FOUNDATIONONE® CDx

PATIENT
Humayun, Asaf

TUMOR TYPE
Unknown primary adenocarcinoma

COUNTRY CODE
PK

REPORT DATE
02 Jan 2024

ORDERED TEST #
ORD-1784930-01

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 Unknown primary adenocarcinoma
NAME Humayun, Asaf
DATE OF BIRTH 28 December 1952
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN
ORDERING PHYSICIAN Raza, Saqib
MEDICAL FACILITY AGA KHAN UNIVERSITY HOSPITAL
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205838
PATHOLOGIST Ansar Ahmad, Zeeshan

SPECIMEN
SPECIMEN SITE Pancreas
SPECIMEN ID 2023:PS54903 10
SPECIMEN TYPE Block
DATE OF COLLECTION 13 July 2023
SPECIMEN RECEIVED 22 December 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

AKT3 amplification - equivocal†
KRAS G12D
MTAP loss
CDKN2A/B CDKN2A loss, CDKN2B loss
KDM5C Q1279fs*24
RBM10 T886fs*94
TP53 R175H

† See About the Test in appendix for details.

Report Highlights

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

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 2 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)
AKT3 **-** amplification - equivocal	none	none
10 Trials see p. 10		
KRAS **-** G12D	none	none
10 Trials see p. 12		
MTAP **-** loss	none	none
4 Trials see p. 14		

Electronically signed by Erik Williams, M.D. | 02 January 2024
Lauren L. Ritterhouse Casariego, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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.

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[4-5]. 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)[6].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)[7-14], colorectal cancers (CRCs; 10-15%)[3,15-18], and gastric cancers (12-35%)[19-22] and at lower frequencies in many other tumor types, including esophageal[23-24], small bowel[25-30], hepatobiliary[31-37], prostate[38-41], and urinary tract carcinomas[42-45]. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy[46]. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting[7,10-11,13,47-49]. However, studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[9,12,14,48], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

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 MMR in the tumor[17]. 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[17,50-51]. 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[16,52-53]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[16-17,51,53].

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BIOMARKER

Tumor Mutational Burden

RESULT
2 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[54-57], anti-PD-1 therapies[55-59], and combination nivolumab and ipilimumab[60-68]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[54-57,59,69-73]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[69]; similar findings were observed in the KEYNOTE 028 and 012 trials[59]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[73]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[74]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[72]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[54] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[56].

FREQUENCY & PROGNOSIS

Carcinomas that have been reported to harbor the highest frequencies of elevated TMB include colorectal (CRC) (8-25%)[18,75-77], endometrial (7-24%)[78-80], intestinal type gastric (20%)[78], and non-small cell lung carcinoma (NSCLC; 8-13%)[81-82] . In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[83], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[81]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[83-85], several other large studies did find a strong link[86-89]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[18,77] and with microsatellite instability (MSI)[75-77], which in turn has been reported to correlate with better prognosis[15,90-96]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[80,97-99] and bladder cancer[100], it is also linked with improved prognosis in patients with these tumor types[80,101].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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[102-103] and cigarette smoke in lung cancer[104-105], treatment with temozolomide-based chemotherapy in glioma[106-107], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[18,80,108-110], and microsatellite instability[18,80,110]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[56-57,69].

GENE
AKT3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Activating alterations in AKT3 may predict sensitivity to inhibitors of AKT kinases or the downstream mTOR pathway[111]. Clinical benefit has been achieved for patients with AKT3-amplified solid tumors treated with an mTOR inhibitor[111-113].

FREQUENCY & PROGNOSIS

AKT3 amplification has been identified in 0-1% of various solid tumor types, including breast cancer, melanoma, salivary gland cancer, small cell lung cancer, uterine sarcoma, endometrial cancer, hepatobiliary cancer, ovarian cancer, and other cancer types[114]. Copy number increases of AKT3 have been found to contribute to overexpression of AKT3 protein and increased AKT3 kinase activity observed in some tumor types, such as melanoma[115]. High stromal expression of AKT3 and PI3K has been reported to be correlated with good prognosis in non-small cell lung cancer (NSCLC)[116]. However, AKT activation has been reported to be associated with poor prognosis in patients with breast cancer[117].

FINDING SUMMARY

AKT3 encodes PKB-gamma, an intracellular serine/threonine kinase. AKT3 is one of three members of the AKT gene family, and activation of AKT3 has been implicated in melanoma and breast cancer[118]. AKT3 has been reported to be amplified in cancer[119] and may be biologically relevant in this context[120-121].

GENE
KRAS

ALTERATION
G12D

HGVS VARIANT
NM_004985.3:c.35G>A (p.G12D)

VARIANT CHROMOSOMAL POSITION
chr12:25398284

VARIANT ALLELE FREQUENCY (% VAF)
14.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

While clinical responses have been reported for patients with KRAS-mutated ovarian[122-126], cervical small cell neuroendocrine[127], or uterine cancer[125] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[128-132], pancreatic cancer[133-135], and NSCLC[130,136-137]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[138]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[139-141] and KRAS-mutated endometrioid adenocarcinoma[142]. Preclinical data suggests that KRAS G12D mutations may predict sensitivity to KRAS G12D small-molecule inhibitors, such as MRTX1133[143-147] and RMC9805[148]. Preclinical and clinical data suggest that solid tumors with KRAS mutations, such as G12D and G12V, may benefit from adoptive cell therapy targeting these specific KRAS mutations[149-152]. KRAS G12D-targeted adoptive cell therapy has yielded PRs for 3 pretreated patients with metastatic pancreatic adenocarcinoma[149], colorectal cancer (CRC)[150], and non-small cell lung cancer (NSCLC)[153], respectively. Multiple studies of MEK inhibitors, either as a single-agent or in combination with chemotherapy, have reported low response rates or response rates similar to those of chemotherapy alone for patients with KRAS-mutated non-small cell lung cancer (NSCLC)[130,136-137,154-155]; however, limited clinical data support investigational approaches targeting MEK in KRAS-mutated solid tumors including the combination of the MEK inhibitor mirdametinib and the CDK4/6 inhibitor palbociclib[156] and the dual MEK-pan-RAF inhibitor CH5126766 alone or with the FAK inhibitor defactinib[157-159]. Additional approaches to treat RAS-addicted solid tumors include targeting SOS1 (BI-3406, MRTX0902, BI-1701963, and BAY-293)[160-170] or SHP2 (RMC-4630, TNO155)[171-175], either alone or in combination with other targeted therapies; clinical benefit has been observed following treatment with RMC-4630 across KRAS mutations (including mutations at G12)[171].

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 19% of tumor samples analyzed in COSMIC, including pancreatic (52%), peritoneal (45%), large intestinal (32%), small intestinal (23%), biliary tract (18%), endometrial (16%), ovarian (15%), and lung (14%) tumors (Mar 2023)[176]. Mutations in KRAS have been reported in 32-54% of colorectal cancer cases, with the G12C, G12V, and G13D mutations specifically identified in 7-11%, 26-32%, and 16-24% of cases, respectively[177-182]. Additionally, an activating KRAS mutation has been reported in more than 80% of pancreatic adenocarcinomas, with the majority of mutations found at codon 12[183-186]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[184]. One study found that KRAS mutations were correlated with shorter PFS and OS in cancer of unknown primary (CUP) tumors[187].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[188-189]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, K117R, and K117N have been characterized as activating and oncogenic[188,190-212].

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— **Targeted Therapies** —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A[213-215] or PRMT5 inhibition[214,216-217]. 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[215]. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors[218], dual PRMT1 and PRMT5 inhibitors[219-221], and PRMT5 inhibitors that selectively bind PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193[222-223]. Clinically, 6 PRs were reported in a Phase 1 trial of MRTX1719 for 6 patients with various advanced solid tumors harboring MTAP loss[223]. In preclinical models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA[224-234]. 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 SD for 24% (13/55) of patients[235]. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed[236].

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[237-238]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[239], gastrointestinal stromal tumors[240], mantle cell lymphoma (MCL)[241], melanoma[242-243], gastric cancer[244], myxofibrosarcoma[245], nasopharyngeal carcinoma[246], ovarian carcinoma[237] and non-small cell lung cancer[247]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[248] or in astrocytoma[249]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[250], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[251]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[252-253], esophageal cancer[254-255], osteosarcoma[256], and CRC[257].

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[258-259]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[239,260-261], thereby reducing intracellular arginine methylation[214,216-217] and altering cell signaling[261-262]. 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.

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[263-266]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[267] and palbociclib treatment[268-269]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[270-276]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[271,273-274,277-279], direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited[280-281]. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[282-283], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

In the TCGA datasets, concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in several tumor types, with the highest incidences in glioblastoma multiforme (54%), mesothelioma (45%), esophageal adenocarcinoma (39%), bladder urothelial carcinoma (31%), melanoma (31%), and HNSCC (30%) cases (cBioPortal, Jan 2023)[119,284]. In addition, mutation of CDKN2A has been reported in 45% of cutaneous SCC[285], 21% of HNSCC[286], 17% of lung SCC[287], and 3-4.5% of esophageal SCC[288-289] cases. Loss of p16INK4a expression has been reported in 67-80% of pancreatic ductal adenocarcinomas[290-291] and in 59% of NSCLCs[292]. Inactivation of CDKN2A and/or CDKN2B and loss of p16INK4a and/or p15INK4b protein expression have been correlated with poor patient prognosis in several tumor types, including pancreatic ductal adenocarcinoma, gastric cancer, and lung cancer[290,293-299].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[300-301]. 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[302-303]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[304-305]. One or more alterations observed here are predicted to result in p16INK4a loss of function[306-327]. One or more alterations seen here are predicted to result in p14ARF loss of function[310,327-330]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[331].

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[332]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[333-334]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[335-337]. 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[338-340]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
KDM5C

ALTERATION
Q1279fs*24

HGVS VARIANT
NM_004187.3:c.3834delinsTCA (p.Q1279Hfs*24)

VARIANT CHROMOSOMAL POSITION
chrX:53223525

VARIANT ALLELE FREQUENCY (% VAF)
36.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in KDM5C.

FREQUENCY & PROGNOSIS

In a pan-cancer analysis, KDM5C alterations were detected in 2.1% of cases, with the highest frequencies reported in esophagogastric cancer, endometrial cancer, and renal cell carcinoma[341]. Retrospective analysis of 271 nonredundant studies from cBioPortal (n=45,614) showed KDM5C alterations to associate with shorter OS (53 vs. 102 months, HR=1.31)[341]; however, KDM5C alterations have been associated with improved OS for patients treated with immune checkpoint inhibitors across tumor types[341], including non-small cell lung cancer (NSCLC)[342].

FINDING SUMMARY

KDM5C encodes a histone lysine demethylase that acts, along with related histone-modifying enzymes, to control gene expression in response to developmental and environmental cues[343]. In addition to its role as a histone-modifying demethylase, KDM5C has been suggested to play a role in regulation of the SMAD3 signal transduction response to TGF-beta, a role that would be consistent with function as a tumor suppressor[344]. Germline inactivating mutations in KDM5C cause an X-linked intellectual disability syndrome also characterized by short stature and hyperreflexia[345].

GENE
RBM10

ALTERATION
T886fs*94

HGVS VARIANT
NM_005676.3:c.2654dup (p.T886Nfs*94)

VARIANT CHROMOSOMAL POSITION
chrX:47045772

VARIANT ALLELE FREQUENCY (% VAF)
17.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies approved or clinical trials that directly address genomic alterations in RBM10.

FREQUENCY & PROGNOSIS

Mutations in RBM10 have been identified in numerous cancers at low frequencies, including non-small cell lung cancer (NSCLC) (7.4%), bladder cancer (5.4%), and thyroid cancer (4.6%)[114,346]. Several reports have analyzed the prognostic relevance of RBM10 mutations and expression levels in cancer, but results have been mixed. RBM10 mutations were associated with shorter OS in lung adenocarcinomas[347-348], but with enhanced survival in pancreatic ductal adenocarcinomas compared with RBM10 wildtype tumors[349]. Low RBM10 expression was associated with poor prognosis and shorter OS in patients with hepatocellular carcinoma (HCC) and pancreatic ductal cancer[350-351], while in lung adenocarcinoma, it was associated with a better prognosis and longer OS[352].

FINDING SUMMARY

RBM10 encodes RNA binding motif protein 10, a nuclear RNA-binding protein involved in the regulation of alternative splicing[353-354]. Germline mutations in RBM10 cause TARP syndrome, an X-linked recessive disorder characterized by the development of micrognathia, glossoptosis, and cleft palate[355-356]. RBM10-TFE3 fusions have been reported recurrently in Xp11.2 translocation-positive renal cell carcinomas (RCCs)[357-362] and rarely in PEComa[363-364].

GENE
TP53

ALTERATION
R175H

HGVS VARIANT
NM_000546.4:c.524G>A (p.R175H)

VARIANT CHROMOSOMAL POSITION
chr17:7578406

VARIANT ALLELE FREQUENCY (% VAF)
14.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical and preclinical data suggest that solid tumors with TP53 mutations, such as R175H, Y220C, G245S, and R248W, may benefit from adoptive cell therapy targeting these specific TP53 mutations[153,365]. Clinical benefit has been reported for patients with breast cancer (2 PRs)[365], ovarian cancer (1 PR)[365], and colorectal cancer (CRC; 1 SD)[153] treated with tumor infiltrating lymphocyte-based or modified T-cell receptor-based adoptive cell therapy. 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[366-369] or p53 gene therapy such as SGT53[370-375]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[376]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[377-378]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[139]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[379]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[380]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[381]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[375]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[382]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[383].

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[384]. TP53 loss of heterozygosity (LOH) is frequently seen in tumors and often occurs when one copy of TP53 harbors a mutation; in some tumors, LOH is correlated with progression[385-388]. While the prognostic significance of TP53 alteration or dysregulation varies according to tumor type, studies have shown an association with poor prognosis for patients with breast cancer[389-391], endometrial cancer[392-393], HNSCC[394-396], or urothelial cancer[397-398]. In 1 study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutational burden, and neoantigen presentation; likely as a consequence of this association, TP53 mutations correlated with improved clinical outcomes to the PD-1 inhibitors pembrolizumab and nivolumab in this study[399]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[400-401].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[402]. Alterations such as seen here may disrupt TP53 function or expression[403-407].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 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 Li-Fraumeni syndrome (ClinVar, Sep 2023)[408]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[409-411], including sarcomas[412-413]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[414] to 1:20,000[413]. 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[415]. 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[416-421]. 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[416-417]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[422]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[420,423-424]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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
AKT3

ALTERATION
amplification - equivocal

RATIONALE
AKT3 amplification may lead to AKT-mTOR pathway activation and may predict sensitivity to inhibitors of this pathway.

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

LOCATIONS: Berlin (Germany), München (Germany), Würzburg (Germany), Lübeck (Germany), Tübingen (Germany), Heidelberg (Germany), Mainz (Germany)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
ALK, ROS1, AXL, TRKA, MET, TRKC, EGFR, PARP, CDK4, CDK6, mTOR, MEK, BRAF, SMO

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

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03673787

PHASE 1/2

A Trial of Ipatasertib in Combination With Atezolizumab

TARGETS
AKTs, PD-L1

LOCATIONS: Sutton (United Kingdom)

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Vermont, New Hampshire, Massachusetts, New York, Connecticut

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT05125523

PHASE 1

A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors

TARGETS
mTOR

LOCATIONS: Tianjin (China)

GENE
KRAS

ALTERATION
G12D

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. Preclinical and clinical evidence suggest that KRAS G12D mutations may confer sensitivity to KRAS G12D-targeted, T-cell-receptor-based adoptive cell therapy, KRAS G12D small-molecule inhibitors, or SOS1 inhibitors.

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, RET, PDGFRA, VEGFRs, KIT, MEK

LOCATIONS: Guangzhou (China)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

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

LOCATIONS: Berlin (Germany), München (Germany), Würzburg (Germany), Lübeck (Germany), Tübingen (Germany), Heidelberg (Germany), Mainz (Germany)

NCT04116541

PHASE 2

A Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations/ Characteristics in Advanced / Metastatic Tumors.

TARGETS
CDK6, CDK4, MDM2, MET, ROS1, RET, VEGFRs, ALK, BRAF, KIT, MEK

LOCATIONS: Strasbourg (France), Nice (France), Marseille (France), Lyon (France), Villejuif (France), Toulouse (France), Bordeaux (France)

NCT05737706

PHASE 1/2

Study of MRTX1133 in Patients With Advanced Solid Tumors Harboring a KRAS G12D Mutation

TARGETS
KRAS

LOCATIONS: Massachusetts, Connecticut, New York, Washington, Maryland, Michigan, Virginia, Tennessee, Florida, Arizona

NCT05554367

PHASE 2

Palbociclib and Binimetinib in RAS-Mutant Cancers, A ComboMATCH Treatment Trial

TARGETS
CDK4, CDK6, MEK

LOCATIONS: Idaho, Montana, Michigan

NCT05578092

PHASE 1/2

A Phase 1/2 Study of MRTX0902 in Solid Tumors With Mutations in the KRAS MAPK Pathway

TARGETS
SOS1, KRAS

LOCATIONS: Washington, Maryland, Virginia, Oregon, Ohio, Tennessee, Colorado, Texas

NCT05159245

PHASE 2

The Finnish National Study to Facilitate Patient Access to Targeted Anti-cancer Drugs

TARGETS
BRAF, VEGFRs, RET, KIT, ERBB2, TRKB, ALK, TRKC, ROS1, TRKA, SMO, PD-L1, MEK, CDK4, CDK6

LOCATIONS: Helsinki (Finland), Kuopio (Finland), Tampere (Finland), Turku (Finland)

NCT05533463

PHASE 1

Phase I Study of HRS-4642 in Patients With Advanced Solid Tumors Harboring KRAS G12D Mutation

TARGETS
KRAS

LOCATIONS: ShangHai (China)

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Fredrikstad (Norway), Oslo (Norway), Hamar (Norway), Drammen (Norway), Skien (Norway), Tromsø (Norway), Kristiansand (Norway), Bodø (Norway), Trondheim (Norway), Stavanger (Norway)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Seoul (Korea, Republic of), Marseille (France), Busan (Korea, Republic of), Edegem (Belgium), Barcelona (Spain), Madrid (Spain), Clayton (Australia), Toronto (Canada), Pennsylvania, Oregon

GENE
MTAP

ALTERATION
loss

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05094336

PHASE 1/2

AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Hong Kong (Hong Kong), Shatin, New Territories (Hong Kong), Graz (Austria), Salzburg (Austria), Tainan (Taiwan), Taoyuan (Taiwan), Taipei (Taiwan), Halle (Saale) (Germany), Ulm (Germany), Wuerzburg (Germany)

NCT05732831

PHASE 1/2

Safety and Tolerability of TNG462 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Lyon (France), Barcelona (Spain), Madrid (Spain), Massachusetts, New York, Tennessee, Utah, Villejuif (France), Florida, Texas

NCT05275478

PHASE 1/2

Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Lyon (France), Massachusetts, New York, Virginia, Missouri, Tennessee, Villejuif (France), Texas

NCT05245500

PHASE 1/2

Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion

TARGETS
PRMT5-MTA

LOCATIONS: Massachusetts, New York, Virginia, Wisconsin, Minnesota, Tennessee, Colorado, Florida

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.

ALOX12B
NM_001139.2: c.1766C>T
(p.T589I)
chr17:7976626

ATM
NM_000051.3: c.2698A>G
(p.M900V)
chr11:108139196

CBL
NM_005188.2: c.2269G>A
(p.A757T)
chr11:119169085

FANCA
NM_000135.2: c.2777A>G
(p.H926R)
chr16:89831299

FH
amplification

GRM3
NM_000840.2: c.1112G>A
(p.R371H)
chr7:86416220

LTK
NM_002344.5: c.652T>A
(p.F218I)
chr15:41804020

MSH2
NM_000251.1: c.66C>A
(p.F22L)
chr2:47630396

MST1R
NM_002447.2: c.2194G>T
(p.G732W)
chr3:49934313

POLD1
NM_002691.2: c.581C>G
(p.S194C)
chr19:50905373

TEK
amplification

TENT5C (FAM46C)
NM_017709.3: c.163G>A
(p.V55I)
chr1:118165653

APPENDIX Genes Assayed in FoundationOne®CDx

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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

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

Electronically signed by Erik Williams, M.D. | 02 January 2024
Lauren L. Ritterhouse Casariego, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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 PRINCIPLE

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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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. 2023. 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 fraction-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-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. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. 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.
6. 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.
7. 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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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 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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.15.0
MR Reporting Config Version Config 49
Analysis Pipeline Version v3.29.0
Computational Biology Suite Version 6.29.0

The median exon coverage for this sample is 678x

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FOUNDATION MEDICINE®

Patient Name	Humayun, Asaf	Report Date	28 December 2023

Date of Birth	28 December 1952	Medical Facility	AGA KHAN UNIVERSITY HOSPITAL		
Sex	Male	Ordering Physician	Saqib Raza		
FMI Case #	ORD-1784930-02	Additional Recipient	Not Provided	Specimen Received	22 December 2023
Medical Record #	Not Provided			Date of Collection	13 July 2023
Specimen ID	2023:PS54903 10	Medical Facility #	205838	Specimen Type	FFPE Block-Pancreas
		Pathologist	Ansar Ahmad, Zeeshan		

PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)

Patient Result

*Tumor Proportion Score (TPS) (%)** 0

** See tables 1 and 2 for interpretation.*

Electronically signed by: Naomi Lynn Ferguson, MD Date: 28 December 2023 10:39:43

Table 1: TPS Companion Diagnostic Indications

Tumor Indication	PD-L1 Expression Level	Intended Use
Non-Small Cell Lung Cancer (NSCLC)	TPS ≥1%	PD-L1 IHC 22C3 pharmDx™ is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab).†
	TPS ≥50%	PD-L1 IHC 22C3 pharmDx™ is indicated as an aid in identifying NSCLC patients for treatment with LIBTAYO® (cemiplimab-rwlc).‡

† See the KEYTRUDA® product label for specific clinical circumstances guiding PD-L1 testing.

‡ See the LIBTAYO® product label for specific clinical circumstances guiding PD-L1 testing.

Table 2: Other Tumor Types

Tumor Indication	PD-L1 Expression Level	Intended Use
Non-Companion Diagnostic Tumor Type	TPS cut-off criteria for other tumor types have not been defined for this assay by the US FDA.	N/A

Lauren L. Ritterhouse Casariego, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Performing Laboratory: 7010 Kit Creek Road, Morrisville, NC 27560 · CLIA: 34D2044309

Methodology
PD-L1 IHC 22C3 pharmDx™ is a qualitative immunohistochemical assay using mouse monoclonal anti-PD-L1. Clone 22C3 is intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), esophageal squamous cell carcinoma (ESCC), cervical cancer, head and neck squamous cell carcinoma (HNSCC), and triple-negative breast cancer (TNBC) tissues using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression in NSCLC is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. This product is intended for in vitro diagnostic use. For additional information, refer to the PD-L1 IHC 22C3 pharmDx™ Package Insert.

Clinical Significance of PD-L1 Protein Expression
Programmed death-ligand 1 (PD-L1), expressed on tumor cells and tumor-infiltrating immunocytes, mediates an immune checkpoint by binding to its receptors, programmed death 1 (PD-1) and B7-1, on activated T cells[1–4]. This checkpoint represses T-cell function and can therefore lead to evasion of anti-tumor immunity. On the basis of extensive clinical evidence in various tumor types, PD-L1-positive tumors are more likely to respond to PD-1/PD-L1 checkpoint inhibitors; however, patients with PD-L1-negative tumors may also derive benefit from these agents[4–14]. Checkpoint inhibitors such as the PD-1 antibodies cemiplimab-rwlc, nivolumab, and pembrolizumab and the PD-L1 antibodies atezolizumab, avelumab, and durvalumab are US FDA approved to treat various tumor types.

Note
This test has been cleared or approved by the U.S. Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Foundation Medicine, Inc. per Clinical Laboratory Improvement Amendments (CLIA '88) requirements and in accordance with the College of American Pathologists (CAP).

General Limitations

- Immunohistochemical analysis is dependent on the handling and processing of tissue prior to staining; false negative or inconsistent results may be a consequence of pre-analytic variations.
- As with any immunohistochemistry test, a negative result means that the antigen was not detected, not that the antigen was absent in the cells or tissue assayed.
- This assay has not been validated on cytology samples, decalcified bone specimens, or on tissues with fixatives other than formalin. If any of these apply to the present specimen, results should be interpreted with caution.
- False-negative results may be caused by degradation of the antigen in tissue over time. Results should be interpreted with caution when specimens are not stained within the following cut section storage recommendations: when stored at 2-8°C (preferred), cut sections must be stained within 2 months (cervical cancer), 4.5 months (ESCC), 6 months (NSCLC and HNSCC), or 7.5 months (TNBC) of sectioning; when stored at 25°C, cut sections must be stained within 1 month (ESCC and cervical cancer), 4 months (HNSCC and TNBC), or 6 months (NSCLC).
- For additional information and comprehensive list of limitations, refer to the PD-L1 IHC 22C3 pharmDx™ Package Insert.

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