ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

PATIENT

DISEASE Colon cancer (NOS)

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

PHYSICIAN

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

SPECIMEN

SPECIMEN ID E.F.C.P. 04/11/1958
SPECIMEN TYPE Blood
DATE OF COLLECTION 15 March 2021
SPECIMEN RECEIVED 22 March 2021

Biomarker Findings

Blood Tumor Mutational Burden - 6 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 34%

Genomic Findings

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

KRAS G13C
PIK3CA Q546K
APC T1556fs*3, W699*
DNMT3A splice site 1668-1G>A, Q573*
FAM123B S324*
SMAD4 G419R
TP53 R174fs*2, P190T

0 Therapies with Clinical Benefit
2 Therapies with Lack of Response
20 Clinical Trials

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - 6 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - 34%

GENOMIC FINDINGS		VAF %
KRAS -	G13C	31.3%
10 Trials see p. 12		
PIK3CA -	Q546K	0.2%
10 Trials see p. 14		

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).

Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.

THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
⚠ Cetuximab[1]	None
⚠ Panitumumab[1]	
None	None

⚠ *1. Patient may be resistant to indicated therapy*

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies 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/or exhaustive. Neither the therapies 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 or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *BRCA1*, *BRCA2*, *BRIP1*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

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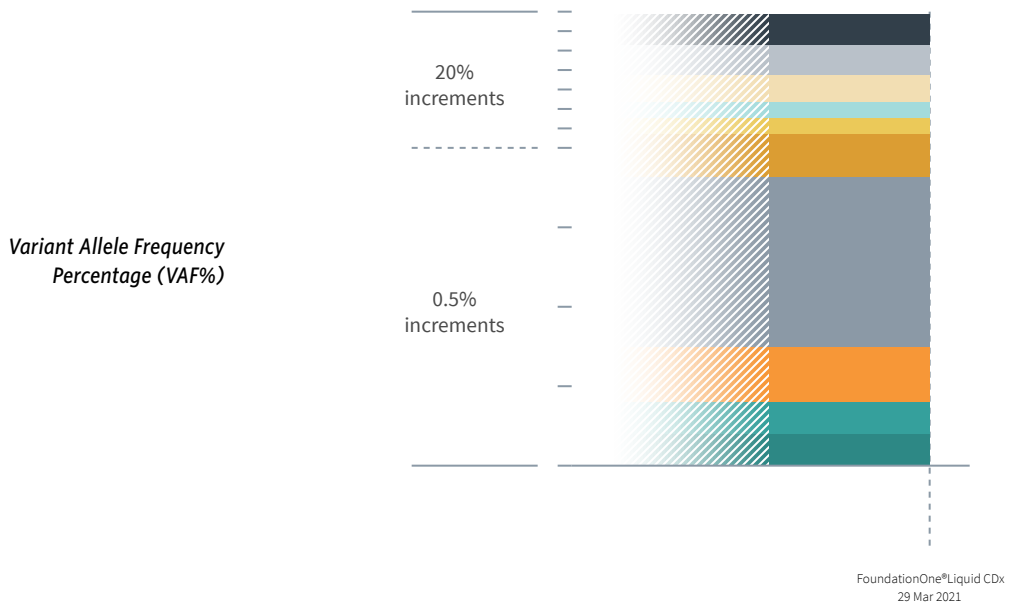

HISTORIC PATIENT FINDINGS		ORD-1048600-01 VAF%
Blood Tumor Mutational Burden		6 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		34%
KRAS	G13C	31.3%
PIK3CA	Q546K	0.2%
APC	W699*	16.4%
	T1556fs*3	16.7%
DNMT3A	Q573*	1.1%
	splice site 1668-1G>A	0.35%
FAM123B	S324*	28%
SMAD4	G419R	14.9%
TP53	R174fs*2	0.2%
	P190T	29.8%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be

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shown.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (TMB) and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)[5-7]. Although direct associations between blood or tissue TMB and prognosis of patients with CRC have not been reported, multiple studies have shown that MSI-H CRCs have a better prognosis than MSI-low (MSI-L) or microsatellite stable (MSS) tumors[8-15].

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[16-17] and cigarette smoke in lung cancer[18-19], treatment with temozolomide-based chemotherapy in glioma[20-21], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[22-26], and microsatellite instability (MSI)[22,25-26]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample 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[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
34%

POTENTIAL TREATMENT STRATEGIES

Specimens with high tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if tumor fraction is not detected as high, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[27-32].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[33]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[34], Ewing sarcoma and osteosarcoma[35], prostate cancer[30], breast cancer[36], leiomyosarcoma[37], esophageal cancer[38], colorectal cancer[39], and gastrointestinal cancer[40].

FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[41], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[42-43].

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GENE
KRAS

ALTERATION
G13C

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
37G>T

POTENTIAL TREATMENT STRATEGIES

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab[44-47] or panitumumab[48-50] in patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Guidelines v.3.2018). Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[51-56]. 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[57-61]. Both clinical[62-63] and preclinical[64-65] 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[63], RAF inhibitors[64], pan-ERBB inhibitors[65], or chemotherapeutic agents[62]. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors[66]. 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[67]. The reovirus Reolysin targets cells with activated RAS signaling[68-70] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[71-79].

FREQUENCY & PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)[80-88]. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC[82-85,89-90].

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[52,91]. 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[52,92-113].

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GENE
PIK3CA

ALTERATION
Q546K

TRANSCRIPT ID
NM_006218

CODING SEQUENCE EFFECT
1636C>A

POTENTIAL TREATMENT STRATEGIES

Clinical and preclinical data in various tumor types indicate that PIK3CA activating alterations may predict sensitivity to therapies targeting PI3K or AKT[114-115]. On the basis of clinical benefit for patients with PIK3CA mutations and preclinical evidence, PIK3CA-mutated tumors may also respond to mTOR inhibitors, including everolimus and temsirolimus[116-121]. In a Phase 1 trial of the dual PI3K/mTOR kinase inhibitor apitolisib, 79% (11/14) of patients with PIK3CA-mutated advanced solid tumors experienced disease control at the recommended Phase 2 dose (3/14 PRs, 8/14 SDs)[122]. A patient with previously treated HER2-negative metastatic breast cancer harboring a PIK3CA H1047R alteration achieved an exceptional response with the pan-class I PI3K inhibitor copanlisib[123]. However, studies of copanlisib and the pan-class I PI3K inhibitor buparlisib have demonstrated limited efficacy against PIK3CA-mutated tumors[124-130]. PI3K-alpha-selective inhibitors such as alpelisib or PI3K-beta-sparing inhibitors such as taselisib may have bigger therapeutic windows than pan-PI3K inhibitors[115]. In PIK3CA-mutated advanced solid tumors, alpelisib and taselisib have achieved low ORRs (0% [0/55] to 6% [7/111]) but high DCRs (55% [36/55] to 58% [64/111])[131]. AKT inhibitors ipatasertib and capivasertib have also been tested in breast cancer. Two Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR = 0.44) or capivasertib (9.3 vs. 3.7 months, HR = 0.30) to paclitaxel in metastatic triple-negative breast cancer harboring PIK3CA/AKT1/PTEN alterations, compared with paclitaxel and placebo[132]. Responses to capivasertib were also reported in 20% (3/15) of patients with PIK3CA-mutated breast cancer in an earlier study[133]. However, a Phase 1 trial reported no PFS benefit for patients with PIK3CA-mutated, ER+/HER2- metastatic breast cancer from the addition of capivasertib to paclitaxel compared with paclitaxel plus placebo (10.9 vs. 10.8 months)[134]. Emerging evidence suggests that the glutaminase inhibitor telaglenastat has clinical activity in CRC. A Phase 1 trial of telaglenastat and capecitabine for patients with CRC who progressed on fluoropyrimidine chemotherapy observed numerically increased PFS in patients with PIK3CA mutation compared to wild-type (26 vs. 16 weeks), including SD >30 weeks for 3 patients with PIK3CA mutation[135]. Multiple clinical studies report that inhibitors of the PI3K-AKT-mTOR pathway have not produced significant clinical benefit as monotherapies to treat colorectal cancer (CRC), even for tumors that harbor alterations in PIK3CA, AKT, and/or PTEN[127,136-141]. One patient with CRC harboring an AKT1 E17K mutation experienced short-term stable disease on monotherapy treatment with the AKT inhibitor AZD5363[141]. Resistance to therapy may arise, at least in part, through activation of the RAS-MAPK pathway[137-139]. Combinations of therapies may be required to overcome this lack of response, as demonstrated by both clinical and preclinical studies evaluating the efficacy of PI3K-AKT-mTOR pathway inhibitors in combination with chemotherapy[142] or inhibitors of the VEGF signaling pathway[143-144]. Activating mutations in PIK3CA may confer resistance to HER2-targeted therapies; combined inhibition of HER2 and the PI3K pathway may be required in HER2-positive tumors with PIK3CA mutation[145-149].

FREQUENCY & PROGNOSIS

PIK3CA mutations have been reported in 10-20% of colorectal cancers[25,81,150-151]. A meta-analysis of 864 patients with colorectal cancer treated with cetuximab- or panitumumab-based therapy showed that PIK3CA mutations, particularly in exon 20 (H1047R), are significantly associated with worse response[152] and shorter progression-free and overall survival[153].

FINDING SUMMARY

PIK3CA encodes p110-alpha, which is the catalytic subunit of phosphatidylinositol 3-kinase (PI3K). The PI3K pathway is involved in cell signaling that regulates a number of critical cellular functions, including cell growth, proliferation, differentiation, motility, and survival[154-155]. PIK3CA alterations that have been characterized as activating, such as observed here, are predicted to be oncogenic[156-176].

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GENE
APC

ALTERATION
T1556fs*3, W699*

TRANSCRIPT ID
NM_000038, NM_000038

CODING SEQUENCE EFFECT
4666_4667insA, 2096G>A

POTENTIAL TREATMENT STRATEGIES
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[177]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[178-179]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[180].

FREQUENCY & PROGNOSIS
APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset[25]. 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)[181]. The prognostic significance of APC mutations in sporadic CRC remains unclear[182].

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[183]. Alterations such as seen here may disrupt APC function or expression[184-188].

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, Sep 2020)[189]. 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)[190-192]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[193], and in the appropriate clinical context germline testing of APC is recommended.

GENE
DNMT3A

ALTERATION
splice site 1668-1G>A, Q573*

TRANSCRIPT ID
NM_022552, NM_022552

CODING SEQUENCE EFFECT
1668-1G>A, 1717C>T

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS
DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2021)[5-6]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2021). 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[194-199]. 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[194-195]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[200]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[198,201-202]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY
The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[203-204]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[205-210]. Alterations such as seen here may disrupt DNMT3A function or expression[211-214].

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GENE
FAM123B

ALTERATION
S324*

TRANSCRIPT ID
NM_152424

CODING SEQUENCE EFFECT
971C>A

POTENTIAL TREATMENT STRATEGIES
There are no targeted therapies available to address genomic alterations in FAM123B.

FREQUENCY & PROGNOSIS
Somatic mutation of FAM123B is rare in most cancers (COSMIC, 2021)[7], but is observed at rates ranging from 5-30% in Wilms tumor[215-217]. No association between FAM123B alteration and clinical features or outcomes of Wilms tumor has been documented.

FINDING SUMMARY
FAM123B, also known as AMER1, encodes the protein WTX, which binds to beta-catenin, enhancing its proteasomal degradation and thereby exerting a repressive effect on WNT pathway signaling[218]. Germline mutation or deletion of FAM123B causes osteopathia striata with cranial sclerosis[219-220].

GENE
SMAD4

ALTERATION
G419R

TRANSCRIPT ID
NM_005359

CODING SEQUENCE EFFECT
1255G>A

POTENTIAL TREATMENT STRATEGIES
There are no therapies to address SMAD4 alterations in cancer. Preclinical studies[221-222] and a clinical study of pancreatic cancer suggest that low SMAD4 expression exhibit increased responsiveness to chemotherapeutic agents such as cisplatin and irinotecan[223].

FREQUENCY & PROGNOSIS
SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[224], pancreatic acinar cell carcinoma[225], cholangiocarcinoma (25%)[226], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[227-228], colorectal adenocarcinoma (CRC; 14%)[25], esophageal adenocarcinoma (14%)[229], and stomach adenocarcinoma (13%)[230]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[231] and intraductal papillary mucinous neoplasms (IPMN)[232]; in clinical samples, SMAD4 homozygous deletion has been observed in 10% of IPMNs and 8% of MCNs, and mutation was also observed in 5% of IPMNs[233]. SMAD4 gene alterations have been associated with reduced overall survival for patients with pancreatic adenocarcinoma[234]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[235-237], appendiceal mucinous neoplasm[238], gastric adenocarcinoma[239-240], esophageal adenocarcinoma[241], esophageal squamous cell carcinoma[242], breast cancer[243], and prostate cancer[244].

FINDING SUMMARY
SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[245-246]. SMAD4 alterations that result in loss or disruption of the MH1 domain (aa 18-142), MH2 domain (aa 323-552), or SAD domain (aa 275-320) are predicted to be inactivating[247-260].

POTENTIAL GERMLINE IMPLICATIONS
Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[261-263], which is associated with an increased risk of gastrointestinal cancers[264]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[265]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

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GENE
TP53

ALTERATION
R174fs*2, P190T

TRANSCRIPT ID
NM_000546, NM_000546

CODING SEQUENCE EFFECT
519_520insTTGTG, 568C>A

POTENTIAL TREATMENT STRATEGIES

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[266-269], or p53 gene therapy and immunotherapeutics such as SGT-53[270-274] and ALT-801[275]. 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) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[276]. 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 in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[277]. 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 in patients with platinum-refractory TP53-mutated ovarian cancer[278]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[279]. 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[280]. 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[281]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in 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[274]. 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[282]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[283-285]. In a Phase 1b trial in 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[286]. 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[287-288]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[289-290]. 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[25,291-296]. In one study comparing colorectal neuroendocrine carcinoma (NECs) and neuroendocrine tumors (NETs), mutations observed in colorectal adenocarcinomas were frequently observed in colorectal NECs but not in colorectal NETs; TP53 mutation was identified in 5/24 NEC samples but not in any of 20 NET samples analyzed, and aberrant p53 expression was significantly more frequent in NECs (88%; 16/20) than in NETs (67%; 17/25)[297]. There are additional reports of TP53 mutation in other types of neuroendocrine carcinomas[298-301]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[302]. Loss of heterozygosity (LOH) at the TP53 locus has been identified in 80% (4/5) of poorly differentiated colorectal NECs in one study[303]. Studies have reported high p53 expression in 50-100% of neuroendocrine carcinomas analyzed[304-307]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[308]. A study of p53 expression in high-grade neuroendocrine carcinomas showed that patients with tumors that overexpressed p53, CD117, and Ki-67 had shorter survival[309]. High p53 expression has also been correlated with poor prognosis for patients with gastroenteropancreatic neuroendocrine tumors[306]. 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[194-199]. 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[194-195]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[200]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[198,201-202]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[310]. Alterations such as seen here may disrupt TP53 function or expression[311-315].

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[316-318], including sarcomas[319-320]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[321] to 1:20,000[320]. 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[322]. In the appropriate clinical context, germline testing of TP53 is recommended.

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Cetuximab

⚠ Patient may be resistant to Cetuximab

Assay findings association

KRAS
G13C

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 in patients with CRC[44-47,323-324] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Guidelines v2.2019). Activating mutations in either KRAS[44-47] or NRAS[153,296] , which function downstream of EGFR, are associated with lack of benefit of cetuximab in patients with CRC and indicate against the use of cetuximab (NCCN Guidelines v2.2019).

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[44-45,324] and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients[46-47,323] . 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[325]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS/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%[326].

Panitumumab

⚠ Patient may be resistant to Panitumumab

Assay findings association

KRAS
G13C

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 in patients with CRC[48,327-328] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Guidelines v2.2019). Activating mutations in either KRAS[48-50] or NRAS[49,294] , which function downstream of EGFR, are associated with lack of benefit of panitumumab in patients with CRC and indicate against the use of panitumumab (NCCN Guidelines v2.2019).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR in patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX4[48] and as monotherapy for chemotherapy-refractory patients[327-328] . An open-label, randomized Phase 2 trial reported that in 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%)[329].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

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ORDERED TEST # ORD-1048600-01

CLINICAL TRIALS

IMPORTANT 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. There may also be compassionate use or early access programs available, which are not listed in this report. 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 are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
KRAS

ALTERATION
G13C

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.

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

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

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

NCT03374254

PHASE 1

Safety and Efficacy of Pembrolizumab (MK-3475) Plus Binimetinib Alone or Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Metastatic Colorectal Cancer (mCRC) Participants (MK-3475-651)

TARGETS
PD-1, MEK

LOCATIONS: Florida, Texas, Pennsylvania, New Jersey, Connecticut, Illinois, Toronto (Canada), Montreal (Canada), Colorado, California

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

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

NCT03981614

PHASE 2

Binimetinib and Palbociclib or TAS-102 in Treating Patients With KRAS and NRAS Mutant Metastatic or Unresectable Colorectal Cancer

TARGETS
CDK4, CDK6, MEK

LOCATIONS: Texas, Georgia, North Carolina, Tennessee, Kansas, Arizona

NCT02613650

PHASE 1

A Trial of mFOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers

TARGETS
MEK

LOCATIONS: Utah

NCT03284502

PHASE 1

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

TARGETS
MEK, RAFs

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

NCT03065387

PHASE 1

Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation

TARGETS
mTOR, EGFR, ERBB2, ERBB4, CDK4, CDK6, MEK

LOCATIONS: Texas

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

GENE
PIK3CA

ALTERATION
Q546K

RATIONALE
PIK3CA activating mutations may lead to activation of the PI3K-AKT-mTOR pathway and may therefore indicate sensitivity to inhibitors of this pathway. Strong clinical data support sensitivity of PIK3CA-mutated solid tumors to the PI3K-alpha inhibitor alpelisib. 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. On the basis of preclinical and limited clinical data, PIK3CA activating mutations may predict sensitivity to glutaminase inhibitors.

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chengdu (China)

NCT03439462

PHASE 1/2

ABI-009 (Nab-rapamycin) in Combination With FOLFOX and Bevacizumab as First-line Therapy in Patients With Advanced or Metastatic Colorectal Cancer

TARGETS
mTOR, VEGFA

LOCATIONS: Louisiana, Texas, New Jersey, Arizona, Nevada, Washington

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS
ALK, ROS1, TRKA, TRKB, TRKC, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha

LOCATIONS: Alabama, Texas, Tennessee, Pennsylvania, Ohio, New Jersey, New York

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

NCT03366103

PHASE 1/2

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

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

LOCATIONS: Maryland, New Jersey, New York

NCT02688881

PHASE 4

Study to Evaluate the Safety and Efficacy of Sirolimus, in Subject With Refractory Solid Tumors

TARGETS
mTOR

LOCATIONS: Seoul (Korea, Republic of)

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NCT03502733

PHASE 1

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

TARGETS
PI3K, PD-1

LOCATIONS: Texas, Maryland

NCT03842228

PHASE 1

Copanlisib, Olaparib, and Durvalumab in Treating Patients With Metastatic or Unresectable Solid Tumors

TARGETS
PI3K, PD-L1, PARP

LOCATIONS: Texas, Massachusetts

NCT03006172

PHASE 1

To Evaluate the Safety, Tolerability, and Pharmacokinetics of GDC-0077 Single Agent in Participants With Solid Tumors and in Combination With Endocrine and Targeted Therapies in Participants With Breast Cancer

TARGETS
PI3K-alpha, Aromatase, ER, CDK4, CDK6

LOCATIONS: Tennessee, New York, Massachusetts, Toronto (Canada), Valencia (Spain), Bordeaux (France), Barcelona (Spain), Surrey (United Kingdom), London (United Kingdom), Villejuif (France)

NCT02861300

PHASE 1/2

CB-839 + Capecitabine in Solid Tumors and Fluoropyrimidine Resistant PIK3CA Mutant Colorectal Cancer

TARGETS
GLS

LOCATIONS: Ohio

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.

BCORL1
G1203S

CD22
T793M

CDK12
E1024K

DNMT3A
D702Y and G685E

EP300
K418R

FGFR4
R443H

MAP3K13
Q725K

NTRK1
G18E

RET
G533S

TET2
M533I

TSC1
M322T

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ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B)	***APC***
AR	***ARAF*** **Exons 4, 5, 7, 11, 13, 15, 16**	*ARFRP1*	*ARID1A*	*ASXL1*	***ATM***	***ATR***	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BCR** Introns 8, 13, 14	***BRAF*** **Exons 11-18,** Introns 7-10	***BRCA1*** Introns 2, 7, 8, 12, 16, 19, 20	***BRCA2*** Intron 2	*BRD4*	*BRIP1*	*BTG1*
BTG2	***BTK*** **Exons 2, 15**	*C11orf30* (EMSY)	*C17orf39* (GID4)	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CCNE1*	*CD22*	*CD70*	*CD74** Introns 6-8	*CD79A*	*CD79B*
CD274 **(PD-L1)**	*CDC73*	***CDH1***	***CDK12***	***CDK4***	***CDK6***	*CDK8*	*CDKN1A*	*CDKN1B*
CDKN2A	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	***CHEK2***	*CIC*	*CREBBP*	***CRKL***
CSF1R	*CSF3R*	*CTCF*	*CTNNA1*	***CTNNB1*** **Exon 3**	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*
DAXX	*DDR1*	***DDR2*** **Exons 5, 17, 18**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	***EGFR*** **Introns 7,** 15**, 24-27**	*EP300*
EPHA3	*EPHB1*	*EPHB4*	***ERBB2***	***ERBB3*** **Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25**	*ERBB4*	*ERCC4*	*ERG*	***ERRFI1***
ESR1 **Exons 4-8**	*ETV4** Intron 8	*ETV5** Introns 6, 7	***ETV6**** **Introns 5, 6**	*EWSR1** Introns 7-13	***EZH2*** **Exons 4, 16, 17, 18**	*EZR** Introns 9-11	*FAM46C*	*FANCA*
FANCC	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*	*FGF19*
FGF23	*FGF3*	*FGF4*	*FGF6*	***FGFR1*** Introns 1, 5, **Intron 17**	***FGFR2*** Intron 1, **Intron 17**	***FGFR3*** **Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17**	*FGFR4*	*FH*
FLCN	*FLT1*	***FLT3*** **Exons 14, 15, 20**	***FOXL2***	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*	*GATA6*
GNA11 **Exons 4, 5**	*GNA13*	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3F3A*	*HDAC1*	*HGF*
HNF1A	***HRAS*** **Exons 2, 3**	*HSD3B1*	*ID3*	***IDH1*** **Exon 4**	***IDH2*** **Exon 4**	*IGF1R*	*IKBKE*	*IKZF1*
INPP4B	*IRF2*	*IRF4*	*IRS2*	*JAK1*	***JAK2*** **Exon 14**	***JAK3*** **Exons 5, 11, 12, 13, 15, 16**	*JUN*	*KDM5A*
KDM5C	*KDM6A*	*KDR*	*KEAP1*	*KEL*	***KIT*** **Exons 8, 9, 11, 12, 13, 17,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)

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KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** (MEK1) Exons 2, 3	***MAP2K2*** (MEK2) Exons 2-4, 6, 7	*MAP2K4*	*MAP3K1*	*MAP3K13*

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MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11A*	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*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*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*	***RET*** Introns 7, 8, **Exons 11, 13-16, Introns 9-11**
RICTOR	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*
SMO	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*
STAT3	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TERC** ncRNA	***TERT**** **Promoter**	*TET2*
TGFBR2	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*	*TYRO3*
U2AF1	***VEGFA***	*VHL*	*WHSC1*	*WTI*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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FoundationOne Liquid 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. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid 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.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx 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 malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also detects select genomic rearrangements, select copy number alterations, tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

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. *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.

QUALIFIED ALTERATION CALLS (EQUIVOCAL)

All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

RANKING OF ALTERATIONS AND THERAPIES

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.
8. Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from observed aneuploid instability in the sample.
9. Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

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to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

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 with no conflicts), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, 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 *BAP1, BRCA1, BRCA2, BRIP1, 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.

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®.

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 Liquid CDx.

TREATMENT DECISIONS ARE THE 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 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 of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, 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 3.0.0

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1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
6. Gao J, et al. Sci Signal (2013) pmid: 23550210
7. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
8. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
9. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
10. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
11. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
12. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
13. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
14. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
15. Laghi L, et al. Dig Dis (2012) pmid: 22722556
16. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
17. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
18. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
19. Rizvi NA, et al. Science (2015) pmid: 25765070
20. Johnson BE, et al. Science (2014) pmid: 24336570
21. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
22. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
23. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
24. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
25. Nature (2012) pmid: 22810696
26. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
27. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
28. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
29. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
30. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
31. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
32. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
33. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
34. Lapin M, et al. J Transl Med (2018) pmid: 30400802
35. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
36. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
37. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
38. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
39. Fan G, et al. PLoS ONE (2017) pmid: 28187169
40. Vu et al., 2020; DOI: 10.1200/PO.19.00204
41. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
42. Zhang EW, et al. Cancer (2020) pmid: 32757294
43. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
44. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
45. Bokemeyer C, et al. Ann. Oncol. (2011) pmid: 21228335
46. Karapetis CS, et al. N. Engl. J. Med. (2008) pmid: 18946061
47. De Roock W, et al. Ann. Oncol. (2008) pmid: 17998284
48. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
49. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
50. Amado RG, et al. J. Clin. Oncol. (2008) pmid: 18316791
51. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
52. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
53. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
54. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
55. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
56. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
57. Tsimberidou et al., 2013; ASCO Abstract e22086
58. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
59. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
60. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
61. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
62. Hochster et al., 2013; ASCO GI Abstract 380
63. Juric et al., 2014; ASCO Abstract 9051
64. Lamba S, et al. Cell Rep (2014) pmid: 25199829
65. Sun C, et al. Cell Rep (2014) pmid: 24685132
66. Luo J, et al. Cell (2009) pmid: 19490893
67. Barzi et al., 2020; AACR Abstract CT235
68. Strong JE, et al. EMBO J. (1998) pmid: 9628872
69. Coffey MC, et al. Science (1998) pmid: 9812900
70. Gong J, et al. Front Oncol (2014) pmid: 25019061
71. Forsyth P, et al. Mol. Ther. (2008) pmid: 18253152
72. Vidal L, et al. Clin. Cancer Res. (2008) pmid: 18981012
73. Gollamudi R, et al. Invest New Drugs (2010) pmid: 19572105
74. Harrington KJ, et al. Clin. Cancer Res. (2010) pmid: 20484020
75. Comins C, et al. Clin. Cancer Res. (2010) pmid: 20926400
76. Lolkema MP, et al. Clin. Cancer Res. (2011) pmid: 21106728
77. Galanis E, et al. Mol. Ther. (2012) pmid: 22871663
78. Karapanagiotou EM, et al. Clin. Cancer Res. (2012) pmid: 22316603
79. Morris DG, et al. Invest New Drugs (2013) pmid: 22886613
80. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717
81. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
82. Chen J, et al. BMC Cancer (2014) pmid: 25367198
83. Li W, et al. BMC Cancer (2015) pmid: 25929517
84. Hu J, et al. Medicine (Baltimore) (2016) pmid: 27977612
85. Zekri J, et al. Genet. Mol. Res. (2017) pmid: 28218784
86. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) pmid: 29048416
87. Wang Y, et al. Virchows Arch. (2018) pmid: 29705968
88. Guo F, et al. Sci Rep (2018) pmid: 29666387
89. Mármol I, et al. Int J Mol Sci (2017) pmid: 28106826
90. Kwak MS, et al. Medicine (Baltimore) (2017) pmid: 28858102
91. Kahn S, et al. Anticancer Res. () pmid: 3310850
92. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
93. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
94. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
95. Sci. STKE (2004) pmid: 15367757
96. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
97. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
98. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
99. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
100. Kim E, et al. Cancer Discov (2016) pmid: 27147599
101. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
102. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
103. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
104. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
105. Scheffzek K, et al. Science (1997) pmid: 9219684
106. Scholl C, et al. Cell (2009) pmid: 19490892
107. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
108. Tyner JW, et al. Blood (2009) pmid: 19075190
109. Valencia A, et al. Biochemistry (1991) pmid: 2029511
110. White Y, et al. Nat Commun (2016) pmid: 26854029
111. Wiest JS, et al. Oncogene (1994) pmid: 8058307
112. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
113. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
114. André F, et al. N. Engl. J. Med. (2019) pmid: 31091374
115. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
116. Park HS, et al. PLoS ONE (2016) pmid: 27105424
117. André F, et al. J. Clin. Oncol. (2016) pmid: 27091708
118. Janku F, et al. Mol. Cancer Ther. (2011) pmid: 21216929
119. Moulder S, et al. Ann. Oncol. (2015) pmid: 25878190
120. Lim SM, et al. Oncotarget (2016) pmid: 26859683
121. Meric-Bernstam F, et al. Clin. Cancer Res. (2012) pmid: 22422409
122. Dolly SO, et al. Clin. Cancer Res. (2016) pmid: 26787751
123. Spathas et al., 2020; DOI: 10.1200/PO.19.00049
124. Santin AD, et al. Gynecol Oncol Rep (2020) pmid: 31934607
125. Campone M, et al. Eur. J. Cancer (2018) pmid: 30241001
126. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
127. Rodon J, et al. Invest New Drugs (2014) pmid: 24652201
128. Bendell JC, et al. J. Clin. Oncol. (2012) pmid: 22162589
129. Heudel PE, et al. Br. J. Cancer (2017) pmid: 28072765
130. Vansteenkiste JF, et al. J Thorac Oncol (2015) pmid: 26098748
131. Juric D, et al. J. Clin. Oncol. (2018) pmid: 29401002
132. Schmid P, et al. J. Clin. Oncol. (2019) pmid: 31841354
133. Banerji et al., 2015; ASCO Abstract 2500
134. Turner NC, et al. Ann. Oncol. (2019) pmid: 30860570
135. Eads et al., 2018; ASCO Abstract 2562
136. Dasari et al., 2016; ASCO Abstract 3563
137. Ng K, et al. Clin. Cancer Res. (2013) pmid: 23743569
138. Ganesan P, et al. Mol. Cancer Ther. (2013) pmid: 24092809
139. Janku F, et al. Cell Rep (2014) pmid: 24440717
140. Bowles DW, et al. Clin Colorectal Cancer (2016) pmid: 27118441
141. Hyman DM, et al. J. Clin. Oncol. (2017) pmid: 28489509
142. Wainberg ZA, et al. Target Oncol (2017) pmid: 29067643
143. Altomare I, et al. Oncologist (2011) pmid: 21795432
144. Wolpin BM, et al. Oncologist (2013) pmid: 23580238
145. Esteva FJ, et al. Am. J. Pathol. (2010) pmid: 20813970
146. Baselga J, et al. J. Clin. Oncol. (2014) pmid: 25332247
147. Chakrabarty A, et al. Oncogene (2010) pmid: 20581867
148. Kataoka Y, et al. Ann. Oncol. (2010) pmid: 19633047
149. Wang L, et al. BMC Cancer (2011) pmid: 21676217
150. Li HT, et al. Oncol. Rep. (2011) pmid: 21424126
151. Brannon AR, et al. Genome Biol. (2014) pmid: 25164765
152. Huang L, et al. Arch Med Sci (2014) pmid: 24701207
153. De Roock W, et al. Lancet Oncol. (2010) pmid: 20619739
154. Samuels Y, et al. Cancer Cell (2005) pmid: 15950905
155. Nat. Rev. Cancer (2009) pmid: 19629070
156. Kang S, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid:

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15647370
157. Ikenoue T, et al. Cancer Res. (2005) pmid: 15930273
158. Gymnopoulos M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17376864
159. Horn S, et al. Oncogene (2008) pmid: 18317450
160. Rudd ML, et al. Clin. Cancer Res. (2011) pmid: 21266528
161. Hon WC, et al. Oncogene (2012) pmid: 22120714
162. Burke JE, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22949682
163. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
164. Laurenti R, et al. Rev Saude Publica (1990) pmid: 2103068
165. Dan S, et al. Cancer Res. (2010) pmid: 20530683
166. Oda K, et al. Cancer Res. (2008) pmid: 18829572
167. Zhao L, et al. Oncogene (2008) pmid: 18794883
168. Lui VW, et al. Cancer Discov (2013) pmid: 23619167
169. Ross RL, et al. Oncogene (2013) pmid: 22430209
170. Rivière JB, et al. Nat. Genet. (2012) pmid: 22729224
171. Shibata T, et al. Cancer Lett. (2009) pmid: 19394761
172. Dogruluk T, et al. Cancer Res. (2015) pmid: 26627007
173. Croessmann S, et al. Clin. Cancer Res. (2018) pmid: 29284706
174. Ng PK, et al. Cancer Cell (2018) pmid: 29533785
175. Spangle JM, et al. (2020) pmid: 32929011
176. Chen L, et al. Nat Commun (2018) pmid: 29636477
177. Zhang L, et al. Nature (2010) pmid: 20348907
178. Lu W, et al. Eur. J. Pharmacol. (2009) pmid: 19026633
179. Tuynman JB, et al. Cancer Res. (2008) pmid: 18281498
180. Lau T, et al. Cancer Res. (2013) pmid: 23539443
181. Fu Y, et al. Int. J. Cancer (2011) pmid: 21455986
182. Quyn AJ, et al. Surgeon (2008) pmid: 19110823
183. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
184. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
185. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
186. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
187. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
188. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
189. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
190. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
191. Annu Rev Pathol (2011) pmid: 21090969
192. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
193. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
194. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
195. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
196. Xie M, et al. Nat. Med. (2014) pmid: 25326804
197. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
198. Severson EA, et al. Blood (2018) pmid: 29678827
199. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
200. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
201. Chabon JJ, et al. Nature (2020) pmid: 32269342
202. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
203. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
204. Prog Mol Biol Transl Sci (2011) pmid: 21507354
205. Yang J, et al. Mol Med Rep () pmid: 21887466
206. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
207. Daskalos A, et al. Cancer (2011) pmid: 21351083
208. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
209. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
210. Kim MS, et al. APMIS (2013) pmid: 23031157
211. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
212. Guo X, et al. Nature (2015) pmid: 25383530
213. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
214. Zhang ZM, et al. Nature (2018) pmid: 29414941
215. Perotti D, et al. Oncogene (2008) pmid: 18391980
216. Ruteshouser EC, et al. Genes Chromosomes Cancer (2008) pmid: 18311776
217. Rivera MN, et al. Science (2007) pmid: 17204608
218. Major MB, et al. Science (2007) pmid: 17510365
219. Jenkins ZA, et al. Nat. Genet. (2009) pmid: 19079258
220. Perdu B, et al. J. Bone Miner. Res. (2010) pmid: 20209645
221. Cui Y, et al. Clin. Cancer Res. (2012) pmid: 22753594
222. Haeger SM, et al. Oncogene (2016) pmid: 25893305
223. Bachet JB, et al. Ann. Oncol. (2012) pmid: 22377565
224. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
225. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
226. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
227. Liu X, et al. Clin. Chem. (2014) pmid: 24821835
228. Maru D, et al. Oncogene (2004) pmid: 14647445
229. Wang K, et al. Oncologist (2015) pmid: 26336083
230. Nature (2014) pmid: 25079317
231. Izeradjene K, et al. Cancer Cell (2007) pmid: 17349581
232. Bardeesy N, et al. Genes Dev. (2006) pmid: 17114584
233. Springer S, et al. Gastroenterology (2015) pmid: 26253305
234. Blackford A, et al. Clin. Cancer Res. (2009) pmid: 19584151
235. Yan P, et al. Clin. Cancer Res. (2016) pmid: 26861460
236. Kozak MM, et al. J. Clin. Pathol. (2015) pmid: 25681512
237. Roth AD, et al. J. Natl. Cancer Inst. (2012) pmid: 23104212
238. Davison JM, et al. Am. J. Surg. Pathol. (2014) pmid: 24618609
239. Kim YH, et al. Ann. Oncol. (2004) pmid: 15033661
240. Xiangming C, et al. Clin. Cancer Res. (2001) pmid: 11234879
241. Singhi AD, et al. Am. J. Surg. Pathol. (2015) pmid: 25634752
242. Natsugoe S, et al. Clin. Cancer Res. (2002) pmid: 12060625
243. de Kruijf EM, et al. Ann. Oncol. (2013) pmid: 23022998
244. Shipitsin M, et al. Br. J. Cancer (2014) pmid: 25032733
245. Nat. Rev. Mol. Cell Biol. (2012) pmid: 22992590
246. Cell (2008) pmid: 18662538
247. Massagué J, et al. Genes Dev. (2005) pmid: 16322555
248. Morén A, et al. Oncogene (2000) pmid: 10980615
249. Xu J, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10781087
250. Luo K, et al. Genes Dev. (1999) pmid: 10485843
251. Jones JB, et al. Nucleic Acids Res. (2000) pmid: 10871368
252. Fink SP, et al. Cancer Res. (2001) pmid: 11196171
253. De Bosscher K, et al. Biochem. J. (2004) pmid: 14715079
254. Shi Y, et al. Nature (1997) pmid: 9214508
255. Miyaki M, et al. Oncogene (1999) pmid: 10340381
256. Prokova V, et al. Biochemistry (2007) pmid: 17994767
257. Wu JW, et al. J. Biol. Chem. (2001) pmid: 11274206
258. Ding L, et al. J. Clin. Invest. (2009) pmid: 19139564
259. Kuang C, et al. Oncogene (2004) pmid: 14647410
260. Watanabe M, et al. EMBO Rep. (2000) pmid: 11265759
261. Houlston R, et al. Hum. Mol. Genet. (1998) pmid: 9811934
262. Woodford-Richens K, et al. Gut (2000) pmid: 10764709
263. Howe JR, et al. J. Med. Genet. (2004) pmid: 15235019
264. Brosens LA, et al. World J. Gastroenterol. (2011) pmid: 22171123
265. Kalia SS, et al. Genet. Med. (2017) pmid: 27854360
266. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
267. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
268. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
269. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
270. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
271. Xu L, et al. Mol. Med. (2001) pmid: 11713371
272. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
273. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
274. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
275. Hajdenberg et al., 2012; ASCO Abstract e15010
276. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
277. Moore et al., 2019; ASCO Abstract 5513
278. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
279. Oza et al., 2015; ASCO Abstract 5506
280. Lee J, et al. Cancer Discov (2019) pmid: 31315834
281. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
282. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
283. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
284. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
285. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
286. Gourley et al., 2016; ASCO Abstract 5571
287. Kwok M, et al. Blood (2016) pmid: 26563132
288. Boudny M, et al. Haematologica (2019) pmid: 30975914
289. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
290. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
291. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
292. Berg M, et al. PLoS ONE (2010) pmid: 21103049
293. Han SW, et al. PLoS ONE (2013) pmid: 23700467
294. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582
295. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
296. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
297. Takizawa N, et al. Hum. Pathol. (2015) pmid: 26434631
298. Van Gele M, et al. Br. J. Cancer (2000) pmid: 10732753
299. Lill C, et al. Eur Arch Otorhinolaryngol (2011) pmid: 21331782
300. Nardi V, et al. Clin. Cancer Res. (2012) pmid: 22261808
301. Grabowski P, et al. Clin. Cancer Res. (2008) pmid: 19010853
302. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
303. Vortmeyer AO, et al. J. Natl. Cancer Inst. (1997) pmid: 9326914
304. Agaimy A, et al. Mod. Pathol. (2013) pmid: 23503646
305. Namikawa T, et al. Med Mol Morphol (2013) pmid: 23306663
306. Liu SZ, et al. Asian Pac. J. Cancer Prev. (2013) pmid: 23534765
307. Tan HL, et al. Clin. Cancer Res. (2014) pmid: 24323898
308. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
309. Erler BS, et al. Tumour Biol. (2011) pmid: 21058037
310. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
311. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
312. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609

Electronically signed by Richard Huang, M.D. | 29 March 2021
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313. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
314. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
315. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
316. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
317. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
318. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
319. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
320. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
321. Lalloo F, et al. Lancet (2003) pmid: 12672316
322. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
323. Cunningham D, et al. N. Engl. J. Med. (2004) pmid: 15269313
324. Jonker DJ, et al. N. Engl. J. Med. (2007) pmid: 18003960
325. Moiseyenko VM, et al. Clin Drug Investig (2018) pmid: 29470838
326. Stein et al., 2020; ASCO GI Abstract 96
327. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
328. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
329. Pietrantonio F, et al. JAMA Oncol (2019) pmid: 31268481

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