FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
PE

REPORT DATE
13 Jan 2022
ORDERED TEST #
ORD-1275918-01

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
DATE OF BIRTH 19 October 1947
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Cervix
SPECIMEN ID 21-6827-2
SPECIMEN TYPE Block
DATE OF COLLECTION 10 August 2021
SPECIMEN RECEIVED 30 December 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

NF1 H1460fs*9
MTAP loss
PIK3R1 Y452_R461>I
BCL6 N73S
CDKN2A/B CDKN2A loss, CDKN2B loss
MAP2K4 loss exons 2-11
TP53 R196Q - subclonal†

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

† See About the Test in appendix for details.

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Selumetinib** (p. 8), **Trametinib** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section	
GENOMIC FINDINGS	**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)**	**THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)**
***NF1* -** H1460fs*9	none	Selumetinib
10 Trials *see p. 10*		Trametinib
***MTAP* -** loss	none	none
1 Trial *see p. 9*		
***PIK3R1* -** Y452_R461>I	none	none
4 Trials *see p. 12*		

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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.

BCL6 - N73S ..... p. 5
CDKN2A/B - CDKN2A loss, CDKN2B loss ..... p. 6
MAP2K4 - loss exons 2-11 ..... p. 6
TP53 - R196Q - subclonal ..... p. 7

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
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-H is generally infrequent in NSCLC, reported in fewer than 1% of samples across several large studies[6-11], whereas data on the reported incidence of MSI-H in SCLC has been limited and conflicting[12-15]. 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[6]. 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[16]. 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[16-18]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[19-21]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16,18,20-21].

BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

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[22-24], anti-PD-1 therapies[22-25], and combination nivolumab and ipilimumab[26-31]. 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);[22-23,26-28,32-39]. Improved OS of patients with NSCLC treated with pembrolizumab plus chemotherapy relative to chemotherapy only[40], or those treated with nivolumab plus ipilimumab also relative to chemotherapy[41], has been observed across all TMB levels.

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[42]. 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[43]. Although some studies have reported a lack of association between smoking and mutational burden in NSCLC[44-45], several other large studies did find a strong association with increased TMB[46-49]. 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[50]. 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)[44]. 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[51]. However, no significant prognostic association of TMB and/or PD-L1 status with survival has been reported in patients with lung SCC[51-52].

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[53-54] and cigarette smoke in lung cancer[32,55], treatment with temozolomide-based chemotherapy in glioma[56-57], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[58-62], and microsatellite instability (MSI)[58,61-62]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[22-23,26-28,32-39,63].

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GENE
NF1

ALTERATION
H1460fs*9

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
4378delC

VARIANT ALLELE FREQUENCY (% VAF)
37.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[64-67], glioma or glioblastoma[67-71], and non-small cell lung cancer[72], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. Loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus, based on limited clinical data[73-75] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[76-77]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[78]. 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[79], 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[80].

FREQUENCY & PROGNOSIS

NF1 mutation has been observed in 6.9-11% of lung adenocarcinoma cases[81] and 7.7-11% of lung squamous cell carcinoma cases[82-84]. Published data investigating the prognostic implications of NF1 alteration in lung cancer are limited (PubMed, Feb 2021). However, decreased NF1 expression was reported in 2 lung adenocarcinoma samples after disease progression on first generation EGFR inhibitor and afatinib; neither sample harbored EGFR T790M mutation[85].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[86]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[87]. Alterations such as seen here may disrupt NF1 function or expression[87-96].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[97-99]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[100-101], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[102]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[103]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[102,104-105], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[106]; dual PRMT1 and PRMT5 inhibition may be more effective[107-109]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[110-120]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and stable disease in 23.6% (13/55) of patients[121].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[122-123]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[124], gastrointestinal stromal tumors[125], mantle cell lymphoma (MCL)[126], melanoma[127-128], gastric cancer[129], myxofibrosarcoma[130], nasopharyngeal carcinoma[131], ovarian carcinoma[122] and non-small cell lung cancer[132]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[133] or in astrocytoma[134]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[135], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[136]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[137-138], esophageal cancer[139-140], osteosarcoma[141], and CRC[142].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[143-144]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[124,145-146], thereby reducing intracellular arginine methylation[102,104,147] and altering cell signaling[146,148]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

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GENE
PIK3R1

ALTERATION
Y452_R461>I

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
1354_1382>AT

VARIANT ALLELE FREQUENCY (% VAF)
8.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical[149-150] and preclinical[151-152] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[149], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[153]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[152,154-157] or AKT[158-159]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[160].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[58], glioblastoma (GBM; 11%)[161], uterine carcinosarcoma (11%)(cBioPortal, Jan 2022)[83-84], and lower grade glioma (5%)[162]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[163-165], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[163]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[166] and metastasis-free survival in breast cancer[167]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[168].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[169]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[170-173], promote tumorigenesis[151,158,170], and promote hyperplasia in the context of PTEN-deficiency[174]. Alterations such as seen here may disrupt PIK3R1 function or expression[152,159-160,164-165,175-183].

GENE
BCL6

ALTERATION
N73S

TRANSCRIPT ID
NM_001706

CODING SEQUENCE EFFECT
218A>G

VARIANT ALLELE FREQUENCY (% VAF)
50.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to directly target alterations in BCL6.

FREQUENCY & PROGNOSIS

BCL6 mutations have been reported in <1% of lung adenocarcinomas and in 3% of lung squamous cell carcinomas[81-82]. BCL6 has been shown to methylated in non-small cell lung cancer (NSCLC), and BCL6 mRNA levels were downregulated in analyzed NSCLC samples[184]. The prognostic impact of BCL6 alterations in the context of non-small cell lung carcinoma has not been extensively investigated (PubMed, Apr 2021).

FINDING SUMMARY

BCL6 encodes B-cell lymphoma protein 6, a transcriptional repressor involved in the normal development of B-lymphocytes[185]. This gene is frequently rearranged or mutated in lymphomas[186], having been observed in follicular lymphoma (FL)[187], DLBCL[188-190], Hodgkin's lymphoma[191] and in MALT lymphoma[192], where they are thought to promote transformation to large cell marginal zone B-cell lymphoma (MZBCL)[193]. These events typically occur in the 5' regulatory region and lead to increased expression of BCL6[194-195]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[196-199]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[200-201], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[202-208]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[209-210], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[203,205-206,211-213].

FREQUENCY & PROGNOSIS

CDKN2A/B loss and CDKN2A mutation have been reported in approximately 19% and 4% of lung adenocarcinomas, respectively[81]. CDKN2A/B loss and CDKN2A mutation have been reported in 26% and 17% of lung squamous cell carcinoma (SCC) samples analyzed in the TCGA dataset, respectively[82]. Loss of p16INK4a protein expression, through CDKN2A mutation, homozygous deletion, or promoter methylation, has been described in 49-68% of non-small cell lung cancer (NSCLC) samples, whereas low p14ARF protein expression has been detected in 21-72% of NSCLC samples[82,214-219]. In patients with lung SCC, loss of CDKN2B associated with poor survival in one study[220]. Loss of p16INK4a protein as well as CDKN2A promoter hypermethylation correlate with poor survival in patients with NSCLC[216,221-223].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[224-225]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[215,226]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[227-228]. One or more alterations observed here are predicted to result in p16INK4a loss of function[229-250]. One or more alterations seen here are predicted to result in p14ARF loss of function[233,250-253]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[254].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[255]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[256-257]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[258-260]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[261-263]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MAP2K4

ALTERATION
loss exons 2-11

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies to address MAP2K4 loss or inactivation.

FREQUENCY & PROGNOSIS

MAP2K4 mutation has been reported in 1% of lung adenocarcinoma samples and <1% of lung squamous cell carcinoma samples analyzed in the TCGA datasets[81-82]. In these same datasets, deletion of MAP2K4 was reported in 2% of lung adenocarcinoma samples, but not in any lung squamous cell carcinoma samples[81-82]. Whether MAP2K4 acts as an oncogene[264-265] or tumor suppressor[266-268] in the context of lung cancer is unclear. Published data investigating the prognostic implications of MAP2K4 in lung cancer are limited (PubMed, Feb 2021).

FINDING SUMMARY

MAP2K4 encodes the protein kinase MKK4, a member of a MAPK signaling cascade that leads to apoptosis in response to cellular stress[266]. MAP2K4 has been proposed to act as a tumor suppressor in several cancer types, including pancreatic cancer, but has also been suggested to act as an oncogene in certain situations[264-270]. Alterations such as seen here may disrupt MAP2K4 function or expression[267,269,271-272].

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GENE
TP53

ALTERATION
R196Q - subclonal

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
587G>A

VARIANT ALLELE FREQUENCY (% VAF)
0.81%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[273-276], or p53 gene therapy and immunotherapeutics such as SGT-53[277-281] and ALT-801[282]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[283]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[284]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[285]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[286]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[287]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[288]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[281]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[289]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[290-292]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[293]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[294-295]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[296-297]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is one of the most commonly mutated genes in lung cancer; mutations have been reported in 43-80% of non-small cell lung cancers (NSCLCs)[81-82,218,298-302], including 42-52% of lung adenocarcinomas and 58-83% of lung squamous cell carcinomas (cBioPortal, COSMIC, Feb 2021)[48-49,81-82]. TP53 homozygous deletion has been observed in 1.4% of lung adenocarcinoma and <1% of lung squamous cell carcinoma cases (cBioPortal, Feb 2021)[83-84]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[303]. Mutations in TP53 have been associated with lymph node metastasis in patients with lung adenocarcinoma[304].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[305]. Alterations such as seen here may disrupt TP53 function or expression[306-310].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[311-313], including sarcomas[314-315]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[316] to 1:20,000[315]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[317]. In the appropriate clinical context, germline testing of TP53 is recommended.

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[318-323]. 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[318-319]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[324]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[322,325-326]. 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 Erik Williams, M.D. | 13 January 2022
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Selumetinib

Assay findings association

NF1
H1460fs*9

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 in neurofibromatosis type 1 (NF1)-associated neurofibroma[64-67,327-331] , glioma[67-71,332] , and non-small cell lung cancer[72], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

In the Phase 2 umbrella trial National Lung Matrix Trial, selumetinib plus docetaxel yielded an ORR of 29% (4/14) for patients with lung adenocarcinoma harboring NF1 loss[72]. 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[333]. 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[334]. A Phase 2 study of selumetinib combined with docetaxel for patients with advanced or metastatic KRAS wild-type NSCLC who were previously treated did not report improved survival benefit compared to docetaxel alone[335]. 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[336]. 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[337]. 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)[338].

Trametinib

Assay findings association

NF1
H1460fs*9

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

On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[64-67,327-331] , glioma[67-71,332] , and non-small cell lung cancer[72], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA

Phase 1 and 2 monotherapy trials of MEK inhibitors such as trametinib and RO4987655 have shown low response rates in patients with non-small cell lung cancer (NSCLC), irrespective of KRAS mutation status, and no improvement in PFS compared to docetaxel[339-341] . 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[342-344] . 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[345]. 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[346-348] . 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[349]. 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[79], 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[80].

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.

ORDERED TEST # ORD-1275918-01

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
MTAP

ALTERATION
loss

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors.

NCT03435250

PHASE 1

Study of AG-270 in Participants With Advanced Solid Tumors or Lymphoma With MTAP Loss

TARGETS
MAT2A

LOCATIONS: Tennessee, New York, Connecticut, Massachusetts, Barcelona (Spain), Villejuif Cedex (France)

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GENE
NF1

ALTERATION
H1460fs*9

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03600701

PHASE 2

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

TARGETS
PD-L1, MEK

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

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

NCT01737502

PHASE 1/2

Sirolimus and Auranofin in Treating Patients With Advanced or Recurrent Non-Small Cell Lung Cancer or Small Cell Lung Cancer

TARGETS
mTOR

LOCATIONS: Florida

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

NCT03334617

PHASE 2

Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy.

TARGETS
PD-L1, PARP, mTORC1, mTORC2, ATR, CD73, STAT3

LOCATIONS: Texas, Tennessee, Virginia, District of Columbia, Maryland, Missouri, Pennsylvania, New York, Massachusetts

NCT03337698

PHASE 1/2

A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus- Non-Small Cell Lung Cancer)

TARGETS
PD-L1, MEK, CEA, CXCR4, EZH2, MDM2, ADORA2A

LOCATIONS: Tennessee, Ohio, Nevada, Malaga (Spain), Madrid (Spain), Valencia (Spain), Pamplona (Spain), Saint Herblain (France), Barcelona (Spain), Toulouse (France)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

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, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Exeter (United Kingdom), Belfast (United Kingdom), Cardiff (United Kingdom), Bristol (United Kingdom), Wirral (United Kingdom), Southampton (United Kingdom), Glasgow (United Kingdom), Birmingham (United Kingdom), Manchester (United Kingdom), Oxford (United Kingdom)

NCT04185831

PHASE 2

A MolEcularly Guided Anti-Cancer Drug Off-Label Trial

TARGETS
PD-L1, MEK, mTOR

LOCATIONS: Gothenburg (Sweden), Uppsala (Sweden)

GENE
PIK3R1

ALTERATION
Y452_R461>I

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors.

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Texas, Maryland

NCT04895579

PHASE 1

Lung Cancer With Copanlisib and Durvalumab

TARGETS
PD-L1, PI3K

LOCATIONS: Kentucky

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.

CDH1
G661D

CIC
K468R

HGF
loss

KDM5C
R828Q

PARP3
I452F

RAD51D
G74R

TP53
P34R

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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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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 1,017x

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Electronically signed by Erik Williams, M.D. | 13 January 2022
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