FOUNDATIONONE®LIQUID CDx

PATIENT Chien, Wen-Lin	**TUMOR TYPE** Unknown primary carcinoma (NOS)	**REPORT DATE** 12 December 2022	
	COUNTRY CODE TW	**ORDERED TEST #** ORD-1517889-01	

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 Chien, Wen-Lin
DATE OF BIRTH 10 December 1971
SEX Male
MEDICAL RECORD # 14285575

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 WLC 12/10/1971
SPECIMEN TYPE Blood
DATE OF COLLECTION 01 December 2022
SPECIMEN RECEIVED 05 December 2022

Biomarker Findings
Blood Tumor Mutational Burden - 4 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.

NF1 I679fs*21
GNAS R201H
TP53 G245S

Report Highlights

- Targeted therapies with potential clinical benefit **approved in another tumor type**: Cobimetinib (p. 7), Selumetinib (p. 7), Trametinib (p. 8)

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 4 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)
NF1 - I679fs*21	0.99%	None	Cobimetinib
			Selumetinib
			Trametinib
10 Trials see p. 9			

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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.

GNAS - R201H .... p. 5   *TP53 -* G245S .... p. 6

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.

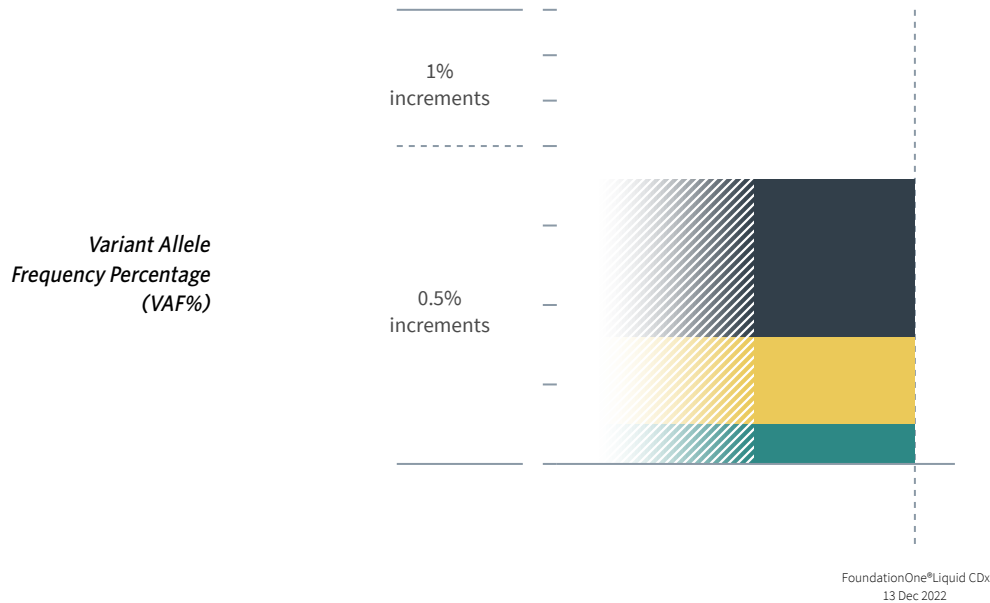Variant Allele Frequency is not applicable for copy number alterations.

Electronically signed by Nimesh Patel, M.D. | 12 December 2022
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

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Variant Allele
Frequency Percentage
(VAF%)

1%
increments

0.5%
increments

FoundationOne®Liquid CDx
13 Dec 2022

HISTORIC PATIENT FINDINGS		ORD-1517889-01 VAF%
Blood Tumor Mutational Burden		4 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
NF1	● I679fs*21	0.99%
GNAS	● R201H	0.25%
TP53	● G245S	0.55%

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

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

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

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BIOMARKER FINDINGS

ORDERED TEST # ORD-1517889-01

BIOMARKER
Blood Tumor Mutational Burden

RESULT
4 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].

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ORDERED TEST # ORD-1517889-01

GENE
NF1

ALTERATION
I679fs*21

TRANSCRIPT ID
NM_001042492.2

CODING SEQUENCE EFFECT
2033_2034insC

VARIANT CHROMOSOMAL POSITION
chr17:29553477

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in neurofibromatosis Type 1-associated neurofibroma[60-63], glioma or glioblastoma[63-67], and non-small cell lung cancer[68], NF1 inactivation may predict sensitivity to MEK inhibitors such as cobimetinib, trametinib, binimetinib, and selumetinib. On the basis of limited clinical data[69-71] and preclinical data[72-73], loss or inactivation of NF1 may predict sensitivity to mTOR inhibitors, including everolimus and temsirolimus. A preclinical study suggests that combined mTOR and MEK inhibition is effective in a model of NF1-deficient malignant peripheral nerve sheath tumors (MPNST)[74].

FREQUENCY & PROGNOSIS

NF1 alterations are common in various solid tumors, with mutations being more frequent than gene loss, and are often seen in melanoma (18%), glioma (14%), gastrointestinal stromal tumor (GIST; 10%), and in salivary gland (6.1%), ovarian (5.4%), breast (4.8%), non-small cell lung (4.7%), non-melanoma skin (4.7%), and endometrial (3.7%) cancer[75]. Published data investigating the prognostic implications of NF1 mutation in carcinomas are limited (PubMed, Jan 2022). NF1 loss was significantly associated with decreased overall and disease-specific survival in patients with grade II and III gliomas, but not in those with GBM[76]. One study reported increased risk of death and poor overall survival in the NF1-mutated melanoma[77]. Another study demonstrated that NF1 is an independent prognostic factor of survival in gastric carcinoma in univariate and multivariate analysis, with no or low NF1 expression significantly associated with shorter OS (P<0.001)[78].

FINDING SUMMARY

NF1 encodes neurofibromin, a GTPase-activating protein (GAP) that is a key negative regulator of the RAS signaling pathway[79]. Neurofibromin acts as a tumor suppressor by repressing RAS signaling[80]. Alterations such as seen here may disrupt NF1 function or expression[80-89].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the NF1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with neurofibromatosis type 1 (ClinVar, Sep 2022)[90]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in NF1 cause the autosomal dominant disorder neurofibromatosis type 1, which is characterized in part by increased risk of developing various tumors, including sarcoma, glioma, breast carcinoma, and neuroendocrine and hematological neoplasms[91-93]. Estimates for the prevalence of the disorder in the general population range from 1:2,500 to 1:3,000[94-95], and in the appropriate clinical context, germline testing of NF1 is recommended.

GENE
GNAS

ALTERATION
R201H

TRANSCRIPT ID
NM_000516.4

CODING SEQUENCE EFFECT
602G>A

VARIANT CHROMOSOMAL POSITION
chr20:57484421

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies targeted to GNAS mutation in cancer. However, there is limited data indicating that a patient with appendiceal adenocarcinoma and a GNAS mutation (R201H) benefited from trametinib for 4 months[96]. Additionally, a patient with GNAS-mutated Erdheim-Chester disease exhibited a PR following treatment with single-agent trametinib[97].

FREQUENCY & PROGNOSIS

The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[98-99] and appendiceal mucinous neoplasms (50-72%)[100-101] as well as in tumors affecting the peritoneum (22%), pituitary gland (20%), bone (14%), pancreas (11%), and small intestine (11%)(COSMIC, 2022)[102]. Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[103-105], colorectal adenocarcinoma (9%)[19], stomach adenocarcinoma (7%)[106], lung adenocarcinoma (6.5%)[107], breast invasive carcinoma (6.5%)[108], pancreatic adenocarcinoma (6%)[109], and sarcomas (5.8%)[110]. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2022)[102,111-112]. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome[113]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer[104-105], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer[114].

FINDING SUMMARY

GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)[115]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase[115]. GNAS has been reported to be amplified in cancer[116] and may be biologically relevant in this context[117-118]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration[119-124] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations[125-127].

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Unknown primary carcinoma (NOS)

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GENOMIC FINDINGS

ORDERED TEST # ORD-1517889-01

GENE
TP53

ALTERATION
G245S

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
733G>A

VARIANT CHROMOSOMAL POSITION
chr17:7577548

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[128-131] or p53 gene therapy such as SGT53[132-136]. 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[137]. 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[138]. 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[139]. 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[140]. 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[141]. 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[142]. 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[143]. 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[136]. 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[144]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[145].

FREQUENCY & PROGNOSIS

Pan-cancer analysis of the TCGA datasets across 12 cancer types identified TP53 as the most frequently mutated gene, with 42% of more than 3,000 tumors harboring a TP53 mutation; in this study TP53 mutation occurred most frequently in ovarian serous carcinoma (95%), lung squamous cell carcinoma (SCC) (79%), head and neck SCC (70%), colorectal adenocarcinoma (59%), lung adenocarcinoma (52%), and bladder urothelial carcinoma (50%)[146]. TP53 loss of heterozygosity (LOH) is frequently seen in tumors and often occurs when one copy of TP53 harbors a mutation; in some tumors, LOH is correlated with progression[147-150]. While the prognostic significance of TP53 alteration or dysregulation varies according to tumor type, studies have shown an association with poor prognosis for patients with breast cancer[151-153], endometrial cancer[154-155], HNSCC[156-158], or urothelial cancer[159-160]. In one study of 55 patients with lung adenocarcinoma, TP53 alterations correlated with immunogenic features including PD-L1 expression, tumor mutation burden and neoantigen presentation; likely as a consequence of this association TP53 mutations correlated with improved clinical outcomes to PD-1 inhibitors pembrolizumab and nivolumab in this study[161]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[162].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[163]. Alterations such as seen here may disrupt TP53 function or expression[164-168].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[90]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[169-171], including sarcomas[172-173]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[174] to 1:20,000[173]. 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[175]. 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[176-181]. 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[176-177]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[182]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[180,183-184]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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THERAPIES WITH CLINICAL BENEFIT   IN OTHER TUMOR TYPE

Cobimetinib

Assay findings association

NF1
I679fs*21

AREAS OF THERAPEUTIC USE
Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[60-63,185-189] , glioma[63-67,190] , and non-small cell lung cancer[68], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
Single-agent cobimetinib has shown clinical activity in the context of histiocytic neoplasms, including Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease, nodular histiocytosis, and mixed histiocytosis[191-198] . A Phase 1 study of cobimetinib monotherapy in solid tumors reported CRs for 1.0% (1/97) of patients and PRs for 6.2% (6/97) of patients, all of whom had melanoma[199]. Clinical benefit following treatment with cobimetinib has been seen for patients with non-small cell lung cancer (NSCLC)[199-200] , adenoid cystic carcinoma[199], and anaplastic pleomorphic xanthoastrocytoma[201].

Selumetinib

Assay findings association

NF1
I679fs*21

AREAS OF THERAPEUTIC USE
Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[60-63,185-189] , glioma[63-67,190] , and non-small cell lung cancer[68], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
Selumetinib has demonstrated efficacy in NF1-associated neurofibroma in Phase 2 studies[61,185-186] and a Phase 1 study[60]. Phase 2 studies reported clinical responses in low-grade glioma[64,202] , melanoma[203-207] , and in lung[68,208-209] and endometrial cancer[210]. A Phase 2 study of selumetinib for patients with activating alterations in the MAPK pathway reported a DCR of 15% (3/20), with no objective responses observed[211]. Phase 1 studies of selumetinib to treat patients with solid tumors reported 1/15 PR for a patient with colorectal cancer (CRC) and 5/15 SDs for patients with tonsil squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and CRC[212]; 2/39 PRs (for patients with CRC) and 18/39 SDs were achieved when selumetinib was administered in combination with cyclosporin A[213]. Multiple Phase 1 studies combining selumetinib with erlotinib or temsirolimus[214], docetaxel or dacarbazine[215], AKT inhibitors[216], or cixutumumab (an anti-IGF-1R antibody)[217] reported clinical responses for patients with advanced solid tumors including NSCLC, thyroid carcinoma, tongue SCC, and ovarian cancer.

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THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Trametinib

Assay findings association

NF1
I679fs*21

AREAS OF THERAPEUTIC USE
Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION
On the basis of clinical evidence in neurofibromatosis type 1 (NF1)-associated neurofibroma[60-63,185-189], glioma[63-67,190], and non-small cell lung cancer[68], NF1 inactivation may predict sensitivity to MEK inhibitors.

SUPPORTING DATA
A Phase 1 trial of trametinib in 206 patients with solid tumors reported 21 (10%) objective responses[218]. Phase 1 monotherapy trials of RO4987655, another MEK inhibitor, have shown significant response rates in patients with melanoma, including those with BRAF and NRAS mutations, but very low response rates in patients with other solid tumors, including those with KRAS mutations[219-220]. A Phase 1b trial of trametinib in combination with gemcitabine in patients with solid tumors showed a complete response in a patient with breast cancer, as well as partial responses in pancreatic and salivary gland cancer[221]. A Phase 1b trial of combination treatment with the MEK inhibitor binimetinib and the PI3K-alpha inhibitor alpelisib reported disease control (partial responses or stable disease) in 47% (21/45) of patients, including partial responses in 2 of 3 patients with KRAS-mutant ovarian cancer and 1 of 3 patients with NRAS-mutant melanoma; a 43% rate of stable disease was observed in patients with KRAS-mutant colorectal cancer, with responses independent of PIK3CA mutation status[222]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[223], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[224].

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

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CLINICAL TRIALS

ORDERED TEST # ORD-1517889-01

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
NF1

ALTERATION
I679fs*21

RATIONALE
On the basis of clinical evidence and strong preclinical evidence, NF1 inactivation may predict sensitivity to MEK inhibitors. Limited clinical data and strong preclinical data indicate that loss or inactivation of NF1 may also predict sensitivity to mTOR inhibitors.

NCT03239015	**PHASE 2**
Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	**TARGETS** EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04337463	**PHASE NULL**
ATG-008 Combined With Toripalimab in Advanced Solid Tumors	**TARGETS** mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

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), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado, Toronto (Canada), Indiana

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)

NCT05125523	**PHASE 1**
A Study of Sirolimus for Injection (Albumin Bound) in Patients With Advanced Solid Tumors	**TARGETS** mTOR

LOCATIONS: Tianjin (China)

FOUNDATIONONE®LIQUID CDx

PATIENT
Chien, Wen-Lin

TUMOR TYPE
Unknown primary carcinoma (NOS)

REPORT DATE
12 December 2022

ORDERED TEST # ORD-1517889-01

CLINICAL TRIALS

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)

NCT03498521

PHASE 2

A Phase II Randomized Study Comparing the Efficacy and Safety of Targeted Therapy or Cancer Immunotherapy Versus Platinum-Based Chemotherapy in Patients With Cancer of Unknown Primary Site

TARGETS
ALK, RET, SMO, AKTs, PARP, PD-L1, EGFR, VEGFA, MEK, BRAF, ERBB2, TRKB, TRKC, ROS1, TRKA

LOCATIONS: Kecskemet (Hungary), Monterrey (Mexico), Cdmx (Mexico), Temuco (Chile), Recoleta (Chile)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

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

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NCT04965818

PHASE 1/2

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

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

FOUNDATIONONE®LIQUID CDx

PATIENT
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TUMOR TYPE
Unknown primary carcinoma
(NOS)

REPORT DATE
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ORDERED TEST #   ORD-1517889-01

APPENDIX   Variants of Unknown Significance

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

APC V1125A	*CARD11* S694L	*CD22* S230P	*CREBBP* S908I
EGFR D800V	*EPHA3* H61Q	*FGF6* L3M	*FGFR1* P469S
IRS2 A512T	*MAP3K1* L78P	*NTRK3* G547R	*PALB2* S652N
PDCD1LG2 (PD-L2) Y106C			

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FOUNDATIONONE®LIQUID CDx

PATIENT
Chien, Wen-Lin

TUMOR TYPE
Unknown primary carcinoma (NOS)

REPORT DATE
12 December 2022

APPENDIX Genes assayed in FoundationOne®Liquid CDx

ORDERED TEST # ORD-1517889-01

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

PATIENT
Chien, Wen-Lin

TUMOR TYPE
Unknown primary carcinoma (NOS)

REPORT DATE
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APPENDIX · Genes assayed in FoundationOne®Liquid CDx

ORDERED TEST # ORD-1517889-01

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 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,*

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FOUNDATIONONE®LIQUID CDx

PATIENT
Chien, Wen-Lin

TUMOR TYPE
Unknown primary carcinoma
(NOS)

REPORT DATE
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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.

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FOUNDATIONONE®LIQUID CDx

PATIENT
Chien, Wen-Lin

TUMOR TYPE
Unknown primary carcinoma (NOS)

REPORT DATE
12 December 2022

APPENDIX   About FoundationOne®Liquid CDx

ORDERED TEST #   ORD-1517889-01

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

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FOUNDATIONONE®LIQUID CDx

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APPENDIX | References

ORDERED TEST # ORD-1517889-01

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6. Saori et al., 2021; ESMO Abstract 80P
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APPENDIX   References

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