivan RJ, et al. Cancer Discov (2018) pmid: 29247021
94. Gibney GT, et al. Nat Rev Clin Oncol (2013) pmid: 23712190
95. el Habbal M, et al. Am. J. Cardiol. (1989) pmid: 2913734
96. Zhang C, et al. Nature (2015) pmid: 26466569
97. Yao Z, et al. Nat. Med. (2019) pmid: 30559419
98. Janku et al., 2018; ASCO Abstract 2583
99. An et al., 2013; ASCO Abstract 8101
100. Paik PK, et al. J. Clin. Oncol. (2011) pmid: 21483012
101. Brustugun OT, et al. Lung Cancer (2014) pmid: 24552757
102. Carneiro JG, et al. Genet Res (Camb) (2014) pmid: 24594201
103. Li S, et al. Br. J. Cancer (2014) pmid: 24743704
104. Chen D, et al. PLoS ONE (2014) pmid: 24979348
105. Holderfield M, et al. Nat. Rev. Cancer (2014) pmid: 24957944
106. Burotto M, et al. Cancer (2014) pmid: 24948110
107. Davies H, et al. Nature (2002) pmid: 12068308
108. Kandoth C, et al. Nature (2013) pmid: 24132290
109. Greaves WO, et al. J Mol Diagn (2013) pmid: 23273605
110. Klein O, et al. Eur. J. Cancer (2013) pmid: 23237741
111. Wellbrock C, et al. Cancer Res. (2004) pmid: 15059882
112. Fisher R, et al. Cancer Manag Res (2012) pmid: 22904646
113. Yang H, et al. Cancer Res. (2010) pmid: 20551065
114. Gentilcore G, et al. BMC Cancer (2013) pmid: 23317446
115. van den Brom RR, et al. Eur. J. Cancer (2013) pmid: 23473613
116. Klein O, et al. Eur. J. Cancer (2013) pmid: 23490649
117. Ponti G, et al. J. Clin. Pathol. (2013) pmid: 23463675
118. Ponti G, et al. J Hematol Oncol (2012) pmid: 23031422
119. Parakh S, et al. J Clin Pharm Ther (2015) pmid: 25382067
120. Lee LH, et al. JCI Insight (2017) pmid: 28194436
121. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
122. Nature (2012) pmid: 22960745
123. Augert A, et al. J Thorac Oncol (2017) pmid: 28007623
124. Ardeshir-Larijani F, et al. Clin Lung Cancer (2018) pmid: 29627316
125. Hillman RT, et al. Nat Commun (2018) pmid: 29950560
126. Abudureheman A, et al. J. Cancer Res. Clin. Oncol. (2018) pmid: 29532228
127. Vicent GP, et al. Genes Dev. (2011) pmid: 21447625
128. Hannibal MC, et al. Am. J. Med. Genet. A (2011) pmid: 21671394
129. Fagan RJ, et al. Cancer Lett. (2019) pmid: 31128216
130. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
131. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
132. Xie M, et al. Nat. Med. (2014) pmid: 25326804
133. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
134. Severson EA, et al. Blood (2018) pmid: 29678827
135. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
136. Chabon JJ, et al. Nature (2020) pmid: 32269342
137. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
138. Varela I, et al. Nature (2011) pmid: 21248752
139. Mar BG, et al. Nat Commun (2014) pmid: 24662245
140. Wang Q, et al. Sci China Life Sci (2014) pmid: 25077743
141. Zhu X, et al. Nat. Genet. (2014) pmid: 24509477
142. Sun XJ, et al. J. Biol. Chem. (2005) pmid: 16118227
143. Faber PW, et al. Hum. Mol. Genet. (1998) pmid: 9700202
144. Al Sarakbi W, et al. BMC Cancer (2009) pmid: 19698110
145. Cui Y, et al. Clin. Cancer Res. (2012) pmid: 22753594
146. Haeger SM, et al. Oncogene (2016) pmid: 25893305
147. Bachet JB, et al. Ann. Oncol. (2012) pmid: 22377565
148. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
149. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
150. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
151. Liu X, et al. Clin. Chem. (2014) pmid: 24821835
152. Maru D, et al. Oncogene (2004) pmid: 14647445
153. Wang K, et al. Oncologist (2015) pmid: 26336083
154. Nature (2014) pmid: 25079317
155. Izeradjene K, et al. Cancer Cell (2007) pmid: 17349581
156. Bardeesy N, et al. Genes Dev. (2006) pmid: 17114584
157. Springer S, et al. Gastroenterology (2015) pmid:

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

26253305
158. Blackford A, et al. Clin. Cancer Res. (2009) pmid: 19584151
159. Yan P, et al. Clin. Cancer Res. (2016) pmid: 26861460
160. Kozak MM, et al. J. Clin. Pathol. (2015) pmid: 25681512
161. Roth AD, et al. J. Natl. Cancer Inst. (2012) pmid: 23104212
162. Davison JM, et al. Am. J. Surg. Pathol. (2014) pmid: 24618609
163. Kim YH, et al. Ann. Oncol. (2004) pmid: 15033661
164. Xiangming C, et al. Clin. Cancer Res. (2001) pmid: 11234879
165. Singhi AD, et al. Am. J. Surg. Pathol. (2015) pmid: 25634752
166. Natsugoe S, et al. Clin. Cancer Res. (2002) pmid: 12060625
167. de Kruijf EM, et al. Ann. Oncol. (2013) pmid: 23022998
168. Shipitsin M, et al. Br. J. Cancer (2014) pmid: 25032733
169. Nat. Rev. Mol. Cell Biol. (2012) pmid: 22992590
170. Cell (2008) pmid: 18662538
171. Massagué J, et al. Genes Dev. (2005) pmid: 16322555
172. Morén A, et al. Oncogene (2000) pmid: 10980615
173. Xu J, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10781087
174. Luo K, et al. Genes Dev. (1999) pmid: 10485843
175. Jones JB, et al. Nucleic Acids Res. (2000) pmid: 10871368
176. Fink SP, et al. Cancer Res. (2001) pmid: 11196171
177. De Bosscher K, et al. Biochem. J. (2004) pmid: 14715079
178. Shi Y, et al. Nature (1997) pmid: 9214508
179. Miyaki M, et al. Oncogene (1999) pmid: 10340381
180. Prokova V, et al. Biochemistry (2007) pmid: 17994767
181. Wu JW, et al. J. Biol. Chem. (2001) pmid: 11274206
182. Ding L, et al. J. Clin. Invest. (2009) pmid: 19139564
183. Kuang C, et al. Oncogene (2004) pmid: 14647410
184. Watanabe M, et al. EMBO Rep. (2000) pmid: 11265759
185. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
186. Houlston R, et al. Hum. Mol. Genet. (1998) pmid: 9811934
187. Woodford-Richens K, et al. Gut (2000) pmid: 10764709
188. Howe JR, et al. J. Med. Genet. (2004) pmid: 15235019
189. Brosens LA, et al. World J. Gastroenterol. (2011) pmid: 22171123
190. Kalia SS, et al. Genet. Med. (2017) pmid: 27854360
191. Planchard D, et al. Lancet Oncol. (2017) pmid: 28919011
192. Planchard D, et al. Lancet Oncol. (2016) pmid: 27283860
193. Subbiah V, et al. J. Clin. Oncol. (2018) pmid: 29072975
194. J Toxicol Sci (1989) pmid: 2639210
195. Westin SN, et al. Gynecol Oncol (2019) pmid: 31623857
196. Kreitman et al., 2018; ASH Abstract 391
197. Laganà et al., 2018; DOI: 10.1200/PO.18.00019
198. Mu Y, et al. Front Oncol (2020) pmid: 32411601
199. Pervere LM, et al. Clin Lung Cancer (2017) pmid: 28024926
200. Clin Drug Investig (2019) pmid: 31250402
201. Kim HC, et al. Onco Targets Ther (2019) pmid: 31440061
202. Adachi Y, et al. BMC Cancer (2020) pmid: 32093631
203. Tsakonas G, et al. Clin Lung Cancer (2020) pmid: 32522509
204. Yamamoto G, et al. J Thorac Oncol (2019) pmid: 31027751
205. Klempner SJ, et al. Cancer Discov (2016) pmid: 27048246
206. Planchard D, et al. Lancet Oncol. (2016) pmid: 27080216
207. Rudin CM, et al. J Thorac Oncol (2013) pmid: 23524406
208. Falchook GS, et al. Thyroid (2015) pmid: 25285888
209. Flaherty KT, et al. N. Engl. J. Med. (2012) pmid: 23020132
210. Long GV, et al. N. Engl. J. Med. (2014) pmid: 25265492
211. Peters S, et al. Melanoma Res. (2014) pmid: 25185693
212. Ascierto PA, et al. Eur. J. Cancer (2020) pmid: 31901705
213. Holbrook K, et al. Cancer (2020) pmid: 31658370
214. Sullivan RJ, et al. Clin Cancer Res (2020) pmid: 32669376
215. Kefford et al., 2013; Melanoma Bridge Meeting Abstract P5
216. McLoughlin EM, et al. J Thorac Oncol (2019) pmid: 31757377
217. Gogas et al., 2020; ASCO Abstract 10012
218. Ascierto et al., 2017; ASCO Abstract 9518
219. Hayes DN, et al. Clin. Cancer Res. (2012) pmid: 22241789
220. Kirkwood JM, et al. Clin. Cancer Res. (2012) pmid: 22048237
221. Patel SP, et al. Cancer (2013) pmid: 22972589
222. Banerji U, et al. Clin. Cancer Res. (2010) pmid: 20179232
223. Boers-Sonderen MJ, et al. Anticancer Drugs (2012) pmid: 22293660
224. Lopez-Chavez A, et al. J. Clin. Oncol. (2015) pmid: 25667274
225. Hainsworth JD, et al. J Thorac Oncol (2010) pmid: 20802351
226. Soria JC, et al. Ann. Oncol. (2017) pmid: 29045535
227. Melosky B, et al. Lung Cancer (2019) pmid: 31200828
228. Greystoke A, et al. Br. J. Cancer (2017) pmid: 28950288
229. Oxnard GR, et al. Ann. Oncol. (2020) pmid: 32139298
230. Bowyer SE, et al. Melanoma Res. (2014) pmid: 24933606
231. Sullivan et al., 2016; ASCO Abstract 9537
232. Dahlman KB, et al. Cancer Discov (2012) pmid: 22798288
233. Banerjee et al., 2014; ASCO Abstract 10065
234. Ross JS, et al. Int. J. Cancer (2016) pmid: 26314551
235. Menzies AM, et al. Pigment Cell Melanoma Res (2015) pmid: 26072686
236. Grisham RN, et al. J. Clin. Oncol. (2015) pmid: 26324360
237. Chmielecki J, et al. Cancer Discov (2014) pmid: 25266736
238. Durham BH, et al. Nat. Med. (2019) pmid: 31768065
239. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
240. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
241. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
242. Kelly et al., 2013; ASCO Abstract 8027
243. Gandara et al., 2013; ASCO Abstract 8028
244. Jänne PA, et al. Lancet Oncol. (2013) pmid: 23200175
245. Carter CA, et al. Ann. Oncol. (2016) pmid: 26802155
246. Banerji et al., 2014; ASCO Abstract e13559
247. Castellano E, et al. Cancer Cell (2013) pmid: 24229709
248. Ku BM, et al. Invest New Drugs (2015) pmid: 25342139
249. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
250. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
251. Patterson et al., 2018; AACR Abstract 3891
252. Chapman PB, et al. N. Engl. J. Med. (2011) pmid: 21639808
253. Kurzrock R, et al. Ann. Oncol. (2020) pmid: 32067683
254. Hyman DM, et al. N. Engl. J. Med. (2015) pmid: 26287849
255. Subbiah V, et al. Cancer Discov (2020) pmid: 32029534
256. Mazieres J, et al. Ann. Oncol. (2020) pmid: 31959346
257. Larkin J, et al. Eur. J. Cancer (2019) pmid: 30580112
258. Kaley T, et al. J. Clin. Oncol. (2018) pmid: 30351999
259. Subbiah et al., 2019; DOI: 10.1200/PO.18.00266
260. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
261. Peters S, et al. J. Clin. Oncol. (2013) pmid: 23733758
262. Liu X, et al. Mol Clin Oncol (2018) pmid: 30214735
263. Robinson SD, et al. Lung Cancer (2014) pmid: 24888229
264. Schrock AB, et al. J Thorac Oncol (2017) pmid: 28315738
265. Lai et al., 2018; ASCO Abstract e13537
266. Ribas A, et al. Lancet Oncol. (2014) pmid: 25037139
267. Klute et al., 2020; ASCO Abstract 122
268. Chic N, et al. Clin Lung Cancer (2020) pmid: 32896487
269. Guidry J, et al. JAAD Case Rep (2020) pmid: 33015265
270. Larkin et al., 2015; ASCO Abstract 9006

Electronically signed by Julie Tse, M.D. | 28 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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