FOUNDATIONONE®LIQUID CDx

PATIENT
Hsu, Chiu-Tsu

TUMOR TYPE
Unknown primary carcinoma (NOS)

COUNTRY CODE
TW

REPORT DATE
17 January 2023

ORDERED TEST #
ORD-1540654-01

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 Unknown primary carcinoma (NOS)
NAME Hsu, Chiu-Tsu
DATE OF BIRTH 15 July 1961
SEX Female
MEDICAL RECORD # 37968459

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 CTH 07/15/1961
SPECIMEN TYPE Blood
DATE OF COLLECTION 06 January 2023
SPECIMEN RECEIVED 10 January 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.

ARID1A S715fs*101
KRAS G12D
AXIN1 R22*
BRAF G466E
DNMT3A K766fs*15
SF3B1 K700E

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*** **K766fs*15** (p. 8), ***SF3B1*** **K700E** (p. 9)

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)
ARID1A -	S715fs*101	1.8%	None	None
7 Trials see p. 10				
KRAS -	G12D	2.0%	None	None
10 Trials see p. 12				

Electronically signed by J. Keith Killian, M.D. | 17 January 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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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.

DNMT3A - K766fs*15 ..... p. 8
SF3B1 - K700E ..... p. 9

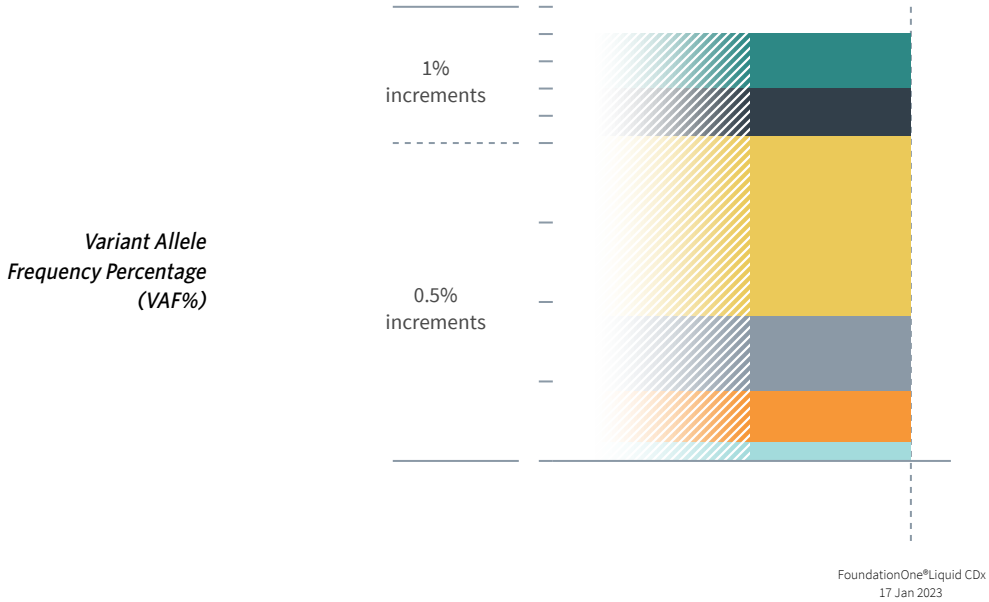
GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

AXIN1 - R22* ..... p. 7
BRAF - G466E ..... p. 8
DNMT3A - K766fs*15 ..... p. 8
SF3B1 - K700E ..... p. 9

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-1540654-01 VAF%
Blood Tumor Mutational Burden		3 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
ARID1A	S715fs*101	1.8%
KRAS	G12D	2.0%
AXIN1	R22*	1.4%
BRAF	G466E	0.12%
DNMT3A	K766fs*15	0.47%
SF3B1	K700E	0.32%

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. 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

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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

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 2022). Published data investigating the prognostic implications of TMB have mainly been investigated in the context of tissue TMB. In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[12], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[13]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[12,14], several other large studies did find a strong link[15-18]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[19-20] and with microsatellite instability (MSI)[20], which in turn has been reported to correlate with better prognosis[21-28]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[29-32] and bladder cancer[33], it is also linked with improved prognosis in patients with these tumor types[30].

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[34-35] and cigarette smoke in lung cancer[36-37], treatment with temozolomide-based chemotherapy in glioma[38-39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[19,30,40-42], and microsatellite instability (MSI)[19,30,42]. 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 high sensitivity for identifying genomic alterations. Such specimens are at low 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[43-48].

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)[49]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[50], Ewing sarcoma and osteosarcoma[51], prostate cancer[46], breast cancer[52], leiomyosarcoma[53], esophageal cancer[54], colorectal cancer[55], and gastrointestinal cancer[56].

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[57], 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[58-59].

GENE
ARID1A

ALTERATION
S715fs*101

TRANSCRIPT ID
NM_006015.4

CODING SEQUENCE EFFECT
2143_2144delTC

VARIANT CHROMOSOMAL POSITION
chr1:27087565-27087567

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies approved to address the mutation or loss of ARID1A in cancer. However, on the basis of limited clinical and preclinical evidence, ARID1A inactivating mutations may lead to sensitivity to ATR inhibitors such as M6620 and ceralasertib[60]. In a Phase 2 study of ceralasertib in solid tumors, 2 patients with endometrial carcinoma in the cohort with loss of ARID1A expression achieved CRs on ceralasertib monotherapy; at least 1 of these 2 patients carried an inactivating ARID1A mutation. In contrast, no responses were observed for patients with normal ARID1A expression treated with ceralasertib combined with olaparib[61]. One patient with small cell lung cancer harboring an ARID1A mutation experienced a PR when treated with M6620 combined with topotecan[62]. In a Phase 1 trial, a patient with metastatic colorectal cancer (CRC) harboring both an ARID1A mutation and ATM loss treated with single-agent M6620 achieved a CR that was ongoing at 29 months[63]. On the basis of limited clinical and preclinical evidence, ARID1A inactivation may predict sensitivity to EZH2 inhibitors[64-65]. A Phase 1 study of EZH2 inhibitor CPI-0209 reported 1 PR for a patient with ARID1A-mutated endometrial cancer[66]. Other studies have reported that the loss of ARID1A may activate the PI3K-AKT pathway and be linked with sensitivity to inhibitors of this pathway[67-69]. Patients with ARID1A alterations in advanced or metastatic solid tumors may derive benefit from treatment with anti-PD-1 or anti-PD-L1 immunotherapy[70]. Loss of ARID1A expression has been associated with chemoresistance to platinum-based therapy for patients with ovarian clear cell carcinoma[71-72] and to 5-fluorouracil in CRC cell lines[73].

FREQUENCY & PROGNOSIS

ARID1A alterations are particularly prevalent in ovarian clear cell carcinoma (46-50%), ovarian and uterine endometrioid carcinomas (24-44%), and cholangiocarcinoma (27%); they are also reported in up to 27% of gastric carcinoma, esophageal adenocarcinoma, Waldenstrom macroglobulinemia, pediatric Burkitt lymphoma, hepatocellular carcinoma, colorectal carcinoma, and urothelial carcinoma samples analyzed (COSMIC, cBioPortal, 2023)[74-82]. ARID1A loss is associated with microsatellite instability in ovarian and endometrial endometrioid adenocarcinomas[31,70,83-85], CRC[70,86-88], and gastric cancer[70,89-93]. ARID1A protein loss is associated with tumors of poor histological grade for many tumor types, including colorectal cancer (CRC)[86-88], cervical cancer[94-95], gastric cancer[89-93], urothelial carcinoma[96-98], ovarian and endometrial cancers[31,72,83-85,99-103], breast carcinoma[104-106], and clear cell renal cell carcinoma[107]; ARID1A mutation has been associated with poor outcomes for patients with cholangiocarcinoma[108-111]. However, prognostic data regarding patient survival are often mixed and conflicting.

FINDING SUMMARY

ARID1A encodes the AT-rich interactive domain-containing protein 1A, also known as Baf250a, a member of the SWI/SNF chromatin remodeling complex. Mutation, loss, or inactivation of ARID1A has been reported in many cancers, and the gene is considered a tumor suppressor[78,92,105,112-117]. ARID1A mutations, which are mostly truncating, have been identified along the entire gene and often correlate with ARID1A protein loss[78,90,113-114,118], whereas ARID1A missense mutations are mostly uncharacterized.

GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985.3

CODING SEQUENCE EFFECT
35G>A

VARIANT CHROMOSOMAL POSITION
chr12:25398284

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[119-124]. While clinical responses have been reported for patients with KRAS-mutated ovarian[125-128], cervical small cell neuroendocrine[129], or uterine cancer[127] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[130-133], pancreatic cancer[134-136], and NSCLC[131,137-138]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[139]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[140-142] and KRAS-mutated endometrioid adenocarcinoma[143]. 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[144]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study[145-146] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[147-148]. 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[149]. 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[150]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[151-152]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[153-154] .

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 18% of tumor samples analyzed in the COSMIC database, including 53% of pancreatic, 45% of peritoneal, 32% of colorectal, 21% of small intestinal, 18% of biliary tract, and 15% of lung tumors (Mar 2022)[74]. Mutations in KRAS have been reported in 32-54% of colorectal cancer cases, with the G12C, G12V, and G13D mutations specifically identified in 7-11%, 26-32%, and 16-24% of cases, respectively[155-160]. Additionally, an activating KRAS mutation has been reported in more than 80% of pancreatic adenocarcinomas, with the majority of mutations found at codon 12[161-164]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[162]. One study found that KRAS mutations were correlated with shorter PFS and OS in cancer of unknown primary (CUP) tumors[165].

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[120,166]. 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, and K117N have been characterized as activating and oncogenic[120,167-189].

GENE
AXIN1

ALTERATION
R22*

TRANSCRIPT ID
NM_003502.3

CODING SEQUENCE EFFECT
64C>T

VARIANT CHROMOSOMAL POSITION
chr16:396962

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies that target AXIN1 mutation or WNT pathway activation, but WNT pathway inhibitors are being studied preclinically and in early clinical trials for solid tumors[190-193].

FREQUENCY & PROGNOSIS

Somatic AXIN1 mutations have been reported in a wide variety of tumor types in the COSMIC database (2022)[74]. Mutations in AXIN1 have been observed in 18% of hepatitis B virus-related hepatocellular carcinoma[194]. These mutations frequently co-occur with mutations in RPS6KA3, a component of the mitogen activated protein kinase (MAPK) pathway[195]. In another study, AXIN1 mutations were reported in 6/54 (11%) of colorectal tumor samples[196]. Aberrant methylation of the AXIN1 promoter in lung tumors has been associated with reduced AXIN1 expression and poor prognosis[197]. An increase in AXIN1 protein expression was reported in non-small cell lung cancer cells resistant to erlotinib; however, the role of AXIN1 expression in drug resistance is not clear[198].

FINDING SUMMARY

AXIN1 encodes a cytoplasmic protein that negatively regulates the WNT signaling pathway through interactions with beta-catenin, GSK3-beta, and APC[199-201].

GENE
BRAF

ALTERATION
G466E

TRANSCRIPT ID
NM_004333.4

CODING SEQUENCE EFFECT
1397G>A

VARIANT CHROMOSOMAL POSITION
chr7:140481411

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Clinical outcomes for patients with activating BRAF alterations treated with BRAF and MEK inhibitors are most extensive at the V600 codon; outcomes are more limited for BRAF class 3 kinase-impaired or inactivating mutations such as one or more of the alterations seen here. A retrospective study of immunotherapies in NSCLC reported a 78% DCR (7/9) for patients with BRAF class 3 mutations[202]. MEK inhibitors alone or in combination with BRAF inhibitors may be efficacious in these alterations; a basket trial of single-agent MEK inhibitor trametinib reported 1 PR, 8 SDs, and 9 PDs for these patients[203], and combination therapies reported individual responses in other basket trials[204-205]. A retrospective analysis in BRAF-mutated melanoma reported PD as the best response in BRAF class 3 alterations for 2 patients treated with MEK inhibitors and 3 patients treated with RAF inhibitors[206]. Single-agent BRAF inhibitor vemurafenib was not effective in a Phase 2 trial in NSCLC, which reported no responses for 6 patients with class 3 BRAF alterations[207]; a basket trial of vemurafenib also observed no responses for these patients (n=3)[208]. Investigational BRAF[209] and ERK[210] inhibitors are also in development; a basket trial of ulixertinib reported no responses and 3 SDs for patients across class 3-mutated tumors[210].

FREQUENCY & PROGNOSIS

BRAF mutation has been most extensively studied in melanoma, where it has been reported in 37-66% of cases[211-214]. BRAF mutation also occurs at high frequencies in patients with papillary craniopharyngiomas (95%)[215], metanephric kidney adenomas (90%)[216], and papillary thyroid carcinoma (45%)[217-219], and has also been reported in lung adenocarcinoma (10%)[220] and colorectal cancer (9%)[19]. Studies on the effect of BRAF alteration on prognosis are conflicting with reports of association with poor prognosis in cholangiocarcinoma[221-223] and colorectal cancer[224-231], improved prognosis in ovarian cancer[232], or no association in NSCLC[233-234] and pancreatic ductal adenocarcinoma[235]. BRAF mutation in papillary thyroid carcinoma have been reported to correlate with poor prognosis in some studies[217,219,236-240], but not in other studies[241-242]. There are similarly conflicting reports regarding the prognostic significance of BRAF mutation in the context of melanoma[243-246].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[247-248]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[211,249]. Alterations such as the class 3 mutation seen here have been shown to require concomitant upstream RAS activity in contrast with independently activating BRAF V600 or class 2 alterations[250-262], and may activate the MEK-ERK signaling pathway via CRAF[250-252,259,263].

GENE
DNMT3A

ALTERATION
K766fs*15

TRANSCRIPT ID
NM_022552.3

CODING SEQUENCE EFFECT
2296_2297delAA

VARIANT CHROMOSOMAL POSITION
chr2:25463195-25463197

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, Feb 2022)[75-76]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

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[264-265]. 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[266-271]. Alterations such as seen here may disrupt DNMT3A function or expression[272-275].

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[276-281]. 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[276-277]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[282]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[280,283-284]. 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
SF3B1

ALTERATION
K700E

TRANSCRIPT ID
NM_012433.2

CODING SEQUENCE EFFECT
2098A>G

VARIANT CHROMOSOMAL POSITION
chr2:198266834

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies suggest that mutations in genes encoding spliceosome components, including SF3B1, may confer sensitivity to spliceosome inhibitors[285-289]. In preclinical models, SF3B1 mutation leads to DNA damage and ATR-CHK1 pathway activation, increasing sensitivity to ATR and CHK1 inhibitors[289]. However, clinical data supporting SF3B1 as biomarkers for the efficacy of these approaches is lacking.

FREQUENCY & PROGNOSIS

In the context of solid tumors, SF3B1 mutations have been reported in uveal melanoma (15-37%)[290-292], adenoid cystic carcinomas of the salivary gland (4%, 1/24)[293] and breast[294] as well as in pancreatic carcinoma[295], glioblastoma, and renal clear cell carcinoma[278]. Mutation of SF3B1 was found to be recurrent in several breast carcinoma subtypes[296-298], and in unselected breast cancers, it correlated with ER-positivity and frequent co-occurrence with AKT1 and PIK3CA mutations[297,299]; the hot spot mutation K700E was found in 16% (3/19) of papillary and 6% of breast mucinous carcinomas[299]. In a retrospective study of primary uveal melanoma, SF3B1 mutation was generally mutually exclusive with BAP1 mutation[290]. In solid tumors, the prognostic implications of SF3B1 alterations are dependent on disease context. In a study of 3,282 breast cancer cases, SF3B1 mutation was significantly associated with poor prognosis for patients with luminal B and progesterone receptor (PR)-negative subtypes of disease[300]. For patients with hepatocellular carcinoma, one study showed that SF3B1 mutation was associated with an advanced stage of disease[301]. SF3B1 mutation has been associated with a medium risk for distant metastasis for patients with uveal melanoma (NCCN Uveal Melanoma Guidelines, v2.2022)[290-292,302].

FINDING SUMMARY

SF3B1 encodes a subunit of the spliceosome, the complex that is responsible for the splicing of pre-mRNA molecules to create mature messenger RNA[303-306]. SF3B1 mutations predominantly occur in HEAT domains 5-7 at codons 625, 662, 666, and 700[299,307-311], which result in neomorphic activity that upregulates aberrant mRNA splicing[312-315]. The consequences of SF3B1 alterations outside of these sites have not been extensively characterized.

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[276-281]. 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[276-277]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[282]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[280,283-284]. 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
ARID1A

RATIONALE
ARID1A loss or inactivation may predict sensitivity to ATR inhibitors.

ALTERATION
S715fs*101

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT04657068

PHASE 1/2

A Study of ART0380 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
ATR

LOCATIONS: London (United Kingdom), Colorado, Oklahoma, Texas, Pennsylvania, Tennessee, Florida

NCT04514497

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344, to Usual Chemotherapy for Advanced Stage Solid Tumors, With a Specific Focus on Patients With Small Cell Lung Cancer, Poorly Differentiated Neuroendocrine Cancer, and Pancreatic Cancer

TARGETS
ATR, TOP1

LOCATIONS: Arizona, Minnesota, Oklahoma, Missouri, Pennsylvania, Connecticut, Tennessee, Florida

NCT04616534

PHASE 1

Testing the Addition of an Anti-cancer Drug, BAY 1895344 ATR Inhibitor, to the Chemotherapy Treatment (Gemcitabine) for Advanced Pancreatic and Ovarian Cancer, and Advanced Solid Tumors

TARGETS
ATR

LOCATIONS: Massachusetts, Maryland

NCT04802174

PHASE 1/2

Lurbinectedin With Berzosertib, an ATR Kinase Inhibitor in Small Cell Cancers and High-Grade Neuroendocrine Cancers

TARGETS
ATR

LOCATIONS: Maryland

NCT04266912

PHASE 1/2

Avelumab and M6620 for the Treatment of DDR Deficient Metastatic or Unresectable Solid Tumors

TARGETS
ATR, PD-L1

LOCATIONS: Texas

NCT03669601

PHASE 1

AZD6738 & Gemcitabine as Combination Therapy

TARGETS
ATR

LOCATIONS: Cambridge (United Kingdom)

GENE
KRAS

ALTERATION
G12D

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.

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS
BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03284502

PHASE 1

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

TARGETS
MEK, RAFs, NRAS

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

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS
PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

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: Massachusetts, Texas, Pennsylvania

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

NCT05159245

PHASE 2

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

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

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

NCT04817956

PHASE 2

Improving Public Cancer Care by Implementing Precision Medicine in Norway

TARGETS
PD-L1, VEGFA, ERBB2, ALK, RET, PARP, SMO, TRKB, TRKC, ROS1, TRKA, MEK, BRAF, PI3K-alpha, FGFR1, FGFR2, FGFR3, MET, KIT, ABL

LOCATIONS: Tromsø (Norway), Bodø (Norway), Hamar (Norway), Oslo (Norway), Fredrikstad (Norway), Drammen (Norway), Trondheim (Norway), Skien (Norway), Førde (Norway), Bergen (Norway)

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

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.

ATRX
Q483P

EPHB1
S774L

NOTCH1
Q1957P

NOTCH2
V1438I

PARP3
R408H

PTCH1
R1303C

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***

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.

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

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) 7.4.0

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. Xiao D, et al. Oncotarget (2016) pmid: 27009843
13. Spigel et al., 2016; ASCO Abstract 9017
14. Shim HS, et al. J Thorac Oncol (2015) pmid: 26200269
15. Govindan R, et al. Cell (2012) pmid: 22980976
16. Ding L, et al. Nature (2008) pmid: 18948947
17. Imielinski M, et al. Cell (2012) pmid: 22980975
18. Kim Y, et al. J. Clin. Oncol. (2014) pmid: 24323028
19. Nature (2012) pmid: 22810696
20. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
21. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
22. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
23. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
24. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
25. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
26. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
27. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
28. Laghi L, et al. Dig Dis (2012) pmid: 22722556
29. Mehnert JM, et al. J. Clin. Invest. (2016) pmid: 27159395
30. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
31. Hussein YR, et al. Mod. Pathol. (2015) pmid: 25394778
32. Church DN, et al. Hum. Mol. Genet. (2013) pmid: 23528559
33. Cazier JB, et al. Nat Commun (2014) pmid: 24777035
34. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
35. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
36. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
37. Rizvi NA, et al. Science (2015) pmid: 25765070
38. Johnson BE, et al. Science (2014) pmid: 24336570
39. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
40. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
41. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
42. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
43. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
44. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
45. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
46. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
47. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
48. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
49. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
50. Lapin M, et al. J Transl Med (2018) pmid: 30400802
51. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
52. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
53. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
54. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
55. Fan G, et al. PLoS ONE (2017) pmid: 28187169
56. Vu et al., 2020; DOI: 10.1200/PO.19.00204
57. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
58. Zhang EW, et al. Cancer (2020) pmid: 32757294
59. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
60. Williamson CT, et al. Nat Commun (2016) pmid: 27958275
61. Aggarwal et al., 2021; ESMO Abstract 512O
62. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
63. Yap TA, et al. J Clin Oncol (2020) pmid: 32568634
64. Bitler BG, et al. Nat. Med. (2015) pmid: 25686104
65. Kim KH, et al. Nat. Med. (2015) pmid: 26552009
66. Papadopoulos et al., 2022; ENA Abstract 188
67. Wiegand KC, et al. BMC Cancer (2014) pmid: 24559118
68. Huang HN, et al. Mod. Pathol. (2014) pmid: 24336158
69. Samartzis EP, et al. Oncotarget (2014) pmid: 24979463
70. Okamura R, et al. J Immunother Cancer (2020) pmid: 32111729
71. Yokoyama Y, et al. J Gynecol Oncol (2014) pmid: 24459582
72. Katagiri A, et al. Mod. Pathol. (2012) pmid: 22101352
73. Xie C, et al. Tumour Biol. (2014) pmid: 24833095
74. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
75. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
76. Gao J, et al. Sci Signal (2013) pmid: 23550210
77. Wu RC, et al. Cancer Biol. Ther. (2014) pmid: 24618703
78. Jones S, et al. Hum. Mutat. (2012) pmid: 22009941
79. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
80. Streppel MM, et al. Oncogene (2014) pmid: 23318448
81. Jiao Y, et al. J. Pathol. (2014) pmid: 24293293
82. Ross JS, et al. Oncologist (2014) pmid: 24563076
83. Huang HN, et al. Histopathology (2015) pmid: 25195947
84. Bosse T, et al. Mod. Pathol. (2013) pmid: 23702729
85. Allo G, et al. Mod. Pathol. (2014) pmid: 23887303
86. Chou A, et al. Hum. Pathol. (2014) pmid: 24925223
87. Ye J, et al. Hum. Pathol. (2014) pmid: 25311944
88. Wei XL, et al. World J. Gastroenterol. (2014) pmid: 25561809
89. Chen K, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25583476
90. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
91. Abe H, et al. Virchows Arch. (2012) pmid: 22915242
92. Wang DD, et al. PLoS ONE (2012) pmid: 22808142
93. Wiegand KC, et al. Hum. Pathol. (2014) pmid: 24767857
94. Katagiri A, et al. Int. J. Gynecol. Cancer (2012) pmid: 22274316
95. Cho H, et al. Hum. Pathol. (2013) pmid: 23427874
96. Gui Y, et al. Nat. Genet. (2011) pmid: 21822268
97. Balbás-Martínez C, et al. PLoS ONE (2013) pmid: 23650517
98. Faraj SF, et al. Hum. Pathol. (2014) pmid: 25175170
99. Rahman M, et al. Hum. Pathol. (2013) pmid: 22939958
100. Maeda D, et al. Int J Mol Sci (2010) pmid: 21614196
101. Lowery WJ, et al. Int. J. Gynecol. Cancer (2012) pmid: 22193641
102. Fadare O, et al. Mod. Pathol. (2013) pmid: 23524907
103. Mao TL, et al. Am. J. Surg. Pathol. (2013) pmid: 24076775
104. Zhang X, et al. Cancer Epidemiol (2012) pmid: 21889920
105. Mamo A, et al. Oncogene (2012) pmid: 21892209
106. Zhao J, et al. Tumour Biol. (2014) pmid: 24430365
107. Lichner Z, et al. Am. J. Pathol. (2013) pmid: 23416164
108. Feng F, et al. Int J Clin Oncol (2021) pmid: 33387086
109. Conci S, et al. Updates Surg (2020) pmid: 32020551
110. Simbolo M, et al. Sci Rep (2018) pmid: 29740198
111. Ruzzenente A, et al. Ann. Surg. Oncol. (2016) pmid: 26717940
112. Guan B, et al. Cancer Res. (2011) pmid: 21900401
113. Wiegand KC, et al. N. Engl. J. Med. (2010) pmid: 20942669
114. Jones S, et al. Science (2010) pmid: 20826764
115. Yan HB, et al. Carcinogenesis (2014) pmid: 24293408
116. Huang J, et al. Nat. Genet. (2012) pmid: 22922871
117. Chan-On W, et al. Nat. Genet. (2013) pmid: 24185513
118. Zang ZJ, et al. Nat. Genet. (2012) pmid: 22484628
119. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
120. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
121. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
122. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
123. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
124. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
125. Monk BJ, et al. J Clin Oncol (2020) pmid: 32822286
126. Farley J, et al. Lancet Oncol. (2013) pmid: 23261356
127. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
128. Han C, et al. Gynecol Oncol Rep (2018) pmid: 29946554
129. Lyons YA, et al. Gynecol Oncol Rep (2014) pmid: 26075998
130. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
131. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
132. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
133. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
134. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152
135. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
136. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
137. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
138. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
139. Liu JF, et al. Gynecol. Oncol. (2019) pmid: 31118140
140. Spreafico et al., 2014; ASCO Abstract 5506
141. Juric et al., 2014; ASCO Abstract 9051
142. Banerji et al., 2014; ASCO Abstract e13559
143. Shapiro GI, et al. Invest New Drugs (2019) pmid: 31020608
144. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
145. Krebs et al., 2021; AACR Abstract CT019
146. Shinde et al., 2020; AACR Abstract CT143
147. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
148. Mainardi S, et al. Nat Med (2018) pmid: 29808006
149. Koczywas et al., 2021; AACR Abstract LB001
150. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
151. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) pmid: 30683722
152. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
153. Hofmann et al., 2021; AACR Abstract CT210
154. Gort et al., 2020; ASCO Abstract TPS3651
155. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717

156. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
157. Huang CW, et al. BMC Cancer (2013) pmid: 24330663
158. Kosmidou V, et al. Hum. Mutat. (2014) pmid: 24352906
159. Maus MK, et al. Lung Cancer (2014) pmid: 24331409
160. Peeters M, et al. J. Clin. Oncol. (2013) pmid: 23182985
161. Feldmann G, et al. J Hepatobiliary Pancreat Surg (2007) pmid: 17520196
162. Rachakonda PS, et al. PLoS ONE (2013) pmid: 23565280
163. Hruban RH, et al. Am. J. Pathol. (1993) pmid: 8342602
164. Maitra A, et al. Best Pract Res Clin Gastroenterol (2006) pmid: 16549325
165. Löffler H, et al. Oncotarget (2016) pmid: 27322425
166. Kahn S, et al. Anticancer Res. () pmid: 3310850
167. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
168. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
169. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
170. Sci. STKE (2004) pmid: 15367757
171. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
172. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
173. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
174. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
175. Kim E, et al. Cancer Discov (2016) pmid: 27147599
176. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
177. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
178. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
179. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
180. Scheffzek K, et al. Science (1997) pmid: 9219684
181. Scholl C, et al. Cell (2009) pmid: 19490892
182. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
183. Tyner JW, et al. Blood (2009) pmid: 19075190
184. Valencia A, et al. Biochemistry (1991) pmid: 2029511
185. White Y, et al. Nat Commun (2016) pmid: 26854029
186. Wiest JS, et al. Oncogene (1994) pmid: 8058307
187. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
188. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
189. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
190. Tanwar PS, et al. PLoS ONE (2011) pmid: 21695255
191. Kogan Y, et al. Biochem. J. (2012) pmid: 22356261
192. Lachenmayer A, et al. Clin. Cancer Res. (2012) pmid: 22811581
193. Zhu J, et al. Carcinogenesis (2012) pmid: 22964660
194. Li J, et al. Oncol. Res. (2013) pmid: 23879168
195. Guichard C, et al. Nat. Genet. (2012) pmid: 22561517
196. Jin LH, et al. Int. J. Cancer (2003) pmid: 14566817
197. Yang LH, et al. Tumour Biol. (2013) pmid: 23192643
198. Fong JT, et al. PLoS ONE (2013) pmid: 24223799
199. Willert K, et al. Genes Dev. (1999) pmid: 10421629
200. Salahshor S, et al. J. Clin. Pathol. (2005) pmid: 15735151
201. Li VS, et al. Cell (2012) pmid: 22682247
202. Marin-Acevedo et al., 2021; ASCO Abstract e21016
203. Johnson DB, et al. Clin Cancer Res (2020) pmid: 31924734
204. Nikanjam M, et al. Mol Cancer Ther (2021) pmid: 33722853
205. Nebhan CA, et al. Oncologist (2021) pmid: 33861486
206. Kim DW, et al. Cancer (2017) pmid: 27911979
207. Mazieres J, et al. Ann. Oncol. (2020) pmid: 31959346
208. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
209. Janku et al., 2021; AACR Abstract CT212
210. Sullivan RJ, et al. Cancer Discov (2018) pmid: 29247021
211. Davies H, et al. Nature (2002) pmid: 12068308
212. Hodis E, et al. Cell (2012) pmid: 22817889
213. Krauthammer M, et al. Nat. Genet. (2012) pmid: 22842228
214. Greaves WO, et al. J Mol Diagn (2013) pmid: 23273605
215. Brastianos PK, et al. Nat. Genet. (2014) pmid: 24413733
216. Choueiri TK, et al. Eur. Urol. (2012) pmid: 22727996
217. Tufano RP, et al. Medicine (Baltimore) (2012) pmid: 22932786
218. Nat. Rev. Cancer (2013) pmid: 23429735
219. Hsiao SJ, et al. Endocr. Relat. Cancer (2014) pmid: 24829266
220. Nature (2014) pmid: 25079552
221. Sia D, et al. Gastroenterology (2013) pmid: 23295441
222. Andersen JB, et al. Gastroenterology (2012) pmid: 22178589
223. Robertson S, et al. Hum. Pathol. (2013) pmid: 24139215
224. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
225. Bokemeyer C, et al. Eur. J. Cancer (2012) pmid: 22446022
226. Gavin PG, et al. Clin. Cancer Res. (2012) pmid: 23045248
227. Laurent-Puig P, et al. J. Clin. Oncol. (2009) pmid: 19884556
228. Ogino S, et al. Clin. Cancer Res. (2012) pmid: 22147942
229. Roth AD, et al. J. Clin. Oncol. (2010) pmid: 20008640
230. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
231. Hsu HC, et al. Oncotarget (2016) pmid: 26989027
232. Grisham RN, et al. Cancer (2013) pmid: 22930283
233. An et al., 2013; ASCO Abstract 8101
234. Chen D, et al. PLoS ONE (2014) pmid: 24979348
235. Schultz NA, et al. Pancreas (2012) pmid: 22699145
236. Elisei R, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066120
237. Li C, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23055546
238. Zeiger MA, et al. Ann. Surg. Oncol. (2013) pmid: 22941167
239. Xing M, et al. JAMA (2013) pmid: 23571588
240. Xing M, et al. J. Clin. Oncol. (2015) pmid: 25332244
241. Gouveia C, et al. JAMA Otolaryngol Head Neck Surg (2013) pmid: 24030686
242. Zoghlami A, et al. Eur Ann Otorhinolaryngol Head Neck Dis (2014) pmid: 23845288
243. Long GV, et al. J. Clin. Oncol. (2011) pmid: 21343559
244. El-Osta H, et al. PLoS ONE (2011) pmid: 22039425
245. Ekedahl H, et al. Br. J. Dermatol. (2013) pmid: 23855428
246. Egberts F, et al. Ann. Oncol. (2014) pmid: 24276025
247. Holderfield M, et al. Nat. Rev. Cancer (2014) pmid: 24957944
248. Burotto M, et al. Cancer (2014) pmid: 24948110
249. Kandoth C, et al. Nature (2013) pmid: 24132290
250. Wan PT, et al. Cell (2004) pmid: 15035987
251. Noeparast A, et al. Oncotarget (2017) pmid: 28947956
252. Smalley KS, et al. Oncogene (2009) pmid: 18794803
253. Smalley KS, et al. Cancer Res. (2009) pmid: 19351826
254. Ikenoue T, et al. Cancer Res. (2004) pmid: 15150094
255. Sen B, et al. Sci Transl Med (2012) pmid: 22649091
256. Kamata T, et al. Cancer Res. (2010) pmid: 20978199
257. Cardarella S, et al. Clin. Cancer Res. (2013) pmid: 23833300
258. Niihori T, et al. Nat. Genet. (2006) pmid: 16474404
259. Moretti S, et al. Biochim. Biophys. Acta (2009) pmid: 19735675
260. Rodriguez-Viciana P, et al. Meth. Enzymol. (2008) pmid: 18413255
261. Anastasaki C, et al. Dis Model Mech (2012) pmid: 22301711
262. Yao Z, et al. Nature (2017) pmid: 28783719
263. Garnett MJ, et al. Mol. Cell (2005) pmid: 16364920
264. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
265. Prog Mol Biol Transl Sci (2011) pmid: 21507354
266. Yang J, et al. Mol Med Rep () pmid: 21887466
267. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
268. Daskalos A, et al. Cancer (2011) pmid: 21351083
269. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
270. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
271. Kim MS, et al. APMIS (2013) pmid: 23031157
272. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
273. Guo X, et al. Nature (2015) pmid: 25383530
274. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
275. Zhang ZM, et al. Nature (2018) pmid: 29414941
276. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
277. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
278. Xie M, et al. Nat. Med. (2014) pmid: 25326804
279. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
280. Severson EA, et al. Blood (2018) pmid: 29678827
281. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
282. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
283. Chabon JJ, et al. Nature (2020) pmid: 32269342
284. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
285. Obeng EA, et al. Cancer Cell (2016) pmid: 27622333
286. Lee SC, et al. Nat. Med. (2016) pmid: 27135740
287. Yoshimi A, et al. Clin. Cancer Res. (2017) pmid: 27836865
288. Lee SC, et al. Nat. Med. (2016) pmid: 27603132
289. Singh S, et al. Leukemia (2020) pmid: 32076118
290. Furney SJ, et al. Cancer Discov (2013) pmid: 23861464
291. Hou C, et al. Ophthalmic Res (2020) pmid: 31614358
292. Yavuzyigitoglu S, et al. Ophthalmology (2016) pmid: 26923342
293. Stephens PJ, et al. J. Clin. Invest. (2013) pmid: 23778141
294. Martelotto LG, et al. J. Pathol. (2015) pmid: 26095796
295. Biankin AV, et al. Nature (2012) pmid: 23103869
296. Banerji S, et al. Nature (2012) pmid: 22722202
297. Ellis MJ, et al. Nature (2012) pmid: 22722193
298. Nature (2012) pmid: 23000897
299. Maguire SL, et al. J. Pathol. (2015) pmid: 25424858
300. Fu X, et al. Oncotarget (2017) pmid: 29383138
301. Nault JC, et al. Hepatology (2020) pmid: 31206197
302. Szalai E, et al. JAMA Ophthalmol (2018) pmid: 30073324
303. Wang C, et al. Genes Dev. (1998) pmid: 9585501
304. Quesada V, et al. Nat. Genet. (2011) pmid: 22158541
305. Wang L, et al. N. Engl. J. Med. (2011) pmid: 22150006
306. Visconte V, et al. Blood (2012) pmid: 22826563
307. Hahn CN, et al. Nat. Genet. (2011) pmid: 22200771
308. Rossi D, et al. Blood (2011) pmid: 22039264
309. Yang J, et al. Genet Test Mol Biomarkers (2013) pmid: 23390883
310. Patnaik MM, et al. Blood (2012) pmid: 22096241

311. Wan Y, et al. Blood (2013) pmid: 23568491
312. Gentien D, et al. Leukemia (2014) pmid: 24434863
313. Schmidt M, et al. Diabetes Res. (1989) pmid: 2576898
314. Darman RB, et al. Cell Rep (2015) pmid: 26565915
315. Alsafadi S, et al. Nat Commun (2016) pmid: 26842708