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 Colon adenocarcinoma (CRC)
NAME Yu, Yung-Yun
DATE OF BIRTH 10 April 1983
SEX Female
MEDICAL RECORD # 13396582

PHYSICIAN

ORDERING PHYSICIAN Jiang, Jeng-Kai
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Liver
SPECIMEN ID S109-17825 B (PF21027)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 16 June 2020
SPECIMEN RECEIVED 12 October 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

KRAS G12V
NRAS wildtype
PIK3R1 L449_K459del
APC Q1067*, F1491fs*16
FLT1 R281Q
PBRM1 I279fs*4
SDHA S384*
TET2 E1151*
TP53 I255N

2 Disease relevant genes with no reportable alterations: ***BRAF, NRAS***

0 Therapies with Clinical Benefit
2 Therapies with Resistance
12 Clinical Trials

PATHOLOGIST COMMENTS

Erik Williams, M.D. 19-Oct-2021

This assay is not designed to distinguish germline (inherited) from somatic variants. However, the SDHA S384* and TET2 E1151* variants found in this case have some characteristics suspicious for germline origin. Clinical correlation is advised.

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 4 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)**
***KRAS* -** G12V		
10 Trials *see p. 11*	*Cetuximab* ⊗ *Panitumumab* ⊗	none
***NRAS* -** wildtype		
0 Trials	*Cetuximab* ⊗ *Panitumumab* ⊗	none
***PIK3R1* -** L449_K459del		
3 Trials *see p. 13*	none	none

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

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

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VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

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

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]. 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]. For patients with chemotherapy-refractory metastatic colorectal cancer, 92% of which were MSS or MSI-Intermediate, a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[6].

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[7-8] and FOLFIRI[9-10]. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy[11-12] but less likely to benefit from irinotecan chemotherapy[13].

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases[3,14-18]. MSS colorectal cancers are molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability[18]. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors[14,19-25].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[16]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[16,26-27]. 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[15,28-29]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,27,29].

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BIOMARKER

Tumor Mutational Burden

RESULT
4 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[30-32], anti-PD-1 therapies[30-33], and combination nivolumab and ipilimumab[34-39]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[30-33,40]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[30]. 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[41] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[31]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for 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[33,40]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥9.8 Muts/MB compared with those with tumors with TMB <9.8 Muts/Mb (~ equivalency <12 Muts/Mb as measured by this assay)[30]. Another retrospective study reported that a TMB ≥12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[42].

FREQUENCY & PROGNOSIS

Elevated TMB has been reported in 8-25% of colorectal cancer (CRC) samples[17,43-45]. Multiple studies have reported that the majority (up to 90%) of hypermutant CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)[17,45]. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and, conversely, that 100% of tumors with low TMB harbor intact MMR[43-45]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which lead to an "ultramutated" phenotype with especially high TMB[17,45]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[17,45], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[17]. In a study for 61 patients with metastatic, microsatellite stable (MSS) CRC treated with best standard of care, plasma TMB scores ≥28 muts/Mb (approximately 14 muts/Mb as measured by this assay) were associated with reduced OS as compared with plasma TMB scores <28 muts/Mb (3.0 vs. 5.3 months, HR 0.76, p=0.007), whereas tissue TMB was not found to be prognostic in this population[46].

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[47-48] and cigarette smoke in lung cancer[49-50], treatment with temozolomide-based chemotherapy in glioma[51-52], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,53-56], and microsatellite instability (MSI)[17,53,56]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[30,40,42].

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GENE
KRAS

ALTERATION
G12V

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>T

VARIANT ALLELE FREQUENCY (% VAF)
11.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[57-58]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[59]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[60]. Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[61-66]. However, multiple clinical trials have reported lack of efficacy of trametinib and other MEK inhibitors when used as monotherapy for treatment of patients with KRAS-mutant CRC[67-71]. Both clinical[72-73] and preclinical[74-75] studies suggest that combinatorial approaches including MEK inhibitors are likely to be more effective for the treatment of CRC, including strategies such as combination of MEK inhibitors with PI3K inhibitors[73], RAF inhibitors[74], pan-ERBB inhibitors[75], or chemotherapeutic agents[72]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[76-77]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[78-79]. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[80]. A Phase 1b/2 study of PLK1 inhibitor onvansertib in combination with FOLFIRI and bevacizumab for patients with KRAS-mutated metastatic CRC previously treated with chemotherapy reported an 87.5% (7/8; 3 PR, 4 SD) clinical benefit rate, with 1 patient going on to successful curative surgery[81].

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[82-85] or panitumumab[86-88] for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v.3.2021).

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)[89-97]. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC[91-94,98-99].

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[62,100]. 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, and K117N have been characterized as activating and oncogenic[62,101-122].

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[82-85] or panitumumab[86-88] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v2.2021).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[17,97,123-128]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[97] and longer survival[128-129] of patients with CRC.

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[62]. No alterations in NRAS were identified in this case.

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GENE
PIK3R1

ALTERATION
L449_K459del

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
1345_1377del33

VARIANT ALLELE FREQUENCY (% VAF)
6.8%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical[130-131] and preclinical[132-133] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[130], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[134]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[133,135-138] or AKT[139-140]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[141].

— Potential Resistance —

Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat CRC, even for tumors that harbor alterations in PIK3CA or PTEN; data are more limited for alterations in other genes in this pathway[142-144].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[53], glioblastoma (GBM; 11%)[145], uterine carcinosarcoma (11%)(cBioPortal, 2021)[146-147], and lower grade glioma (5%)[148]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[149-151], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[149]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[152] and metastasis-free survival in breast cancer[153]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[154].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[155]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[156-159], promote tumorigenesis[132,139,156], and promote hyperplasia in the context of PTEN-deficiency[160]. Alterations such as seen here may disrupt PIK3R1 function or expression[133,140-141,150-151,161-169].

GENE
APC

ALTERATION
Q1067*, F1491fs*16

TRANSCRIPT ID
NM_000038, NM_000038

CODING SEQUENCE EFFECT
3199C>T, 4473delT

VARIANT ALLELE FREQUENCY (% VAF)
11.3%, 13.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[170]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[171-172]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[173].

FREQUENCY & PROGNOSIS

APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset[17]. Inactivation of APC leads to activation of the Wnt/beta-catenin pathway, which is thought to play a role in the adenoma-carcinoma transition in some cancers, including colorectal cancer (CRC)[174]. The prognostic significance of APC mutations in sporadic CRC remains unclear[175]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[176].

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[177]. Alterations such as seen here may disrupt APC function or expression[178-182].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Mar 2021)[183]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[184-186]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[187], and in the appropriate clinical context germline testing of APC is recommended.

GENE
FLT1

ALTERATION
R281Q

TRANSCRIPT ID
NM_002019

CODING SEQUENCE EFFECT
842G>A

VARIANT ALLELE FREQUENCY (% VAF)
2.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Multiple agents that target vascular endothelial growth factor receptor 1 (VEGFR-1) encoded by FLT1, including the multi-tyrosine kinase inhibitors sunitinib, sorafenib, pazopanib, axitinib, regorafenib, and vandetanib, have been approved for use in certain indications, although FLT1 genomic alterations have not been evaluated as biomarkers for efficacy. On the basis of extensive clinical evidence across multiple tumor types, expression of plasma or tumor VEGFR-1 or VEGFR-2 has not been established as a reliable biomarker to predict response to the VEGFA-targeted agent bevacizumab[188-207].

FREQUENCY & PROGNOSIS

FLT1 mutations, mostly of unknown significance, have been reported at low frequency across solid tumors (0-2%), with a higher incidence reported in tumor types that are prone to hypermutation, such as cutaneous, colorectal, urothelial, and endometrial cancers (3-10%) (COSMIC, 2021)[208]. Expression of VEGFR-1 encoded by FLT1 has been frequently reported across tumor types[209-220]. Although many studies have examined a prognostic role for VEGFR-1 expression across various tumor types[218-244], published data investigating the prognostic implications of FLT1 genomic alterations in cancer are limited (PubMed, 2021).

FINDING SUMMARY

FLT1 encodes VEGFR-1, which is involved in angiogenesis and vasculogenesis[245-247]. The significance of most FLT1 genomic alterations has not been established, although alterations predicted to disrupt the FLT1 kinase domain (amino acids 827-1158) are likely to be inactivating.

GENE
PBRM1

ALTERATION
I279fs*4

TRANSCRIPT ID
NM_018313

CODING SEQUENCE EFFECT
835delA

VARIANT ALLELE FREQUENCY (% VAF)
15.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of significant clinical data from prospective studies, PBRM1 inactivation may predict benefit from PD-1-targeting immune checkpoint inhibitors, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, for patients with clear cell renal cell carcinoma and prior anti-angiogenic therapy[248-250]. However, multiple retrospective analyses report that PBRM1 mutation status is not associated with clinical benefit from various immune checkpoint inhibitors in other solid tumor types, including non-small cell lung cancer, urothelial carcinoma, melanoma, or esophagogastric cancer, suggesting that the impact of PBRM1 loss of function may depend on tumor type[251-254].

FREQUENCY & PROGNOSIS

Somatic mutations in PBRM1 are prevalent in clear cell renal cell carcinomas (ccRCC) (41%)[255], intrahepatic cholangiocarcinomas (9-13%)[256-259], and bladder urothelial carcinomas (6-14%)[260-262]. PBRM1 mutations are detected in other tumor types, including in 37% (11/30) of papillary meningiomas and 4% (2/54) of thymic carcinomas[263-264] and in skin (6%), large intestine (5%), stomach (5%), soft tissue (3%), and lung (2%) (COSMIC, 2021)[208]. Preclinical studies have shown that loss of PBRM1 increases the proliferation of ccRCC cell lines[255]. PBRM1 protein loss or mutation is correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC[265-267], extrahepatic cholangiocarcinoma[258], and pancreatic cancer[268]. However, one ccRCC study reported no correlation between PBRM1 mutation and cancer-specific survival[269]. In ccRCC, PBRM1 alterations are generally observed to be mutually exclusive with BAP1 alterations[255,270]; a retrospective analysis of 145 primary ccRCCs found a decreased median overall survival for patients with mutations in both BAP1 and PBRM1 compared with patients having either mutated gene alone[271]. A trend toward worse survival was also seen in patients with intrahepatic cholangiocarcinoma harboring mutations in chromatin modifiers (including BAP1, ARID1A, or PBRM1)[257].

FINDING SUMMARY

PBRM1 (Polybromo-1), also known as BAF180, encodes a subunit of ATP-dependent chromatin-remodeling complexes and a required cofactor for ligand-dependent transactivation by nuclear hormone receptors[272]. Mutation, loss, or inactivation of PBRM1 has been reported in several cancers, suggesting PBRM1 is a tumor suppressor[255,257,273]. Alterations such as seen here may disrupt PBRM1 function or expression[274-279].

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GENE
SDHA

ALTERATION
S384*

TRANSCRIPT ID
NM_004168

CODING SEQUENCE EFFECT
1151C>A

VARIANT ALLELE FREQUENCY (% VAF)
49.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies available to directly target the loss or inactivation of SDH genes. Preclinical studies have shown that succinate, which can accumulate as a result of SDH inactivation, promotes angiogenesis via VEGF upregulation[280-281]. Case studies have reported objective responses in patients with renal cell carcinoma harboring either SDHA or SDHC alterations treated with multikinase inhibitors that target VEGFR, including sunitinib and pazopanib[282]; however, these clinical data are limited. In a Phase 2 trial of vandetanib for children and adults with gastrointestinal stromal tumors (GISTs) with decreased SDH expression that were wild-type for KIT and PDGFRA, no partial or complete responses were observed and 2/9 patients experienced prolonged stable disease[283].

FREQUENCY & PROGNOSIS

Somatic mutations in SDHA are rare, and have been observed in fewer than 1% of tumors across all cancer types (COSMIC, 2021)[208]. Deficiency in succinate dehydrogenase activity has been associated with an aggressive subset of renal cell carcinoma with distinctive clinical and morphological features, affecting mostly younger patients[284-288].

FINDING SUMMARY

SDHA encodes the succinate dehydrogenase complex, subunit A, flavoprotein. This protein is involved in the mitochondrial respiratory chain. SDH deficiency due to germline inactivating mutations in SDH genes is associated with paraganglioma-pheochromocytoma syndrome, Leigh syndrome, and gastrointestinal stromal tumors (GIST), which typically do not harbor mutations in KIT or PDGFRA and are not sensitive to treatment with imatinib[289-292].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the SDHA 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 hereditary paraganglioma-pheochromocytoma syndrome and mitochondrial complex II deficiency (ClinVar, Mar 2021)[183]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. In the context of hereditary pheochromocytoma and paraganglioma, SDHA mutations are more rare and less penetrant than mutations in other SDH genes, and have been identified in 3 to 7% of patients with genetically unexplained disease[293-295]. In the appropriate clinical context, germline testing of SDHA is recommended.

GENE
TET2

ALTERATION
E1151*

TRANSCRIPT ID
NM_017628

CODING SEQUENCE EFFECT
3451G>T

VARIANT ALLELE FREQUENCY (% VAF)
46.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in TET2 in solid tumors.

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Jan 2021)[146-147]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2021).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[296-297]. Alterations such as seen here may disrupt TET2 function or expression[298-302].

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[303-308]. 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[303-304]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[309]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[307,310-311]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Erik Williams, M.D. | 19 October 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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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TP53

ALTERATION
I255N

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
764T>A

VARIANT ALLELE FREQUENCY (% VAF)
22.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[312-315], or p53 gene therapy and immunotherapeutics such as SGT-53[316-320] and ALT-801[321]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[322]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[323]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[324]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[325]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[326]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[327]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[320]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[328]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246[329-331]. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[332]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[333-334]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[335-336]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases[17,337-342]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[343]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[344].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[345]. Alterations such as seen here may disrupt TP53 function or expression[346-350].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[351-353], including sarcomas[354-355]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[356] to 1:20,000[355]. 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[357]. 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[303-308]. 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[303-304]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[309]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[307,310-311]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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Cetuximab

Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12V

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC[82-85,358-359] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS[82-85] or NRAS[126,342] , which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Colon Cancer Guidelines v3.2021).

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wild-type CRC, both as first-line combination therapy with FOLFIRI or FOLFOX4[82-83,359] and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients[84-85,358] . A prospective study of first-line cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 10.5% (2/19) of participants experiencing PRs and 57.9% (11/19) experiencing SDs[360]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and a DCR of 92.3%[361]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[362]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[363].

Panitumumab

Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS
G12V

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC[86,362,364] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v2.2021). Activating mutations in either KRAS[86-88] or NRAS[87,340] , which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX4[86] and as monotherapy for chemotherapy-refractory patients[362,364] . An open-label, randomized Phase 2 trial reported that for patients with unresectable RAS-wild-type colorectal adenocarcinoma treated with first-line panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS 59% vs. 49%)[365]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[362]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[363].

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.

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ORDERED TEST # ORD-1207522-01

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
KRAS

ALTERATION
G12V

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS mutation may predict sensitivity to PLK1 inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant colorectal cancer; combination therapies may be more effective.

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Hwasun (Korea, Republic of), Pusan (Korea, Republic of), Seongnam (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of)

NCT04303403

PHASE 1

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

TARGETS
JAK2, JAK1, MEK

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

ORDERED TEST # ORD-1207522-01

CLINICAL TRIALS

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

NCT03829410

PHASE 1/2

Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation

TARGETS
PLK1, VEGFA

LOCATIONS: California, Arizona, Minnesota, Kansas, Arkansas, Virginia, Florida

NCT03475004

PHASE 2

Study of Pembrolizumab, Binimetinib, and Bevacizumab in Patients With Refractory Colorectal Cancer

TARGETS
PD-1, MEK, VEGFA

LOCATIONS: Colorado

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

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

LOCATIONS: Massachusetts

NCT04111458

PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

GENE
PIK3R1

ALTERATION
L449_K459del

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. Several clinical studies have shown that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit when used as a monotherapy in patients with colorectal cancer; combination therapies may be required to overcome this lack of response.

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT03711058

PHASE 1/2

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

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03502733

PHASE 1

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

TARGETS
PI3K, PD-1

LOCATIONS: Maryland, 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.

ATR
N2080D

EP300
M869V

KDM5C
S20R

MAP2K2 (MEK2)
P298L

MLL2
V401M

MTOR
T1834_T1837del

PBRM1
Y181C

RAD51C
D215G

ROS1
R1617S

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

1. 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. Observed TMB is dependent on characteristics

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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

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

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating

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physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 970x

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

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