FOUNDATIONONE®LIQUID CDx

PATIENT
Hsiao Chen, Mei-Hung

TUMOR TYPE
Liver intrahepatic cholangiocarcinoma

COUNTRY CODE
TW

REPORT DATE
13 June 2023

ORDERED TEST #
ORD-1646037-01

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 Liver intrahepatic cholangiocarcinoma
NAME Hsiao Chen, Mei-Hung
DATE OF BIRTH 08 January 1939
SEX Female
MEDICAL RECORD # 46006900

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID MHHC 01/08/1939
SPECIMEN TYPE Blood
DATE OF COLLECTION 02 June 2023
SPECIMEN RECEIVED 06 June 2023

Biomarker Findings

Blood Tumor Mutational Burden - 3 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

KRAS Q61H
CDKN2A/B CDKN2B rearrangement intron 1
DNMT3A E482fs*169, F414fs*7
SMAD4 D493H
TET2 Q618*, L596fs*5
TP53 L130V

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A*** **E482fs*169, F414fs*7** (p. 7), ***TET2*** **L596fs*5, Q618*** (p. 8)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 3 Muts/Mb	**No therapies or clinical trials. See Biomarker Findings section**
Microsatellite status - MSI-High Not Detected	**MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).**
Tumor Fraction - Elevated Tumor Fraction Not Detected	**Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).**

GENOMIC FINDINGS		VAF%	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS -	Q61H	6.2%	None	None
4 Trials see p. 10				

Electronically signed by Irene Shyu, M.D. | 13 June 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

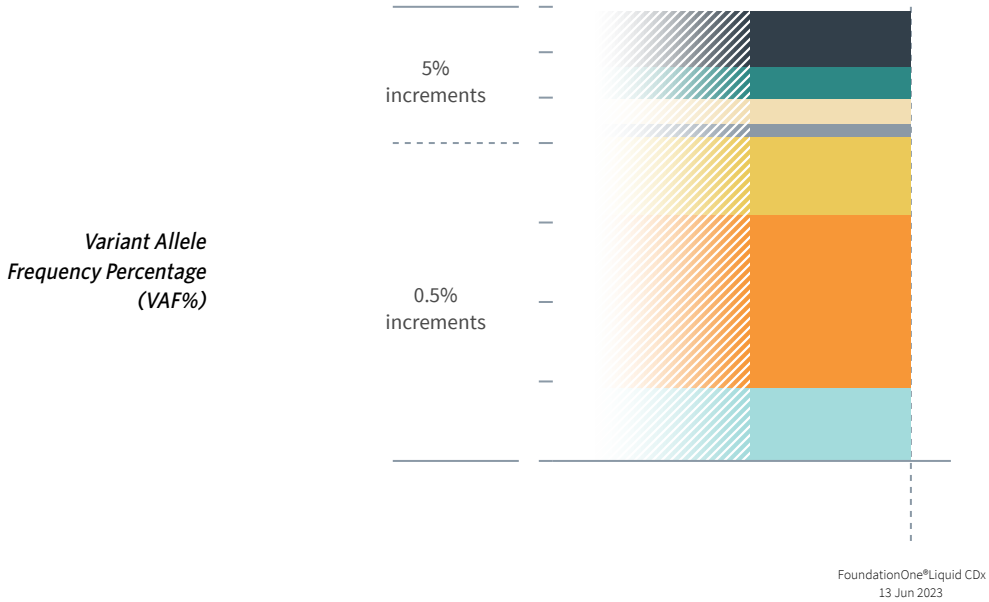
Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the 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, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, 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.



HISTORIC PATIENT FINDINGS		ORD-1646037-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
KRAS	● Q61H	6.2%
CDKN2A/B	CDKN2B rearrangement intron 1	3.9%
DNMT3A	● F414fs*7	3.6%
	● E482fs*169	1.1%
SMAD4	● D493H	0.46%
TET2	● L596fs*5	1.4%
	● Q618*	1.1%
TP53	● L130V	2.7%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx or FoundationOne®CDx tests. Up to five previous tests may be 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. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

Electronically signed by Irene Shyu, M.D. | 13 June 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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

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

Please note that other aspects of this table may have changed from the previous version to reflect the most up-to-date reporting information.

BIOMARKER

Blood Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased blood tumor mutational burden (bTMB) may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-3], anti-PD-1[3-4], anti-PD-1/CTLA4 therapies[5-6] , anti-PD-L1/CTLA4 therapies[7-10]. A Phase 2 multi-solid-tumor trial showed that bTMB ≥16 Muts/Mb (as measured by this assay) was associated with improved survival from treatment with a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor[5]. In non-small cell lung cancer (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 Muts/Mb-16 Muts/Mb[1,8-10]. In head and neck squamous cell carcinoma (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[11]. In colorectal cancer (CRC), a Phase 2 study showed that bTMB TMB ≥28 Muts/Mb (approximate equivalency ≥14 Muts/Mb as measured by this assay) was associated with improved OS from a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor[7].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (PubMed, Mar 2023). Published data investigating the prognostic implications of bTMB levels in biliary tract cancer are limited (PubMed, Jul 2022). Although cases with hypermutated biliary tract cancer were enriched in a subgroup with poor prognosis in 1 study[12], TMB-high (≥10 mut/Mb) status in biliary adenocarcinoma not treated with immunotherapy was not significantly associated with OS in another study, in which patients with TMB-high tumors experienced numerically longer OS compared with patients with TMB-low tumors (11.5 vs. 8.4 months, adjusted HR=0.65)[13].

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[14-15] and cigarette smoke in lung cancer[16-17], treatment with temozolomide-based chemotherapy in glioma[18-19], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[20-24], and microsatellite instability (MSI)[20,23-24]. 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[1-2,4]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus higher sensitivity for identifying genomic alterations. Such specimens are at a lower risk of false negative results. However, if elevated tumor fraction is not detected, 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[25-30].

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)[31]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[32], Ewing sarcoma and osteosarcoma[33], prostate cancer[28], breast cancer[34], leiomyosarcoma[35], esophageal cancer[36], colorectal cancer[37], and gastrointestinal cancer[38].

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[39], 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[40-41].

Electronically signed by Irene Shyu, M.D. | 13 June 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

GENE
KRAS

ALTERATION
Q61H

HGVS VARIANT
NM_004985.3:c.183A>C (p.Q61H)

VARIANT CHROMOSOMAL POSITION
chr12:25380275

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[42-47]. However, Phase 1 and Phase 2 trials of MEK inhibitor monotherapies reported no objective responses (4/4 SD) for patients with biliary tract cancer harboring KRAS mutations[48-49]. Although a Phase 1/2 study of binimetinib in combination with gemcitabine and cisplatin observed a 33% ORR (1 PR, n=3) for patients with KRAS-mutated advanced biliary tract cancer, this was comparable with the 36% ORR (3 CRs, 9 PRs, n=33) of the overall study population[50]. One study reported that patients with mutations in the RAS-MAPK pathway may be sensitive to binimetinib and capecitabine; patients with KRAS-, NRAS-, or MEK-mutated gemcitabine-pretreated biliary tract cancer experienced improved mPFS (5.4 vs. 2.6 months, p=0.031), mOS (10.8 vs. 5.3 months, p=0.011), and ORR (40% vs. 12.5%) as compared with patients lacking these mutations[51]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[52]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated LGSOC and 12% (2/17) for patients with KRAS-mutated NSCLC in a Phase 1 study[53-54] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[55-56]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[57]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[58]. Preclinical studies suggest that KRAS activating mutations may confer sensitivity to SOS1 inhibitors such as BI-3406, MRTX0902, BI-1701963, and BAY-293 as single agents[59-64] or in combination with covalent KRAS G12C inhibitors[64] and MEK inhibitors[65-66].

FREQUENCY & PROGNOSIS

KRAS mutations have been observed with an incidence of 13-50% in cholangiocarcinoma[67-73]. One study observed a higher frequency of KRAS mutations in intrahepatic cholangiocarcinomas with bile duct histology (23/98) versus tumors with cholangiolar histology (1/76)[70]. While some studies have reported no association between KRAS mutation and prognosis in cholangiocarcinoma[70,74], other studies have reported an association of KRAS mutation with poorer survival in patients with gallbladder or extrahepatic biliary tract cancers[75-76].

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[43,77]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, K117R, and K117N have been characterized as activating and oncogenic[43,78-100].

GENE
CDKN2A/B

ALTERATION
CDKN2B rearrangement intron 1

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[101-104], direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited[105-106].

FREQUENCY & PROGNOSIS

CDKN2A mutations and CDKN2A/B homozygous loss have been reported in 2.5-6% and 14% of cholangiocarcinomas, respectively[107-108]. Homozygous loss of the chromosomal region 9p21, which contains CDKN2A and CDKN2B, has been reported in 43% (3/7) of biliary dysplasias, as well as in 50% (3/6) of primary sclerosing cholangitis (PSC)-associated cholangiocarcinoma samples, and 50% (8/16) of sporadic cholangiocarcinoma samples[109]. In addition, loss of heterozygosity at 9p21 has been found in 89% (8/9) of PSC-associated cholangiocarcinoma samples[110]. However, in another study, homozygous deletion of CDKN2A was reported in 4% (2/51) of cholangiocarcinoma samples[111]. A study of 94 liver fluke-associated cholangiocarcinomas reported loss of p14ARF, p15INK4b, and p16INK4a protein expression in 31%, 58%, and 82% of cases, respectively[112]. Promoter methylation of CDKN2A or CDKN2B affecting the p14ARF, p16INK4a, or p15INK4b loci has been reported in 25-40%, 50-76%, and 49-50% of cholangiocarcinomas, respectively[111-114]. Loss of p16INK4a protein expression has been suggested to serve as a prognostic marker in cholangiocarcinoma, as promoter methylation of CDKN2A and loss of p16INK4a expression have been found to be correlated with poor survival in patients with cholangiocarcinoma[112,115-116].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[117-118]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[119-120]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[121-122]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[123].

GENE
DNMT3A

ALTERATION
E482fs*169, F414fs*7

HGVS VARIANT
NM_022552.3:c.1444del (p.E482Rfs*169),
NM_022552.3:c.1238dup (p.F414Lfs*7)

VARIANT CHROMOSOMAL POSITION
chr2:25468918-25468919, chr2:25469529

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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, COSMIC, PubMed, Feb 2023)[124-126]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2023).

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[127-128]. 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[129-134]. Alterations such as seen here may disrupt DNMT3A function or expression[135-138].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. 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[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
SMAD4

ALTERATION
D493H

HGVS VARIANT
NM_005359.5:c.1477G>C (p.D493H)

VARIANT CHROMOSOMAL POSITION
chr18:48604655

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SMAD4. Preclinical studies in colorectal cancer have reported associations of SMAD4 inactivation or loss with sensitivity to inhibitors of Aurora kinase A[148] and the Wnt/beta-catenin pathway[149].

— Nontargeted Approaches —

Clinical studies have reported associations of SMAD4 loss or low SMAD4 expression with improved responses to chemotherapeutic agents in patients with pancreatic cancer[150-152] and non-small cell lung cancer (NSCLC)[153]. Other clinical studies in pancreatic cancer have reported an association of high SMAD4 expression with better responses to neoadjuvant chemotherapy[154] and adjuvant chemoradiotherapy[155].

FREQUENCY & PROGNOSIS

SMAD4 mutation or homozygous deletion is most frequently observed in pancreatic adenocarcinoma (43%)[156], pancreatic acinar cell carcinoma (26%)[157], cholangiocarcinoma (25%)[158], small intestine cancer (20%)[159], appendiceal adenocarcinoma (14-20% mutation; 57% deletion)[160-161], colorectal adenocarcinoma (CRC; 14%)[23], esophageal adenocarcinoma (14%)[162], and stomach adenocarcinoma (13%)[163]. In preclinical studies, SMAD4 loss of function has been implicated in the development of mucinous neoplasms of the pancreas, including mucinous cystic neoplasms (MCN)[164] and intraductal papillary mucinous neoplasms (IPMN)[165]; 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[166]. SMAD4 gene alterations have been associated with reduced OS for patients with pancreatic adenocarcinoma[167]. Reduced SMAD4 expression has been associated with worse prognosis in various cancer types, including CRC[168-170], appendiceal mucinous neoplasm[171], gastric adenocarcinoma[172-173], esophageal adenocarcinoma[174], esophageal squamous cell carcinoma[175], breast cancer[176], and prostate cancer[177].

FINDING SUMMARY

SMAD4, also known as DPC4, encodes a tumor suppressor that regulates transcriptional activity downstream of TGF-beta receptor signaling[178-179]. 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[180-193].

POTENTIAL GERMLINE IMPLICATIONS

Germline SMAD4 mutations, including those at the R361 hotspot, have been observed in patients with juvenile polyposis syndrome[194-196], which is associated with an increased risk of gastrointestinal cancers[197]. The penetrance of deleterious SMAD4 mutations in patients with colon cancer is estimated at 20% by age 35 and 70% by age 65[198]. In the appropriate clinical context, germline testing of SMAD4 is recommended.

GENE
TET2

ALTERATION
Q618*, L596fs*5

HGVS VARIANT
NM_001127208.2:c.1852C>T (p.Q618*),
NM_001127208.2:c.1785del (p.L596Sfs*5)

VARIANT CHROMOSOMAL POSITION
chr4:106156951, chr4:106156883-106156884

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

TET2 alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies[199]. Published data investigating the prognostic implications of TET2 alterations in solid tumors are limited (PubMed, Jan 2023).

FINDING SUMMARY

TET2 encodes a tumor suppressor involved in reversing DNA methylation marks, a process critical for proper gene regulation[200-201]. Alterations such as seen here may disrupt TET2 function or expression[202-206].

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. 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[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
TP53

ALTERATION
L130V

HGVS VARIANT
NM_000546.4:c.388C>G (p.L130V)

VARIANT CHROMOSOMAL POSITION
chr17:7578542

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[207-210] or p53 gene therapy such as SGT53[211-215]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[216]. 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 cancer[217]. 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 cancer[218]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[219]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[220]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[221]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[222]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[215]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[223]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[224].

FREQUENCY & PROGNOSIS

Inactivation of p53, through mutation, deletion, or loss of heterozygosity (LOH), has been observed in 25-63% of gallbladder carcinomas and 10-61% of cholangiocarcinomas[12,72,107-108,225-230]. TP53 mutations occur more frequently in tumors caused by liver fluke (O. viverrini) infection (40%) than in cholangiocarcinoma cases not related to infection (9%)[107]. Aberrant TP53 expression, which is indicative of TP53 dysregulation, has been observed in 20–62% of gallbladder carcinomas and 25% (5/20) of cholangiocarcinomas[231-233]. Data regarding the prognostic significance of TP53 mutation in cholangiocarcinoma are conflicting[158,234-241]. Overexpression of p53 protein has been associated with reduced patient survival in poorly differentiated gallbladder adenocarcinomas and biliary tract cancers[242-243]; however, another study did not find such a correlation[236].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[244]. Alterations such as seen here may disrupt TP53 function or expression[245-249].

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[250-252], including sarcomas[253-254]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[255] to 1:20,000[254]. 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[256]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[139-144]. 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[139-140]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[145]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[143,146-147]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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
Q61H

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors. Preclinical evidence suggests that KRAS activating mutations may predict sensitivity to SOS1 inhibitors. Limited clinical evidence suggests that MEK inhibitors in combination with chemotherapy may be an effective treatment for patients with KRAS-, NRAS-, or MEK-mutated biliary tract cancer.

NCT04892017

PHASE 1/2

A Safety, Tolerability and PK Study of DCC-3116 in Patients With RAS or RAF Mutant Advanced or Metastatic Solid Tumors.

TARGETS
ULK1, ULK2, MEK

LOCATIONS: Oregon, Massachusetts, New York, Texas, Pennsylvania

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS
MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT05578092

PHASE 1/2

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

TARGETS
SOS1, KRAS

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

NCT03905148

PHASE 1

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

TARGETS
RAFs, EGFR, MEK

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

NOTE One or more variants of unknown significance (VUS) were detected in this patient's tumor. These variants may not have been adequately characterized in the scientific literature at the time this report was issued, and/or the genomic context of these alterations makes their significance unclear. We choose to include them here in the event that they become clinically meaningful in the future.

ABL1
rearrangement

CD79B
NM_000626.2: c.218A>C
(p.N73T)
chr17:62007646

CHEK2
NM_007194.3: c.1049C>T
(p.P350L)
chr22:29092935

CREBBP
NM_004380.2: c.2635C>T
(p.P879S)
chr16:3820816

DNMT3A
NM_022552.3: c.2177G>T
(p.G726V)
chr2:25463316,
NM_022552.3: c.2339T>C
(p.I780T)
chr2:25462068 and
NM_022552.3: c.1713_1721del
(p.Q573_A575del)
chr2:25467153-25467162

FANCA
NM_000135.2: c.4331C>T
(p.P1444L)
chr16:89805046

FANCG
NM_004629.1: c.464G>A
(p.R155H)
chr9:35078184

MSH3
NM_002439.3: c.605A>G
(p.Q202R)
chr5:79965941

PDGFRA
NM_006206.4: c.1202C>A
(p.A401D)
chr4:55136880

SPEN
NM_015001.2: c.3398A>G
(p.Y1133C)
chr1:16256133

SRC
NM_005417.3: c.1474G>A
(p.E492K)
chr20:36031645

TERT
NM_198253.2: c.-188G>T
chr5:1295292

TSC1
NM_000368.4: c.965T>C
(p.M322T)
chr9:135786904

Electronically signed by Irene Shyu, M.D. | 13 June 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1646037-01

APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

ABL1 **Exons 4-9**	*ACVR1B*	***AKT1*** **Exon 3**	*AKT2*	*AKT3*	***ALK*** **Exons 20-29, Introns 18, 19**	*ALOX12B*	*AMER1* (FAM123B or WTX)	***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**	*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**	*EMSY* (C11orf30)	*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	*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*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (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)	***KRAS***

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have complete exonic (coding) coverage unless otherwise noted.

LTK	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*	*MAPK1*
MCL1	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***	*MITF*
MKNK1	*MLH1*	***MPL*** **Exon 10**	*MRE11* (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**
NSD2 (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*	***PALB2***
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*	*PRKN* (PARK2)	*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*	*TENT5C* (FAM46C)	*TERC** ncRNA	***TERT**** **Promoter**
TET2	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*	*TSC2*
TYRO3	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

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 reports 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 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.

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 the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
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 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.

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.

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 >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 *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, 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.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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 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

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 (RG) 7.9.0

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
4. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
5. Schenker et al., 2022; AACR Abstract CT022
6. Saori et al., 2021; ESMO Abstract 80P
7. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
8. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
9. Si H, et al. Clin Cancer Res (2021) pmid: 33355200
10. Leighl NB, et al. J Thorac Oncol (2022) pmid: 34800700
11. Li et al., 2020; ASCO Abstract 6511
12. Nakamura H, et al. Nat. Genet. (2015) pmid: 26258846
13. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
14. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
15. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
16. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
17. Rizvi NA, et al. Science (2015) pmid: 25765070
18. Johnson BE, et al. Science (2014) pmid: 24336570
19. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
20. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
21. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
22. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
23. Nature (2012) pmid: 22810696
24. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
25. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
26. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
27. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
28. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
29. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
30. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
31. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
32. Lapin M, et al. J Transl Med (2018) pmid: 30400802
33. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
34. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
35. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
36. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
37. Fan G, et al. PLoS ONE (2017) pmid: 28187169
38. Vu et al., 2020; DOI: 10.1200/PO.19.00204
39. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
40. Zhang EW, et al. Cancer (2020) pmid: 32757294
41. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
42. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
43. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
44. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
45. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
46. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
47. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
48. Finn RS, et al. Invest New Drugs (2018) pmid: 29785570
49. Bekaii-Saab T, et al. J. Clin. Oncol. (2011) pmid: 21519026
50. Lowery MA, et al. Clin. Cancer Res. (2019) pmid: 30563938
51. Kim et al., 2018; ASCO Abstract 4079
52. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
53. Krebs et al., 2021; AACR Abstract CT019
54. Shinde et al., 2020; AACR Abstract CT143
55. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
56. Mainardi S, et al. Nat Med (2018) pmid: 29808006
57. Koczywas et al., 2021; AACR Abstract LB001
58. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
59. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
60. He H, et al. J Med Chem (2022) pmid: 36173339
61. Zhang S, et al. J Med Chem (2022) pmid: 36384290
62. Liu M, et al. ACS Med Chem Lett (2023) pmid: 36793426
63. Ramharter J, et al. J Med Chem (2021) pmid: 33719426
64. Ketcham JM, et al. J Med Chem (2022) pmid: 35833726
65. Plangger A, et al. Discov Oncol (2022) pmid: 36048281
66. Ma Y, et al. Cancers (Basel) (2022) pmid: 36139627
67. Hsu M, et al. Cancer (2013) pmid: 23335286
68. Voss JS, et al. Hum. Pathol. (2013) pmid: 23391413
69. Chang YT, et al. J. Gastroenterol. Hepatol. (2014) pmid: 24372748
70. Liau JY, et al. Mod. Pathol. (2014) pmid: 24406866
71. O'Dell MR, et al. Cancer Res. (2012) pmid: 22266220
72. Borger DR, et al. Oncologist (2012) pmid: 22180306
73. Andersen JB, et al. Gastroenterology (2012) pmid: 22178589
74. Borbath I, et al. Ann. Oncol. (2013) pmid: 23975665
75. Javle M, et al. Hum. Pathol. (2014) pmid: 24508317
76. Malats N, et al. J. Clin. Oncol. (1995) pmid: 7602358
77. Kahn S, et al. Anticancer Res. () pmid: 3310850
78. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
79. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
80. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
81. Sci. STKE (2004) pmid: 15367757
82. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
83. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
84. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
85. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
86. Kim E, et al. Cancer Discov (2016) pmid: 27147599
87. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
88. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
89. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
90. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
91. Scheffzek K, et al. Science (1997) pmid: 9219684
92. Scholl C, et al. Cell (2009) pmid: 19490892
93. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
94. Tyner JW, et al. Blood (2009) pmid: 19075190
95. Valencia A, et al. Biochemistry (1991) pmid: 2029511
96. White Y, et al. Nat Commun (2016) pmid: 26854029
97. Wiest JS, et al. Oncogene (1994) pmid: 8058307
98. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
99. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
100. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
101. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
102. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
103. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
104. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
105. Su D, et al. Nat Commun (2019) pmid: 31700061
106. Tramontana TF, et al. JCO Precis Oncol (2020) pmid: 32923894
107. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
108. Jiao Y, et al. Nat. Genet. (2013) pmid: 24185509
109. DeHaan RD, et al. Hum. Pathol. (2007) pmid: 17239935
110. Ahrendt SA, et al. J. Surg. Res. (1999) pmid: 10334895
111. Tannapfel A, et al. J. Pathol. (2002) pmid: 12210082
112. Chinnasri P, et al. Hum. Pathol. (2009) pmid: 19200577
113. Klump B, et al. Clin. Cancer Res. (2003) pmid: 12738733
114. Yang B, et al. Mod. Pathol. (2005) pmid: 15467712
115. Lee S, et al. Am. J. Pathol. (2002) pmid: 12213730
116. Karamitopoulou E, et al. Am. J. Clin. Pathol. (2008) pmid: 18854271
117. Quelle DE, et al. Cell (1995) pmid: 8521522
118. Mutat. Res. (2005) pmid: 15878778
119. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
120. Oncogene (1999) pmid: 10498883
121. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
122. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
123. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
124. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
125. Gao J, et al. Sci Signal (2013) pmid: 23550210
126. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
127. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
128. Prog Mol Biol Transl Sci (2011) pmid: 21507354
129. Yang J, et al. Mol Med Rep () pmid: 21887466
130. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
131. Daskalos A, et al. Cancer (2011) pmid: 21351083
132. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
133. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
134. Kim MS, et al. APMIS (2013) pmid: 23031157
135. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
136. Guo X, et al. Nature (2015) pmid: 25383530
137. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
138. Zhang ZM, et al. Nature (2018) pmid: 29414941
139. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
140. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
141. Xie M, et al. Nat. Med. (2014) pmid: 25326804
142. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
143. Severson EA, et al. Blood (2018) pmid: 29678827
144. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
145. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
146. Chabon JJ, et al. Nature (2020) pmid: 32269342
147. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
148. Shi C, et al. Oncogene (2022) pmid: 35393542
149. Park JW, et al. Cancer Med (2022) pmid: 35274815
150. Ormanns S, et al. Int J Mol Sci (2017) pmid: 28534865
151. Fei N, et al. Clin Transl Sci (2021) pmid: 34002944
152. Bachet JB, et al. Ann. Oncol. (2012) pmid: 22377565
153. Ziemke M, et al. Lung Cancer (2017) pmid: 28577946
154. Kassardjian A, et al. Pancreas (2020) pmid: 32897998
155. Pen SL, et al. Radiother Oncol (2021) pmid: 33667587
156. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
157. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
158. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
159. Takeda et al., 2022; ASCO GI Abstract 642

Electronically signed by Irene Shyu, M.D. | 13 June 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

160. Liu X, et al. Clin. Chem. (2014) pmid: 24821835
161. Maru D, et al. Oncogene (2004) pmid: 14647445
162. Wang K, et al. Oncologist (2015) pmid: 26336083
163. Nature (2014) pmid: 25079317
164. Izeradjene K, et al. Cancer Cell (2007) pmid: 17349581
165. Bardeesy N, et al. Genes Dev. (2006) pmid: 17114584
166. Springer S, et al. Gastroenterology (2015) pmid: 26253305
167. Blackford A, et al. Clin. Cancer Res. (2009) pmid: 19584151
168. Yan P, et al. Clin. Cancer Res. (2016) pmid: 26861460
169. Kozak MM, et al. J. Clin. Pathol. (2015) pmid: 25681512
170. Roth AD, et al. J. Natl. Cancer Inst. (2012) pmid: 23104212
171. Davison JM, et al. Am. J. Surg. Pathol. (2014) pmid: 24618609
172. Kim YH, et al. Ann. Oncol. (2004) pmid: 15033661
173. Xiangming C, et al. Clin. Cancer Res. (2001) pmid: 11234879
174. Singhi AD, et al. Am. J. Surg. Pathol. (2015) pmid: 25634752
175. Natsugoe S, et al. Clin. Cancer Res. (2002) pmid: 12060625
176. de Kruijf EM, et al. Ann. Oncol. (2013) pmid: 23022998
177. Shipitsin M, et al. Br. J. Cancer (2014) pmid: 25032733
178. Nat. Rev. Mol. Cell Biol. (2012) pmid: 22992590
179. Cell (2008) pmid: 18662538
180. Massagué J, et al. Genes Dev. (2005) pmid: 16322555
181. Morén A, et al. Oncogene (2000) pmid: 10980615
182. Xu J, et al. Proc. Natl. Acad. Sci. U.S.A. (2000) pmid: 10781087
183. Luo K, et al. Genes Dev. (1999) pmid: 10485843
184. Jones JB, et al. Nucleic Acids Res. (2000) pmid: 10871368
185. Fink SP, et al. Cancer Res. (2001) pmid: 11196171
186. De Bosscher K, et al. Biochem. J. (2004) pmid: 14715079
187. Shi Y, et al. Nature (1997) pmid: 9214508
188. Miyaki M, et al. Oncogene (1999) pmid: 10340381
189. Prokova V, et al. Biochemistry (2007) pmid: 17994767
190. Wu JW, et al. J. Biol. Chem. (2001) pmid: 11274206
191. Ding L, et al. J. Clin. Invest. (2009) pmid: 19139564
192. Kuang C, et al. Oncogene (2004) pmid: 14647410
193. Watanabe M, et al. EMBO Rep. (2000) pmid: 11265759
194. Houlston R, et al. Hum. Mol. Genet. (1998) pmid: 9811934
195. Woodford-Richens K, et al. Gut (2000) pmid: 10764709
196. Howe JR, et al. J. Med. Genet. (2004) pmid: 15235019
197. Brosens LA, et al. World J. Gastroenterol. (2011) pmid: 22171123
198. Kalia SS, et al. Genet. Med. (2017) pmid: 27854360
199. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
200. Ito S, et al. Nature (2010) pmid: 20639862
201. Guo JU, et al. Cell (2011) pmid: 21496894
202. Iyer LM, et al. Cell Cycle (2009) pmid: 19411852
203. Ko M, et al. Nature (2010) pmid: 21057493
204. Yang H, et al. Oncogene (2013) pmid: 22391558
205. Hu L, et al. Cell (2013) pmid: 24315485
206. Wang Y, et al. Mol. Cell (2015) pmid: 25601757
207. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
208. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
209. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
210. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
211. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
212. Xu L, et al. Mol. Med. (2001) pmid: 11713371
213. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
214. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
215. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
216. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
217. Moore et al., 2019; ASCO Abstract 5513
218. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
219. Oza et al., 2015; ASCO Abstract 5506
220. Lee J, et al. Cancer Discov (2019) pmid: 31315834
221. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
222. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
223. Gourley et al., 2016; ASCO Abstract 5571
224. Park H, et al. ESMO Open (2022) pmid: 36084396
225. Li M, et al. Nat. Genet. (2014) pmid: 24997986
226. Ross JS, et al. Oncologist (2014) pmid: 24563076
227. Suto T, et al. J Surg Oncol (2000) pmid: 10738270
228. Ong CK, et al. Nat. Genet. (2012) pmid: 22561520
229. Javle M, et al. Cancer (2016) pmid: 27622582
230. Nault JC, et al. Semin. Liver Dis. (2011) pmid: 21538283
231. Won HS, et al. BMC Cancer (2010) pmid: 20955617
232. Chaube A, et al. BMC Cancer (2006) pmid: 16686942
233. Chuang SC, et al. World J Surg (2004) pmid: 15573254
234. Ruzzenente A, et al. Ann. Surg. Oncol. (2016) pmid: 26717940
235. Xiaofang L, et al. World J Surg Oncol (2012) pmid: 22230750
236. Ajiki T, et al. Hepatogastroenterology () pmid: 8799388
237. J Surg Oncol (2006) pmid: 16724348
238. Guo R, et al. Hum. Pathol. (2014) pmid: 24746206
239. Boerner T, et al. Hepatology (2021) pmid: 33765338
240. Conci S, et al. Updates Surg (2020) pmid: 32020551
241. Simbolo M, et al. Sci Rep (2018) pmid: 29740198
242. Lee CS, et al. Pathology (1995) pmid: 7567135
243. Ahrendt SA, et al. J Hepatobiliary Pancreat Surg (2000) pmid: 11180865
244. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
245. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
246. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
247. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
248. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
249. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
250. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
251. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
252. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
253. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
254. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
255. Lalloo F, et al. Lancet (2003) pmid: 12672316
256. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713