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 Bile duct adenocarcinoma

DATE OF BIRTH 11 February 1958
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Small Intestine
SPECIMEN ID 16-5336 9
SPECIMEN TYPE Block
DATE OF COLLECTION 21 August 2016
SPECIMEN RECEIVED 23 April 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

FBXW7 G423V
NF1 E2448*
CCND1 amplification - equivocal†
CTNNB1 S45F
ERBB3 Q809R
MTAP loss exons 2-8
CDKN2A/B CDKN2B loss, CDKN2A loss
EP300 Q341*
FGF19 amplification - equivocal†
FGF3 amplification - equivocal†
FGF4 amplification - equivocal†
SMAD4 R361H

1 Disease relevant genes with no reportable alterations: ***FGFR2***

† See About the Test in appendix for details.

4 Therapies with Clinical Benefit
0 Therapies with Lack of Response
25 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 1 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

Electronically signed by Matthew Hiemenz, M.D. | 05 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
FBXW7 - G423V	none	Everolimus
10 Trials *see p. 18*		Temsirolimus
NF1 - E2448*	none	Selumetinib
10 Trials *see p. 21*		Trametinib
CCND1 - amplification - equivocal	none	none
7 Trials *see p. 13*		
CTNNB1 - S45F	none	none
9 Trials *see p. 15*		
ERBB3 - Q809R	none	none
4 Trials *see p. 17*		
MTAP - loss exons 2-8	none	none
1 Trial *see p. 20*		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

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

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 has been variously reported in 0-42% of gallbladder carcinomas[6-12]. MSI-H is infrequent in cholangiocarcinoma, reported in 1% of samples[13]. A non-zero level of MSI has been reported in 18-49% of cholangiocarcinoma cases[14-17], although the studies did not specify what fraction of cases were MSI-H. A higher frequency of MSI (63%) was reported in patients with intrahepatic cholangiocarcinoma associated with exposure to Thorotrast[16]. No significant difference in median overall survival or prognosis was found in MSI-H gallbladder carcinomas when compared to MSS cases[6,10,12]. One study reported that MSI is associated with poor prognosis in liver fluke-related cholangiocarcinoma[15].

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[18]. 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[18-20]. 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[21-23]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[18,20,22-23].

BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[24-26], anti-PD-1 therapies[24-27], and combination nivolumab and ipilimumab[28-32]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[24-27,33]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[24]. 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[34] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[25]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[27,33]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Bile duct adenocarcinoma harbors a median TMB of 2.5 mutations per megabase (muts/Mb), and 2.6% of cases have high TMB (>20 muts/Mb)[35]. One study reported that hypermutated cases were enriched in a poor prognosis subgroup of patients with biliary tract cancer[36].

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[37-38] and cigarette smoke in lung cancer[39-40], treatment with temozolomide-based chemotherapy in glioma[41-42], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[43-47], and microsatellite instability (MSI)[43,46-47]. 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[25-26,33].

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GENE
FBXW7

ALTERATION
G423V

TRANSCRIPT ID
NM_033632

CODING SEQUENCE EFFECT
1268G>T

VARIANT ALLELE FREQUENCY (% VAF)
26.3%

POTENTIAL TREATMENT STRATEGIES
FBXW7 inactivating alterations may indicate sensitivity to mTOR inhibitors[48-49]. Several case studies reported clinical benefit for patients with FBXW7-mutated cancers, including lung adenocarcinoma[50], renal cell carcinoma[51], and cervical squamous cell carcinoma[52]. FBXW7 inactivation may also result in resistance to anti-tubulin chemotherapies based on results from preclinical studies[53].

FREQUENCY & PROGNOSIS
FBXW7 mutations were found in 35% (7/20) of cholangiocarcinomas in one study[54] and in 15% (3/20) of extrahepatic, compared to 5.5% (3/55) of intrahepatic cholangiocarcinomas in another[55]. FBXW7 mutations have been reported in 5% of biliary tract carcinomas in the COSMIC database (Sep 2020)[56] and 3% (1/32) of gallbladder carcinoma samples analyzed in one sequencing study[57]. Low FBXW7 protein expression was associated with increased metastasis or inferior survival in patients with cholangiocarcinoma[55,58].

FINDING SUMMARY
FBXW7 encodes the F-box protein subunit of the SCF ubiquitin ligase complex, which targets proteins for degradation[59]. FBXW7 inactivation is associated with chromosomal instability and with stabilization of proto-oncogenes, such as mTOR, MYC, cyclin E, NOTCH, and JUN; FBXW7 is therefore considered a tumor suppressor[54,59]. Alterations such as seen here may disrupt FBXW7 function or expression[54,60-66].

GENE
NF1

ALTERATION
E2448*

TRANSCRIPT ID
NM_001042492

CODING SEQUENCE EFFECT
7342G>T

VARIANT ALLELE FREQUENCY (% VAF)
35.3%

POTENTIAL TREATMENT STRATEGIES
On the basis of clinical evidence in neurofibromatosis type 1[67-68] and neurofibromatosis-associated glioma or glioblastoma[69-70], as well as extensive preclinical evidence in several tumor types[71-76], 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 the approved agents everolimus and temsirolimus, based on limited clinical data[77-79] and strong preclinical data in models of malignant peripheral nerve sheath tumor (MPNST)[80-81]. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient MPNST[82]. 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[83], 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[84]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS
NF1 mutation has been reported in 5.3% of pancreatic carcinomas, up to 4.0% of cholangiocarcinomas, 4.2% of bile duct adenocarcinomas, and 4.4% of gallbladder adenocarcinomas (COSMIC, Jul 2020)[56,85-88]. The prognostic significance of NF1 alteration in pancreatic and biliary tract carcinomas has not been determined (PubMed, Jul 2020).

FINDING SUMMARY
NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[89]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[90]. The consequences of alterations that may leave the GAP-related domain intact, such as seen here, are unclear; however, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

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[91-93]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[94-95], and in the appropriate clinical context, germline testing of NF1 is recommended.

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GENE
CCND1

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[96-101], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[100,102]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[103]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[103]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[104]. CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[105-106]; in these studies, CCND1 amplification was associated with significantly decreased response rate[106] and OS (HR=1.6-2.0)[105-106] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[105-106].

FREQUENCY & PROGNOSIS
CCND1 amplification has been reported in up to 2% of cholangiocarcinomas in large genomic studies and 11-25% (4/36 and 5/20) in smaller studies (cBioPortal, Jan 2021)[107-109]. Cyclin D1 overexpression has been reported in 41-68% of gallbladder carcinomas, intrahepatic and extrahepatic cholangiocarcinoma, as well as in preneoplastic bile duct lesions, gallbladder adenomas and low-grade dysplasias, suggesting cyclin D1 alteration is an early event in tumorigenesis[110-117]. Cyclin D1 overexpression has been associated with tumor progression in biliary intraepithelial neoplasia and intraductal papillary neoplasm of the bile duct, as well as in gallbladder mucosa hyperplasia, and with poor prognosis in extrahepatic cholangiocarcinoma and gallbladder cancer[110-111,115,118-119]. However, other studies have found no significant correlation between cyclin D1 expression and prognosis in biliary tract cancers, including gallbladder adenocarcinoma[120-121].

FINDING SUMMARY
CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[122] and may lead to excessive proliferation[123-124].

GENE
CTNNB1

ALTERATION
S45F

TRANSCRIPT ID
NM_001904

CODING SEQUENCE EFFECT
134C>T

VARIANT ALLELE FREQUENCY (% VAF)
24.7%

POTENTIAL TREATMENT STRATEGIES
Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[125-127]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[79,128] or endometrial carcinoma[129]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[130-132]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a PR rate in 2 out of 4 patients and SD rate of in 1 out of 4 patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[133]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[134-137]. Phase 1 and 2 clinical trials of gamma-secretase inhibitor PF-03084014 have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[138-139], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[126,140-142].

FREQUENCY & PROGNOSIS
CTNNB1 mutations have been reported in 0.6-1.0% of cholangiocarcinomas and 0.0-4.1% of gallbladder carcinomas[57,143-145]. Alterations in the beta catenin pathway, such as increased beta-catenin translocation to the nucleus and increased WNT/beta-catenin pathway activation, are commonly observed in intrahepatic cholangiocarcinoma[146-148]. Reduced beta-catenin expression, or reduced membrane localization, has been associated with poor differentiation, tumor size, and lymph node metastasis in intrahepatic cholangiocarcinoma[149-150]. Another study correlated reduced beta-catenin expression with tumor differentiation and tumor progression rather than tumor invasion and proliferation in this tumor context[151]. Preclinical studies targeting beta-catenin signaling in cholangiocarcinoma cell lines demonstrated reduced cell growth and apoptosis[148,152-154]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[155].

FINDING SUMMARY
CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[156]. CTNNB1 exon 3 mutations, such as observed here, lead to increased beta-catenin protein stability and activation of the WNT pathway, and are considered to be activating[157-175].

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GENE
ERBB3

ALTERATION
Q809R

TRANSCRIPT ID
NM_001982

CODING SEQUENCE EFFECT
2426A>G

VARIANT ALLELE FREQUENCY (% VAF)
51.7%

POTENTIAL TREATMENT STRATEGIES

ERBB3 cooperates with other ERBB family members, in particular ERBB2, for efficient signaling[176-179]. Therefore, ERBB3 amplification or activating mutation may predict sensitivity to therapies targeting ERBB2, including antibodies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1), and dual EGFR/HER2 TKIs such as lapatinib and afatinib. Preclinical studies support the sensitivity of cells with ERBB3 activating mutations to various anti-ERBB2 agents[178,180-181]. In a Phase 2 study of afatinib in platinum-refractory urothelial cancer, 2 patients with activating ERBB3 mutations but no EGFR or HER2 activating alterations experienced clinical benefit and PFS > 6 months[182]. Other studies in solid tumors have reported mixed efficacy for afatinib for patients with uncharacterized ERBB3 mutations[183-184]. Case studies report clinical benefit from lapatinib combined with either capecitabine[183] or trastuzumab[183,185] for patients with breast cancer harboring activating ERBB3 mutations. However, Phase 2 trials have suggested limited efficacy of other ERBB2-targeting TKIs against ERBB3 mutations, with no objective response to neratinib in any of 16 patients with ERBB3-mutated solid tumors[186] or dacomitinib in either of 2 patients with ERBB3-mutated cutaneous squamous cell carcinoma[187].

FREQUENCY & PROGNOSIS

ERBB3 mutation was reported in 11.8% (6/51) of gallbladder carcinomas in one study[57]. ERBB3 mutations were reported in 7% (2/28) of cholangiocarcinoma samples analyzed in one study[85] but in none of the analyzed samples in three other studies[86-88]. Another study of 47 gallbladder carcinomas and 57 cholangiocarcinomas reported ERBB3 overexpression in 19-34% of patients[188]. Mutation within the ERBB pathway has been correlated with shorter overall survival in patients with gallbladder carcinoma[57].

FINDING SUMMARY

ERBB3 (also known as HER3) encodes a member of the epidermal growth factor receptor (EGFR) family[189]. ERBB3 mutations such as observed here have been shown to be activating[57,178,181,190].

GENE
MTAP

ALTERATION
loss exons 2-8

POTENTIAL TREATMENT STRATEGIES

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[191]. 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[192]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[191,193-194], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[195]; dual PRMT1 and PRMT5 inhibition may be more effective[196-198]. 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[199-209]. 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[210].

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[211-212]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[213], gastrointestinal stromal tumors[214], mantle cell lymphoma (MCL)[215], melanoma[216-217], gastric cancer[218], myxofibrosarcoma[219], nasopharyngeal carcinoma[220], ovarian carcinoma[211] and non-small cell lung cancer[221]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[222] or in astrocytoma[223]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[224], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[225]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[226-227], esophageal cancer[228-229], osteosarcoma[230], and CRC[231].

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[232-233]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[213,234-235], thereby reducing intracellular arginine methylation[191,193,236] and altering cell signaling[235,237]. 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
CDKN2B loss, CDKN2A loss

POTENTIAL TREATMENT STRATEGIES

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[238-241]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[242-243], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[98-99,104,244-247]; 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[248-249], 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[97-98,104,246,250-251].

FREQUENCY & PROGNOSIS

CDKN2A mutations and CDKN2A/B homozygous loss have been reported in 2.5-6% and 14% of cholangiocarcinomas, respectively[86,88]. CDKN2A alterations have been reported in 8.7% of gallbladder carcinomas analyzed in the COSMIC database, while CDKN2B alterations were not observed in any of 153 gallbladder carcinomas analyzed (Feb 2021)[56]. Homozygous deletion of the CDKN2A locus was reported in 26% of gallbladder carcinomas in one study, while loss of heterozygosity at 9p21 was reported in 57% of samples[252]. Homozygous loss of the chromosomal region 9p21, which contains CDKN2A and CDKN2B, has been reported in 43% (3/7) of biliary dysplasias, as well as in 50% (3/6) of primary sclerosing cholangitis (PSC)-associated cholangiocarcinoma samples, and 50% (8/16) of sporadic cholangiocarcinoma samples[253]. In addition, loss of heterozygosity at 9p21 has been found in 89% (8/9) of PSC-associated cholangiocarcinoma samples[254]. However, in another study, homozygous deletion of CDKN2A was reported in 4% (2/51) of cholangiocarcinoma samples[255]. A study of 94 liver fluke-associated cholangiocarcinomas reported loss of p14ARF, p15INK4b, and p16INK4a protein expression in 31%, 58%, and 82% of cases, respectively[256]. CDKN2A promoter methylation may be a more frequent mechanism for alteration of p16INK4a expression, reported in up to 72% of gallbladder adenocarcinomas[257-258]. Studies have reported loss or reduction of p16INK4a protein expression in 35-63% of gallbladder carcinomas[114,252,258]. Promoter methylation of CDKN2A or CDKN2B affecting the p14ARF, p16INK4a, or p15INK4b loci has been reported in 25-40%, 50-76%, and 49-50% of cholangiocarcinomas, respectively[255-256,259-260]. Loss of p16INK4a protein expression has been suggested to serve as a prognostic marker in cholangiocarcinoma, as promoter methylation of CDKN2A and loss of p16INK4a expression have been found to be correlated with poor survival in patients with cholangiocarcinoma[256,261-262]. Expression of p16INK4a has been found to be correlated with low tumor stage and good prognosis in patients with gallbladder adenocarcinoma[120]. Methylation of the CDKN2A promoter correlated with decreased p16INK4a expression but was not associated with survival in patients with gallbladder cancer[258].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[263-264]. 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[265-266]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[267-268]. One or more alterations observed here are predicted to result in p16INK4a loss of function[269-290]. One or more alterations seen here are predicted to result in p14ARF loss of function[273,290-293]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[294].

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[295]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[296-297]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[298-300]. 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[301-303]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

GENE
EP300

ALTERATION
Q341*

TRANSCRIPT ID
NM_001429

CODING SEQUENCE EFFECT
1021C>T

VARIANT ALLELE FREQUENCY (% VAF)
18.9%

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in EP300, but the use of histone deacetylase inhibitors is being investigated in clinical trials recruiting patients with either lymphoma or urothelial carcinoma harboring EP300 alterations.

FREQUENCY & PROGNOSIS
Gene fusions conjoining EP300 with MLL have been identified in acute myeloid leukemia (AML) with t(11; 22)(q23; q13) chromosomal rearrangements[304], and infrequent somatic mutations of EP300 have been documented in several cancer types, including B-cell lymphoma[305], colorectal cancer[306], bladder cancer[307], esophageal squamous cell carcinoma[308], and cervical squamous cell carcinoma[309]. High tumor tissue expression of p300 has been linked with unfavorable outcomes in breast[310-311], colorectal[312], prostate[313], laryngeal[314], nasopharyngeal[315], non-small cell lung[316], small cell lung[317-318], hepatocellular[319], and esophageal squamous cell[320] carcinomas. A study of 327 patients with melanoma found a correlation between high expression of BRAF and cytoplasmic p300 and disease progression[321].

FINDING SUMMARY
EP300 encodes p300, a multifunctional regulatory protein with transcriptional coactivation and acetyltransferase activities. P300 is structurally similar to CREBBP and has been implicated in the control of a diverse array of cellular processes, including interferon-mediated transcriptional response to viral infection[322], astrocyte differentiation[323], and DNA repair[324]. P300 cooperates with MDM2 to regulate turnover of the tumor suppressor p53[325].

GENE
FGF19

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies that directly address genomic alterations in FGF19. However, FGF19 amplification predicts sensitivity to FGFR4 inhibitors in liver cancer cell lines[326-327]; selective FGFR4 inhibition reduced tumor burden in an FGF19-amplified HCC xenograft model[328]. A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with previously treated hepatocellular carcinoma (HCC), most of whom had received prior sorafenib treatment, reported a 16.7% ORR (11/66, 1 CR, ongoing for >1.5 years) and a median PFS of 3.3 months for FGF19-IHC-positive patients; poorer outcomes (0% ORR, PFS of 2.3 months) were observed for patients with negative or unknown FGF19 IHC scores[329]. Acquisition of FGFR4 mutations may represent a mechanism of resistance for patients with FGF19 overexpression who initially responded but then progressed on fisogatinib[327]. Preliminary results from the dose escalation part of a Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, showed an ORR of 7.6% (4/53), SD rate of 52.8% (28/53), and a median time to progression of 4.1 months; responses were observed in both FGF19-positive and FGF19-negative cases[330]. In a retrospective analysis, a trend toward response to sorafenib treatment and FGF19 copy number gain was observed in patients with HCC, and 2 patients harboring FGF19 copy number gain experienced a CR[331]. A case study reported activity of pan-FGFR inhibitors in FGF-amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[332]. Other therapies targeting FGF19 or FGFR4 signaling are in development[333].

FREQUENCY & PROGNOSIS
In the TCGA datasets, FGF19 amplification has been reported with highest incidence in esophageal carcinoma (34%), head and neck squamous cell carcinoma (23%), breast carcinoma (15%), lung squamous cell carcinoma (13%), and cholangiocarcinoma (11%) (cBioPortal, 2021)[107-108]. In HCC, FGF19 is an important driver gene[328,334-335], and FGF19 protein expression correlates with tumor progression and poorer prognosis[336]. Exogenous FGF19 has been shown to promote prostate cancer tumorigenesis in a preclinical study[337], and the presence of FGF19-positive tissues is an independent factor for worse prognosis following radical prostatectomy[338].

FINDING SUMMARY
FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[328,339]. FGF19 lies in a region of chromosome 11q13 frequently amplified in a diverse range of malignancies that also contains FGF3, FGF4, and CCND1[340]. Correlation between FGF19 amplification and protein expression has been demonstrated in hepatocellular carcinoma (HCC)[341] but was not observed in several other tumor types[335].

Electronically signed by Matthew Hiemenz, M.D. | 05 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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GENE
FGF3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[342].

FREQUENCY & PROGNOSIS
FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[123].

FINDING SUMMARY
FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[343].

GENE
FGF4

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES
FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[344-345] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[344]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[342].

FREQUENCY & PROGNOSIS
FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[123] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, 2021)[107-108].

FINDING SUMMARY
FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[346] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[347]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[123,344,348-351] and may confer sensitivity to the multi-kinase inhibitor sorafenib[344].

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GENE
SMAD4

ALTERATION
R361H

TRANSCRIPT ID
NM_005359

CODING SEQUENCE EFFECT
1082G>A

VARIANT ALLELE FREQUENCY (% VAF)
53.4%

POTENTIAL TREATMENT STRATEGIES

There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[352-353] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[354].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[355], pancreatic acinar cell carcinoma[356], cholangiocarcinoma (25%)[55], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[357-358], colorectal adenocarcinoma (CRC; 14%)[46], esophageal adenocarcinoma (14%)[359], and stomach adenocarcinoma (13%)[360]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[361] and intraductal papillary mucinous neoplasms (IPMN)[362]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[363]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[364]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[365-367], appendiceal mucinous neoplasm[368], gastric adenocarcinoma[369-370], esophageal adenocarcinoma[371], esophageal squamous cell carcinoma[372], breast cancer[373], and prostate cancer[374].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[375-376]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[377-390].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the SMAD4 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with juvenile polyposis syndrome (ClinVar, Mar 2021)[391]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[392-394], which is associated with an increased risk of gastrointestinal cancers[395]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[396]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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Everolimus

Assay findings association

FBXW7
G423V

AREAS OF THERAPEUTIC USE

Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or gastrointestinal tract. Everolimus is also approved to treat either renal angiomyolipoma or subependymal giant cell astrocytoma in association with tuberous sclerosis complex (TSC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[50], renal cell carcinoma[51], and cervical squamous cell carcinoma[397], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

A Phase 2 study of everolimus in patients with advanced biliary tract cancer showed 2.6% (1/38) PR and 42.1% (16/38) SD, and a median PFS of 3.2 months[398]. Another Phase 2 study of everolimus in patients with biliary tract cancer reported 7.4% (2/27) PR, 48.1% (13/27) SD, and a median PFS of 6 months[399]. An observational study of everolimus in biliary tract cancer reported a disease control rate of 50%, but a high incidence (64%) of severe toxicities in patients with biliary tract cancer[400]. A Phase 1 trial of everolimus combined with sorafenib reported SD >10 weeks in 62% of cholangiocarcinoma patients[401]. A Phase 1 trial evaluating everolimus in combination with gemcitabine and/or cisplatin for the treatment of patients with solid tumors reported 0% PR, 60% SD, and 40% PD in an expansion cohort of 10 patients with cholangiocarcinoma or gallbladder carcinoma[402]. 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[83], 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[84].

Selumetinib

Assay findings association

NF1
E2448*

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[67,70] and strong preclinical evidence[72-76] , NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

A Phase 2 study of selumetinib in patients with advanced biliary tract carcinomas who received 1 or fewer prior treatments reported mPFS of 3.7 months, mOS of 9.8 months, 3 PRs, and 14 SDs of > 6 weeks in 28 patients[403]. In a Phase 1b study of selumetinib plus cisplatin and gemcitabine in patients with advanced or metastatic biliary tract, gallbladder, or ampullary carcinoma, 3 PRs were reported in 8 evaluable patients with a mPFS of 6.4 months[404].

Temsirolimus

Assay findings association

FBXW7
G423V

AREAS OF THERAPEUTIC USE

Temsirolimus is an intravenous mTOR inhibitor that is FDA approved for the treatment of advanced renal cell carcinoma. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of several case reports describing clinical benefit for patients with FBXW7-mutated cancers treated with mTOR inhibitors, including lung adenocarcinoma[50], renal cell carcinoma[51], and cervical squamous cell carcinoma[397], FBXW7 loss or inactivation may predict sensitivity to everolimus or temsirolimus.

SUPPORTING DATA

Clinical data on the efficacy of temsirolimus for the treatment of biliary tract cancers are limited (PubMed, Jan 2021). A Phase 1 trial of bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced solid tumors showed that the combination was well tolerated and resulted in six-month SD in 21% of patients, with a 21% rate of partial or complete remission[405]. In a Phase 2 clinical trial in non-small cell lung cancer (NSCLC), temsirolimus showed clinical benefit, but further studies are warranted[406]. A Phase 2 study of temsirolimus in patients with KRAS-mutant colorectal cancer reported limited efficacy; however, all patients who exhibited tumor reduction were found to have low levels of mutated KRAS in plasma samples[407]. A Phase 2 clinical trial in patients with pancreatic cancer reported that temsirolimus monotherapy had limited efficacy, and may have contributed to disease progression[408]. A study examining the efficacy of temsirolimus-involving regimens in 24 patients with mesenchymal/metaplastic breast cancer (MpBCs) reported 2 CRs, 4 PRs, 2 instances of SD longer than 6 months, and 4 instances of SD shorter than 6 months[409].

Trametinib

Assay findings association

NF1
E2448*

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[67,70] and strong preclinical evidence[72-76] , NF1 inactivation may predict sensitivity to MEK inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

SUPPORTING DATA

The Phase 2 SWOG S1310 study reported low efficacy for single-agent trametinib in patients with biliary tract cancer and progression on gemcitabine and platinum chemotherapy, with an inferior ORR (8% vs. 10%), DCR (16% vs. 55%), median PFS (1.3 vs. 2.3 months, HR=2.95), and median OS (4.3 vs. 8.0 months, HR=2.02) as compared with 5-FU or capecitabine[410]. Other early phase monotherapy studies have reported similarly low efficacy for MEK1/2 inhibitors, including trametinib, binimetinib, and selumetinib, for patients with biliary tract cancers, with reported ORRs of 5% to 12% and DCRs of 54% to 80% (n = 20 to 30); although some responding patients harbored mutation in NF1 or NRAS, others did not have detectable alterations in the MAPK pathway[403,411-414] . Improved efficacy has been suggested by early studies combining MEK1/2 inhibitors with chemotherapeutic agents. In advanced biliary tract cancer, combination of selumetinib or binimetinib with cisplatin and gemcitabine has elicited ORRs of 36% to 38% and DCRs of 74% to 100% (n = 8 to 35)[404,415] , while combination of binimetinib with capecitabine elicited an ORR of 18% and a DCR of 76% (n = 34)[416]. Modest activity has been seen in patients with cholangiocarcinoma treated with trametinib in combination with the VEGF-targeting agent pazopanib[417]. 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[83], 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[84].

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-1077866-01

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
CCND1

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent CDK4/6 inhibitors.

ALTERATION
amplification - equivocal

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03965845

PHASE 1/2

A Study of Telaglenastat (CB-839) in Combination With Palbociclib in Patients With Solid Tumors

TARGETS
CDK4, CDK6, GLS

LOCATIONS: Texas, Georgia

NCT03454035

PHASE 1

Ulixertinib/Palbociclib in Patients With Advanced Pancreatic and Other Solid Tumors

TARGETS
MAPK3, MAPK1, CDK4, CDK6

LOCATIONS: North Carolina

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

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, RET, ROS1, VEGFRs

LOCATIONS: Toulouse (France), Marseille (France), Lyon (France), Nice (France)

ORDERED TEST # ORD-1077866-01

CLINICAL TRIALS

NCT02897375

PHASE 1

Palbociclib With Cisplatin or Carboplatin in Advanced Solid Tumors

TARGETS
CDK4, CDK6

LOCATIONS: Georgia

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

GENE
CTNNB1

ALTERATION
S45F

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York, California

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

NCT03017833

PHASE 1

Sapanisertib and Metformin in Treating Patients With Advanced or Metastatic Relapsed or Refractory Cancers

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03430882

PHASE 1

Sapanisertib, Carboplatin, and Paclitaxel in Treating Patients With Recurrent or Refractory Malignant Solid Tumors

TARGETS
mTORC1, mTORC2

LOCATIONS: Texas

NCT03065062

PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS
PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

GENE
ERBB3

ALTERATION
Q809R

RATIONALE
Clinical and preclinical data support sensitivity of ERBB3 activating mutations to HER2-targeting TKIs, including afatinib and lapatinib. ERBB3 amplification or activating mutations may confer sensitivity to therapies targeting ERBB3.

NCT02795156

PHASE 2

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

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

LOCATIONS: Florida, Tennessee, Missouri, Wisconsin, Colorado

NCT02451553

PHASE 1

Afatinib Dimaleate and Capecitabine in Treating Patients With Advanced Refractory Solid Tumors, Pancreatic Cancer or Biliary Cancer

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Washington

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: Gent (Belgium), Brussels (Belgium), Liège (Belgium)

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

GENE
FBXW7

ALTERATION
G423V

RATIONALE
Loss or inactivation of FBXW7 may lead to increased mTOR activation and may predict sensitivity to mTOR inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

ORDERED TEST # ORD-1077866-01

CLINICAL TRIALS

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, RET, SRC, VEGFRs

LOCATIONS: Texas

NCT02159989

PHASE 1

Sapanisertib and Ziv-Aflibercept in Treating Patients With Recurrent Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery

TARGETS
PIGF, VEGFA, VEGFB, mTORC1, mTORC2

LOCATIONS: Texas

NCT02321501

PHASE 1

Phase I/Ib Dose Escalation & Biomarker Study of Ceritinib (LDK378) + Everolimus for Locally Advanced or Metastatic Solid Tumors With an Expansion in Non-Small Cell Lung Cancer (NSCLC) Characterized by Abnormalities in Anaplastic Lymphoma Kinase (ALK) Expression

TARGETS
ROS1, ALK, mTOR

LOCATIONS: Texas

ORDERED TEST # ORD-1077866-01

CLINICAL TRIALS

GENE
MTAP

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors.

ALTERATION
loss exons 2-8

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)

Electronically signed by Matthew Hiemenz, M.D. | 05 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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GENE
NF1

ALTERATION
E2448*

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. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

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

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

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)

NCT03366103

PHASE 1/2

Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors

TARGETS
mTORC1, mTORC2, BCL-W, BCL-XL, BCL2

LOCATIONS: Maryland, New Jersey, New York, California

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT03217669

PHASE 1

Epacadostat (INCB24360) in Combination With Sirolimus in Advanced Malignancy

TARGETS
IDO1, mTOR

LOCATIONS: Kansas

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ORDERED TEST # ORD-1077866-01

CLINICAL TRIALS

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT03768375

PHASE 2

Molecularly Target Therapy With FORFIRINOX in Advanced or Recurrent Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

TARGETS
EGFR, mTOR, ERBB2

LOCATIONS: Shanghai (China)

NCT03239015

PHASE 2

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

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

LOCATIONS: Shanghai (China)

NCT01552434

PHASE 1

Bevacizumab, Temsirolimus Alone and in Combination With Valproic Acid or Cetuximab in Patients With Advanced Malignancy and Other Indications

TARGETS
VEGFA, HDAC, mTOR, EGFR

LOCATIONS: Texas

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.

GATA6
D66H

SDHA
E116K

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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 Alterations and Therapies

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit.

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

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

**Interquartile Range = 1st Quartile to 3rd Quartile*

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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.

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SELECT ABBREVIATIONS

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

MR Suite Version 4.0.0

The median exon coverage for this sample is 965x

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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