

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 Rectum adenocarcinoma (CRC)	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN SITE Rectum
	NAME Liang, Shih-Hsun		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN ID S111-20925 D
	DATE OF BIRTH 28 July 1960		ADDITIONAL RECIPIENT None		SPECIMEN TYPE Slide Deck
	SEX Male		MEDICAL FACILITY ID 205872		DATE OF COLLECTION 27 May 2022
	MEDICAL RECORD # 12700071		PATHOLOGIST Not Provided		SPECIMEN RECEIVED 14 July 2022

Biomarker Findings

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

Genomic Findings

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

KRAS wildtype
NRAS G12D
APC Q1294*, Q789fs*31
AURKA amplification
ARFRP1 amplification
BCL2L1 amplification
GNAS amplification
SRC amplification
TP53 G245S
ZNF217 amplification

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

Report Highlights

- Targeted therapies with **potential resistance** based on this patient's genomic findings: **✖ Cetuximab** (p. 11), **Panitumumab** (p. 11)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 12)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 3 Muts/Mb

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section





No therapies or clinical trials. see Biomarker Findings section


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GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS - wildtype	Cetuximab 	none
0 Trials	Panitumumab 	
NRAS - G12D	Cetuximab 	none
10 Trials see p. 14	Panitumumab 	
APC - Q1294*, Q789fs*31	none	none
3 Trials see p. 12		
AURKA - amplification	none	none
2 Trials see p. 13		

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

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.

ARFRP1 - amplification.....	p. 7	SRC - amplification.....	p. 8
BCL2L1 - amplification.....	p. 7	TP53 - G245S.....	p. 9
GNAS - amplification.....	p. 8	ZNF217 - amplification.....	p. 10

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.

ORDERED TEST # ORD-1412469-01

BIOMARKER FINDINGS

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 inhibitors¹⁻³, including approved therapies nivolumab and pembrolizumab⁴. 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 microsatellite-stable (MSS) metastatic colorectal cancer (CRC), 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. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)⁷. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months⁸ and 5.7 months⁹, and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR¹⁰.

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX¹¹⁻¹² and FOLFIRI¹³⁻¹⁴. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy¹⁵⁻¹⁶ but less likely to benefit from irinotecan chemotherapy¹⁷.

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases^{3,18-22}. MSS colorectal cancers are

molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability²². Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors^{18,23-29}.

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 tumor²⁰. 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^{20,30-31}. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers^{19,32-33}. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins^{19-20,31,33}.

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BIOMARKER FINDINGS

BIOMARKER

Tumor Mutational Burden

RESULT

3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1³⁴⁻³⁶, anti-PD-1 therapies³⁴⁻³⁷, and combination nivolumab and ipilimumab³⁸⁻⁴³. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors^{34-37,44-48}. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥ 10 Muts/Mb (as measured by this assay) compared with those with TMB < 10 Muts/Mb in a large cohort that included multiple tumor types⁴⁴; similar findings were observed in the KEYNOTE 028 and 012 trials³⁷. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores < 10 Muts/Mb (HR=0.68)⁴⁸. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples⁴⁹. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb

than those with TMB ≥ 10 and < 16 Muts/Mb⁴⁷. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥ 16 -20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy⁵⁰ or those with lower TMB treated with PD-1 or PD-L1-targeting agents³⁵. 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)³⁴. 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 inhibitors⁵¹.

FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples^{21,52-53}. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)^{21,52}. 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 MMR⁵². A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB^{21,52}. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB^{21,52}, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC²¹. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A study

of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones⁵⁴. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS⁵⁵. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival⁵⁶. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies⁵⁷. In a study for 61 patients with metastatic, 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 compared with plasma TMB scores < 28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, $p=0.007$), whereas tTMB was not found to be prognostic in this population⁵⁸.

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 melanoma⁵⁹⁻⁶⁰ and cigarette smoke in lung cancer⁶¹⁻⁶², treatment with temozolomide-based chemotherapy in glioma⁶³⁻⁶⁴, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes^{21,65-68}, and microsatellite instability (MSI)^{21,65,68}. 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^{34,44,51}.

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ORDERED TEST # ORD-1412469-01

GENOMIC FINDINGS

GENE

KRAS

 ALTERATION
wildtype

with clinical benefit of treatment with EGFR-targeting antibodies cetuximab⁶⁹⁻⁷² or panitumumab⁷³⁻⁷⁵ for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Guidelines v3.2021).

that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC^{78-81,85-86}.

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

Lack of mutations in KRAS or NRAS is associated

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations⁷⁶⁻⁸⁴. Numerous studies have reported

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 formation⁸⁷⁻⁸⁸. No alterations in KRAS were identified in this case.

GENE

NRAS

 ALTERATION
G12D

 TRANSCRIPT ID
NM_002524

 CODING SEQUENCE EFFECT
35G>A

 VARIANT ALLELE FREQUENCY (% VAF)
37.8%

binimetinib, and selumetinib. Preclinical studies have suggested that MEK inhibitors, either alone or in combination with other therapies, may exhibit at least some activity in NRAS-mutated CRC⁹⁹⁻¹⁰⁰. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors¹⁰¹⁻¹⁰⁴, the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear¹⁰⁵.

FREQUENCY & PROGNOSIS

NRAS mutation, commonly at codon 61, has been observed in 2-9% of colorectal cancers¹⁰⁶⁻¹¹⁰. For patients with CRC, NRAS mutations have been reported to be associated with increased frequency of metastasis⁸⁴ and shorter survival¹¹¹⁻¹¹².

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 pathways⁸⁷. NRAS alterations affecting amino acids G12, G13, G60, Q61, as well as mutations I24N, T50I, T58I, and A146T have been characterized as activating and oncogenic^{87,113-128}.

POTENTIAL TREATMENT STRATEGIES
— Targeted Therapies —

On the basis of clinical evidence in hematologic malignancies⁸⁹⁻⁹⁵ and solid tumors^{89,96-98}, NRAS activating alterations may predict sensitivity to MEK inhibitors, such as trametinib, cobimetinib,

— Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab⁶⁹⁻⁷² or panitumumab⁷³⁻⁷⁵ for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

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GENOMIC FINDINGS

GENE

APC

ALTERATION

Q1294*, Q789fs*31

TRANSCRIPT ID

NM_000038, NM_000038

CODING SEQUENCE EFFECT

3880C>T, 2366delA

VARIANT ALLELE FREQUENCY (% VAF)

33.2%, 32.5%

interact with transcriptional co-activator CBP¹³⁰⁻¹³¹. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days¹³²; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386¹³³⁻¹³⁴.

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset²¹. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples¹³⁵. The prognostic significance of APC mutations in sporadic CRC remains unclear¹³⁶. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study¹³⁷.

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 differentiation¹³⁸. Alterations such as seen here may disrupt APC function or expression¹³⁹⁻¹⁴³.

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 2022)¹⁴⁴. 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)¹⁴⁵⁻¹⁴⁷. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth¹⁴⁸, and in the appropriate clinical context germline testing of APC is recommended.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs¹²⁹, and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to

GENE

AURKA

ALTERATION

amplification

with solid tumors reported SD as best response for 4/14 patients; both patients with AURKA amplification experienced PD¹⁵³. For patients with advanced prostate cancer treated with alisertib, presence of AURKA amplification was associated with improved OS (p=0.05) but not PFS (p=0.4) when compared with benefit for patients without AURKA amplification¹⁵⁴.

— Nontargeted Approaches —

In some cancer types, including colorectal cancer, AURKA amplification has been associated with resistance to taxane therapy¹⁵⁵⁻¹⁵⁷.

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, putative high-level amplification of AURKA has been found in 8% of cases²¹. Studies in the literature have reported AURKA amplification in

53-68% of colorectal tumors and have identified AURKA as a key gene in the progression of colorectal adenomas to carcinomas¹⁵⁸⁻¹⁶³. In patients with some tumor types, such as colon and breast, Aurora kinase A overexpression has been associated with more aggressive disease and poor prognosis, but the earlier studies may have been confounded by the presence of other genes in the amplified chromosome region 20q13^{160,164-165}.

FINDING SUMMARY

AURKA encodes the protein Aurora A kinase, a serine/threonine kinase that plays a critical role in cell division and maintenance of chromosome structure. AURKA is commonly amplified in cancer, and Aurora kinase A overexpression has been shown to lead to defects in chromosomal stability¹⁵⁷.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that target Aurora kinase A (AURKA); however, several inhibitors of AURKA are in clinical trials¹⁴⁹⁻¹⁵⁰. Objective responses have been observed for patients with genomically unselected solid tumors following treatment with the investigational AURKA inhibitor alisertib, though a high incidence of serious adverse events was reported for patients with urothelial cancer¹⁵¹⁻¹⁵². A retrospective analysis of a pilot trial of alisertib for patients

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GENOMIC FINDINGS

GENE

ARFRP1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address alterations in ARFRP1. Amplification of ARFRP1 has been reported to be significantly associated with the amplification of potential cancer drivers such as AURKA and the CCN (cyclin) genes¹⁶⁶, but

it is not known whether amplification of ARFRP1 in this context has therapeutic relevance.

FREQUENCY & PROGNOSIS

ARFRP1 mutations are rare across tumor types (<1%), whereas ARFRP1 amplification has been reported at high frequency, particularly in endometrial carcinosarcoma (11%), ovarian serous carcinoma (7-15%), colorectal adenocarcinoma (7%), and gastric, lung, breast, and esophageal carcinomas (6-7% each) (COSMIC, cBioPortal, Jan 2022)^{21,167-171}. However, the implications of ARFRP1 amplification for cancer prognosis have not been evaluated in published studies (PubMed, Jan 2022).

FINDING SUMMARY

ARFRP1 encodes ADP-ribosylation factor-related protein 1, a small GTPase involved in vesicular transport¹⁷²⁻¹⁷³. ARFRP1 is reportedly essential for the trafficking of several proteins, including ARL1, E-cadherin, and IGF1¹⁷⁴⁻¹⁷⁶. A single nucleotide polymorphism affecting ARFRP1 has been significantly associated with a risk of developing glioma by one study¹⁷⁷. Although ARFRP1 has important roles in normal metabolism and hepatic and intestinal functions^{176,178-179}, it has not been studied extensively in the context of cancer.

GENE

BCL2L1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Multiple investigational therapies that target BCL-2 family members, including ABT-737, navitoclax, pelcitoclax, A-1331852, and obatoclax, have been studied in preclinical studies or early-stage clinical trials¹⁸⁰⁻¹⁸¹; clinical studies have been conducted in genomically unselected populations. Single-agent navitoclax has been evaluated in

Phase 1 and Phase 2 studies where it demonstrated limited efficacy (ORR 2.6%, SD rate 20-23%); 2 patients achieved PRs, including a patient with small cell lung cancer who benefited for over 2 years¹⁸²⁻¹⁸³. Navitoclax has also been evaluated in combination with the EGFR TKI erlotinib, though no ORs were observed (27% SD rate, [3/11])¹⁸⁴. In a Phase 1 trial for patients with advanced non-small cell lung cancer (NSCLC), the combination of pelcitoclax and EGFR TKI osimertinib resulted in an ORR of 15% (3/20)¹⁸⁵.

FREQUENCY & PROGNOSIS

BCL2L1 amplification has been observed in 1-6% of solid tumor samples, including colorectal (5%) and ovarian (6%) cancers¹⁸⁶⁻¹⁸⁷. Studies suggest that expression of BCL-XL may be associated with

poor prognosis for patients with ovarian cancer¹⁸⁸, pleural mesothelioma¹⁸⁹, and colorectal cancer (CRC)¹⁹⁰. Elevated BCL-XL levels protect cancer cells against apoptosis in multiple cancer types, and has been associated with chemotherapy resistance for patients with ovarian cancer^{188,191} and resistance to radiation and targeted therapies in preclinical studies^{189,192-196}.

FINDING SUMMARY

BCL2L1 encodes BCL-XL, an anti-apoptotic member of the BCL-2 protein family that is frequently overexpressed in cancer¹⁹⁷⁻¹⁹⁹. In colorectal cancer (CRC), 20q gain has been associated with BCL-XL protein overexpression²⁰⁰.

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GENOMIC FINDINGS

GENE

GNAS

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies targeted to GNAS mutation in cancer. However, there is limited data indicating that a patient with appendiceal adenocarcinoma and a GNAS mutation (R201H) benefited from trametinib for 4 months²⁰¹. Additionally, a patient with GNAS-mutated Erdheim-Chester disease exhibited a PR following treatment with single-agent trametinib²⁰².

FREQUENCY & PROGNOSIS

The highest incidences of GNAS mutations have

been reported in intraductal papillary mucinous neoplasms (40–66%)^{203–204} and appendiceal mucinous neoplasms (50–72%)^{205–206} as well as in tumors affecting the peritoneum (22%), pituitary gland (20%), bone (14%), pancreas (11%), and small intestine (11%)(COSMIC, 2022)¹⁶⁷. Amplification of GNAS has been reported in ovarian epithelial carcinomas (12–30%)^{186,207–208}, colorectal adenocarcinoma (9%)²¹, stomach adenocarcinoma (7%)¹⁷¹, lung adenocarcinoma (6.5%)²⁰⁹, breast invasive carcinoma (6.5%)²¹⁰, pancreatic adenocarcinoma (6%)¹⁷⁰, and sarcomas (5.8%)²¹¹. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2022)^{167,212–213}. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome²¹⁴. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer^{207–208}, while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with

gastric cancer²¹⁵.

FINDING SUMMARY

GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)²¹⁶. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase²¹⁶. GNAS has been reported to be amplified in cancer¹⁶⁹ and may be biologically relevant in this context^{217–218}. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration^{219–224} are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations^{225–227}.

GENE

SRC

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Dasatinib, a SRC and tyrosine kinase inhibitor, is approved for use in Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL). Bosutinib, which targets both ABL and SRC kinases, is approved to treat Ph+ CML with resistance or intolerance to prior therapy. Clinical trials of these agents and other SRC inhibitors are in progress in various cancer types^{228–229}.

— Nontargeted Approaches —

Overexpression of SRC in colorectal carcinoma may be associated with resistance to chemotherapy²³⁰.

FREQUENCY & PROGNOSIS

In the Colorectal Adenocarcinoma TCGA dataset, putative high-level amplification of SRC has been found in 12% of cases²¹. Dysregulation of the SRC family of kinases (SFK) in general has been reported in 80% of colorectal tumors, with 5–10-fold increases of SFK activity^{231–233}. Increased SFK expression and activity, including that of SRC, has been shown to occur early in colon carcinogenesis and play a role in colorectal tumor progression, with one study reporting strong SRC expression in 95% of adenomatous colon tissue^{234–238}. Increased SRC activity has been correlated with more aggressive CRC, shorter OS,

and general poor patient prognosis^{230,232–233,236–237}.

In contrast, one study of patients with CRC reported that amplification of chromosome 20q, which includes SRC, is significantly associated with wildtype KRAS/NRAS/BRAF, microsatellite stability, and improved OS in patients with metastatic disease²³⁹.

FINDING SUMMARY

The protein encoded by SRC belongs to a family of related non-receptor tyrosine kinases, members of which have been implicated in the growth and progression of a number of tumors, including breast, colon, and pancreatic cancer^{240–242}. SRC has been reported to be amplified in cancer¹⁶⁹ and may be biologically relevant in this context^{217–218}.

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

ORDERED TEST # ORD-1412469-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

G245S

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

733G>A

VARIANT ALLELE FREQUENCY (% VAF)

52.9%

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 adavosertib²⁴³⁻²⁴⁶, or p53 gene therapy and immunotherapeutics such as SGT-53²⁴⁷⁻²⁵¹ and ALT-801²⁵². In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype²⁵³. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer²⁵⁴. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer²⁵⁵. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone²⁵⁶. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel²⁵⁷. A Phase

1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations²⁵⁸. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring²⁵⁹. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage²⁵¹. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246²⁶⁰⁻²⁶². 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% DCR²⁶³. 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 studies²⁶⁴⁻²⁶⁵; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies²⁶⁶⁻²⁶⁷. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases^{21,268-273}. A study reported p53 expression in 49% of analyzed colorectal cancer cases²⁷⁴. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC²⁷⁵.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers²⁷⁶. Alterations such

as seen here may disrupt TP53 function or expression²⁷⁷⁻²⁸¹.

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Mar 2022)¹⁴⁴. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers²⁸²⁻²⁸⁴, including sarcomas²⁸⁵⁻²⁸⁶. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000²⁸⁷ to 1:20,000²⁸⁶. 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 30²⁸⁸. 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 expansion²⁸⁹⁻²⁹⁴. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy²⁸⁹⁻²⁹⁰. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease²⁹⁵. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{293,296-297}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1412469-01

GENOMIC FINDINGS

GENE

ZNF217

ALTERATION

amplification

has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells³⁰².

may contribute to tumorigenesis³¹⁴⁻³¹⁶, and increased expression or activation of ERBB3^{303,317}, FAK³⁰³, Aurora kinase A³⁰⁰, AKT³⁰¹, and TGF-beta/SMAD signaling³⁰³ has been demonstrated in ZNF217-expressing tumors or cells.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha²⁹⁸⁻²⁹⁹. ZNF217 overexpression has also been associated with resistance to paclitaxel³⁰⁰ and doxorubicin³⁰¹ in breast cancer cell lines. ZNF217

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast³⁰³, ovarian³⁰⁴⁻³⁰⁵, gastric³⁰⁶⁻³⁰⁷, colon³⁰⁸, prostate³⁰⁹, esophageal³¹⁰, and urothelial carcinomas³¹¹, glioblastoma³¹², and ovarian carcinosarcomas³¹³. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that

FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression^{301,318}. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines³¹⁹. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture³²⁰⁻³²¹.

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THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

Cetuximab

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

NRAS
G12D

KRAS
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^{69-72,322-323}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS⁶⁹⁻⁷² or NRAS^{109,273}, 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 Guidelines v3.2021).

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype CRC, both in combination with FOLFIRI, FOLFOX₄, or

irinotecan^{69-70,322-324} and as monotherapy for chemotherapy-refractory patients^{72,325}. A prospective study of cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 11% (2/19) of participants experiencing PRs and 58% (11/19) experiencing SDs³²⁶. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype metastatic CRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%³²⁷. 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)³²⁸. 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)³²⁹.

Panitumumab

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

NRAS
G12D

KRAS
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^{73,328,330}; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS⁷³⁻⁷⁵ or NRAS^{74,271}, 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 Guidelines v3.2021).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and

ORR for patients with KRAS wildtype CRC, both in combination with FOLFOX₄, FOLFIRI, irinotecan, or best supportive care^{73,331-333} and as monotherapy for chemotherapy-refractory patients^{271,328,330}. A Phase 2 trial reported that for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX₄, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS, 59% vs. 49%)³³⁴. 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)³²⁸. 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)³²⁹.

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-1412469-01

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
APC
ALTERATION
 Q1294*, Q789fs*31

RATIONALE
 Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT04008797
PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
 Beta-catenin, CBP, FGFRs, KIT, PDGFRA, RET, VEGFRs

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT05091346
PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

TARGETS
 Beta-catenin, CBP, PD-1

LOCATIONS: Osaka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), California

NCT03264664
PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
 Beta-catenin, CBP

LOCATIONS: Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom)

ORDERED TEST # ORD-1412469-01

CLINICAL TRIALS
GENE
AURKA
RATIONALE

Amplification of AURKA may sensitize cells to inhibitors of Aurora kinase A.

ALTERATION

amplification

NCT04742959
PHASE 1/2

Crossover Relative Bioavailability and Dose Escalation Study of TT-00420 Tablet in Patients With Advanced Solid Tumors

TARGETS

Aurora kinase A, Aurora kinase B

LOCATIONS: California, Illinois, Ohio, Texas, New Jersey

NCT04555837
PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS

Aurora kinase A, PD-1

LOCATIONS: Texas

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CLINICAL TRIALS
GENE
NRAS
ALTERATION
G12D
RATIONALE

Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways.

NRAS activating mutations or amplification may therefore sensitize tumors to inhibitors of these downstream pathways.

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)

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

JAK1, JAK2, 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)

NCT03377361
PHASE 1/2

An Investigational Immuno-therapy Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Patients With Previously Treated Cancer of the Colon or Rectum That Has Spread

TARGETS

PD-1, MEK, CTLA-4, BRAF, KIT, RET, VEGFRs

LOCATIONS: Southport (Australia), Elizabeth Vale (Australia), Blacktown (Australia), Clayton (Australia), Heidelberg (Australia), Olomouc (Czechia), Hradec Kralove (Czechia), Brno (Czechia), Padova (Italy), Milan (Italy)

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CLINICAL TRIALS
NCT05159245
PHASE 2

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

TARGETS

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

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

NCT04965818
PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS

MEK, FGFRs

LOCATIONS: California, Indiana, Texas

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

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

EGFR, RAFs, MEK

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

NCT04720976
PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS

MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah

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APPENDIX
Variants of Unknown Significance

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.

ASXL1
amplification

BRCA2
amplification

CDK8
amplification

CUL4A
amplification

DAXX
L332F

DDR2
T681I

DIS3
M509V and amplification

FGF14
amplification

FLT1
amplification

FLT3
amplification

IRS2
amplification

MLL2
A2925V

PARP3
R379Q

RB1
amplification

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APPENDIX
Genes Assayed in FoundationOne®CDx

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

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

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B or WTX)	
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKKN1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK1	NTRK2	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1
PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI
PRKN (PARK2)	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51
RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENTSC (FAM46C)	TET2	TGFBR2	TIPARP
TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL
WT1	XPO1	XRCC2	ZNF217	ZNF703				

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV1
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**
TPRSS2								

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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APPENDIX
About FoundationOne®CDx

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.


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. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

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- Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
 - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score $\geq 16\%$ will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
 - 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.

- 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.
- 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.
- Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of *HER2* overexpression as 20% in breast cancer. Based on the F1CDx *HER2* CDx concordance study, approximately 10% of *HER2* amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant

patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

*Interquartile Range = 1st Quartile to 3rd Quartile

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

VARIANTS THAT MAY REPRESENT

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About FoundationOne®CDx

CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version 6.3.0

The median exon coverage for this sample is 927x

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