

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 Stomach adenocarcinoma (NOS)	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN ID CSL 04/30/1940
	NAME Lin, Chung-Sen		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN TYPE Blood
	DATE OF BIRTH 30 April 1940		ADDITIONAL RECIPIENT None		DATE OF COLLECTION 19 January 2022
	SEX Male		MEDICAL FACILITY ID 205872		SPECIMEN RECEIVED 22 January 2022
	MEDICAL RECORD # 37301181		PATHOLOGIST Not Provided		

Biomarker Findings

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

Genomic Findings

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

KRAS G12D
ASXL1 S833fs*18, D1012fs*12
TP53 C275F

† See About the Test in appendix for details.

Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 7)
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **ASXL1** D1012fs*12, **S833fs*18** (p. 5)

BIOMARKER FINDINGS

Blood Tumor Mutational Burden - 3 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - Elevated Tumor Fraction Not Detected

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

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

Tumor fraction is 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 %

KRAS - G12D 0.35%

10 Trials see p. 7

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)

None

THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

None

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.

ASXL1 - S833fs*18, D1012fs*12 p. 5

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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.

ASXL1 - S833fs*18, D1012fs*12 **p. 5** **TP53 - C275F** **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.

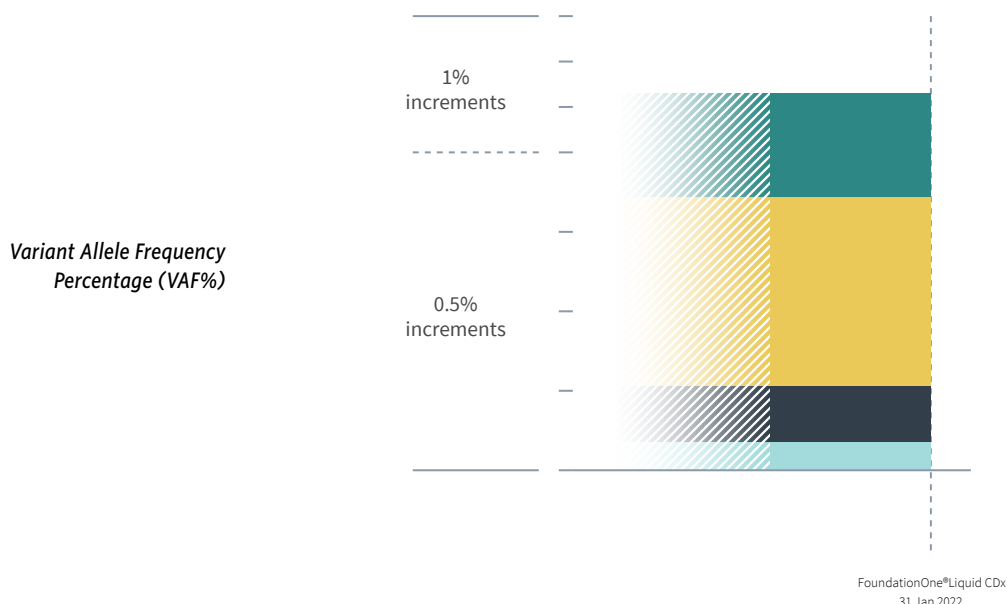
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ORDERED TEST # ORD-1285687-01



HISTORIC PATIENT FINDINGS

ORD-1285687-01
VAF%

Blood Tumor Mutational Burden

3 Muts/Mb

Microsatellite status

MSI-High Not Detected

Tumor Fraction

Elevated Tumor Fraction Not Detected

KRAS	● G12D	0.35%
ASXL1	● D1012fs*12	1.6%
	● S833fs*18	1.2%
TP53	● C275F	0.18%

NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be 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 $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.

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

BIOMARKER

Blood Tumor Mutational Burden

RESULT

3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1¹⁻² and anti-PD-1³ therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb¹. In HNSCC, a Phase 3 trial showed

that bTMB ≥ 16 Muts/Mb (approximate equivalency ≥ 8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor⁴.

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2021)⁵⁻⁷. For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS⁸⁻¹⁰. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level¹¹. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS ($p=0.038$) compared to those with TMB-low¹².

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 melanoma¹³⁻¹⁴ and cigarette smoke in lung cancer¹⁵⁻¹⁶, treatment with temozolomide-based chemotherapy in glioma¹⁷⁻¹⁸, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes¹⁹⁻²³, and microsatellite instability (MSI)^{19,22-23}. 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 agents¹⁻³. 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 management²⁴⁻²⁹.

FREQUENCY & PROGNOSIS

Detectable 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)³⁰. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer³¹, Ewing sarcoma and osteosarcoma³², prostate cancer²⁷, breast cancer³³, leiomyosarcoma³⁴, esophageal cancer³⁵, colorectal

cancer³⁶, and gastrointestinal cancer³⁷.

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 content³⁸, 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 therapy³⁹⁻⁴⁰.

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ORDERED TEST # ORD-1285687-01

GENOMIC FINDINGS

GENE

KRAS

ALTERATION

G12D

TRANSCRIPT ID

NM_004985

CODING SEQUENCE EFFECT

35G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib⁴¹⁻⁴⁶. 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 (NSCLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma⁴⁷. Another Phase 1 study of CH5126766 combined with the FAK inhibitor defactinib reported 4 PRs in KRAS-mutated LGSOC⁴⁸. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors⁴⁹⁻⁵⁰. 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 mutations⁵¹. 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 cancer⁵². Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors⁵³⁻⁵⁴. 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 mutations⁵⁵⁻⁵⁶. While clinical responses have been reported for patients with KRAS-mutated ovarian⁵⁷⁻⁶⁰, cervical small cell neuroendocrine⁶¹, or uterine cancer⁵⁹ treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC⁶²⁻⁶⁵, pancreatic cancer⁶⁶⁻⁶⁸, and NSCLC^{63,69-70}. 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) cancer⁷¹. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer⁷²⁻⁷⁴ and KRAS-mutated endometrioid adenocarcinoma⁷⁵.

FREQUENCY & PROGNOSIS

KRAS mutations have been reported in 4% of esophageal and 0-10% of gastric adenocarcinomas⁷⁶⁻⁸³. Studies in the literature have reported KRAS mutations in up to 9% of gastric, esophageal, or gastroesophageal junction cancer cases⁸⁴⁻⁸⁵. KRAS alterations, including mutations⁸⁶ and amplification⁸⁷⁻⁸⁹ are associated with worse prognosis in patients with gastroesophageal cancer. One study reported that KRAS alteration did not significantly associate with OS in a cohort of patients with gastric, esophageal, or gastroesophageal adenocarcinoma⁹⁰. Published data investigating the prognostic implications of KRAS alterations in esophageal squamous cell carcinoma are limited (PubMed, Sep 2021).

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^{42,91}. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, R68S, and K117N have been characterized as activating and oncogenic^{42,92-114}.

GENE

ASXL1

ALTERATION

S833fs*18, D1012fs*12

TRANSCRIPT ID

NM_015338, NM_015338

CODING SEQUENCE EFFECT

2497_2498insA, 3036delC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in ASXL1.

FREQUENCY & PROGNOSIS

ASXL1 alterations occur infrequently across

various solid tumor types¹¹⁵ and are not known to act as drivers in any specific solid cancer type¹¹⁶. Published data investigating the prognostic implications of ASXL1 alterations in solid tumors are limited (PubMed, May 2021). In the context of clonal hematopoiesis, ASXL1 mutations are significantly enriched in current or former smokers¹¹⁷.

FINDING SUMMARY

ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors¹¹⁸⁻¹²⁰. Alterations such as seen here may disrupt ASXL1 function or expression¹²¹⁻¹²³.

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 expansion¹²⁴⁻¹²⁹. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹²⁴⁻¹²⁵. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease¹³⁰. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{128,131-132}. 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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GENOMIC FINDINGS

GENE

TP53

ALTERATION

C275F

TRANSCRIPT ID

NM_000546

CODING SEQUENCE EFFECT

824G>T

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 adavosertib¹³³⁻¹³⁶, or p53 gene therapy and immunotherapeutics such as SGT-53¹³⁷⁻¹⁴¹ and ALT-801¹⁴². 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 wildtype¹⁴³. 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 cancer¹⁴⁴. 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 cancer¹⁴⁵. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone⁷². 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 paclitaxel¹⁴⁶. 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 alterations¹⁴⁷. 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 monitoring¹⁴⁸. 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 shrinkage¹⁴¹. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246¹⁴⁹⁻¹⁵¹. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR¹⁵². ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies¹⁵³⁻¹⁵⁴; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies¹⁵⁵⁻¹⁵⁶. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is frequently mutated in cancers of the gastrointestinal tract, with alterations reported in 34–72% of esophageal, gastroesophageal junction, and gastric adenocarcinomas^{76-77,157-158}. Overexpression of p53 protein, which may occur as a result of mutation, has been reported in approximately 36% of gastric cancers, with p53 expression reported to be more frequent in intestinal-type compared with diffuse-type gastric cancer¹⁵⁹⁻¹⁶². While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma¹⁵⁷⁻¹⁵⁸ others have associated TP53 mutation and elevated

p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma¹⁶³⁻¹⁶⁴ or stomach cancer¹⁶⁵⁻¹⁶⁷.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers¹⁶⁸. Alterations such as seen here may disrupt TP53 function or expression¹⁶⁹⁻¹⁷³.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers¹⁷⁴⁻¹⁷⁶, including sarcomas¹⁷⁷⁻¹⁷⁸. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹⁷⁹ to 1:20,000¹⁷⁸. 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 30¹⁸⁰. 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 expansion¹²⁴⁻¹²⁹. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy¹²⁴⁻¹²⁵. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease¹³⁰. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{128,131-132}. 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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CLINICAL TRIALS

IMPORTANT Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or

research staff. This is not a comprehensive list of all available clinical trials. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or

in order of level of evidence for this patient's tumor type. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
KRAS
ALTERATION
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.

NCT03281369
PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) (Morpheus-Gastric Cancer)

TARGETS

MEK, CXCR4, VEGFRs, PD-L1

LOCATIONS: Taipei City (Taiwan), Zhongzheng Dist. (Taiwan), Tainan (Taiwan), Suwon-si, (Korea, Republic of), Seodaemun-Gu (Korea, Republic of), Seoul (Korea, Republic of), Songpa-gu (Korea, Republic of), Blacktown (Australia), Melbourne (Australia), Clayton (Australia)

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)

NCT03989115
PHASE 1/2

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

TARGETS

SHP2, MEK

LOCATIONS: Seoul (Korea, Republic of), Oregon, California, Colorado, Arizona, Wisconsin, Illinois

NCT03284502
PHASE 1

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

TARGETS

MEK, RAFs

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

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)

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Electronically signed by Donna Ferguson, M.D. | 31 January 2022
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ORDERED TEST # ORD-1285687-01

CLINICAL TRIALS
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), Texas

NCT02079740
PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
 BCL2, BCL-XL, BCL-W, MEK

LOCATIONS: Massachusetts

NCT04111458
PHASE 1

A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation)

TARGETS
 KRAS, SOS1, MEK

LOCATIONS: Frankfurt am Main (Germany), Köln (Germany), Utrecht (Netherlands), Rotterdam (Netherlands), Massachusetts, Tennessee, Texas, North Carolina

NCT02407509
PHASE 1

Phase I Trial of RO5126766

TARGETS
 RAFs, MEK, mTOR

LOCATIONS: London (United Kingdom), Sutton (United Kingdom)

NCT04800822
PHASE 1

PF-07284892 in Participants With Advanced Solid Tumors

TARGETS
 SHP2, ROS1, ALK, MEK, BRAF, EGFR

LOCATIONS: California, Michigan, New York, Tennessee, Texas

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APPENDIX
Variants of Unknown Significance

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

AKT1
 R174C

ARID1A
 A183T

BCL6
 E419V

CHEK2
 G403V

CSF1R
 T75I

FGF4
 P149A

PBRM1
 R1540H

STK11
 F354L

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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)	APC
AR	ARAF Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	BRAF Exons 11-18, Introns 7-10	BRCA1 Introns 2, 7, 8, 12, 16, 19, 20	BRCA2 Intron 2	BRD4	BRIP1	BTG1
BTG2	BTK Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL
CCND1	CCND2	CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B
CD274 (PD-L1)	CDC73	CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B
CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL
CSF1R	CSF3R	CTCF	CTNNA1	CTNNB1 Exon 3	CUL3	CUL4A	CXCR4	CYP17A1
DAXX	DDR1	DDR2 Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	EGFR Introns 7, 15, 24-27	EP300
EPHA3	EPHB1	EPHB4	ERBB2	ERBB3 Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	ERRFI1
ESR1 Exons 4-8	ETV4* Intron 8	ETV5* Introns 6, 7	ETV6* Introns 5, 6	EWSR1* Introns 7-13	EZH2 Exons 4, 16, 17, 18	EZR* Introns 9-11	FAM46C	FANCA
FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14	FGF19
FGF23	FGF3	FGF4	FGF6	FGFR1 Introns 1, 5, Intron 17	FGFR2 Intron 1, Intron 17	FGFR3 Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17	FGFR4	FH
FLCN	FLT1	FLT3 Exons 14, 15, 20	FOXL2	FUBP1	GABRA6	GATA3	GATA4	GATA6
GNA11 Exons 4, 5	GNA13	GNAQ Exons 4, 5	GNAS Exons 1, 8	GRM3	GSK3B	H3F3A	HDAC1	HGF
HNFI1A	HRAS Exons 2, 3	HSD3B1	ID3	IDH1 Exon 4	IDH2 Exon 4	IGF1R	IKBKE	IKZF1
INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2 Exon 14	JAK3 Exons 5, 11, 12, 13, 15, 16	JUN	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KEL	KIT Exons 8, 9, 11, 12, 13, 17, Intron 16	KLHL6	KMT2A (MLL) Introns 6, 8-11, Intron 7	KMT2D (MLL2)

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KRAS	LTK	LYN	MAF	MAP2K1 (MEK1) Exons 2, 3	MAP2K2 (MEK2) Exons 2-4, 6, 7	MAP2K4	MAP3K1	MAP3K13
MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MERTK	MET
MITF	MKNK1	MLH1	MPL Exon 10	MRE11A	MSH2 Intron 5	MSH3	MSH6	MST1R
MTAP	MTOR Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56	MUTYH	MYB* Intron 14	MYC Intron 1	MYCL (MYCL1)	MYCN	MYD88 Exon 4	NBN
NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2 Intron 26	NOTCH3	NPM1 Exons 4-6, 8, 10
NRAS Exons 2, 3	NSD3 (WHSC1L1)	NTSC2	NTRK1 Exons 14, 15, Introns 8-11	NTRK2 Intron 12	NTRK3 Exons 16, 17	NUTM1* Intron 1	P2RY8	PALB2
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA Exons 12, 18, Introns 7, 9, 11
PDGFRB Exons 12-21, 23	PDK1	PIK3C2B	PIK3C2G	PIK3CA Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20) PPP2R2A	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A	PRKCI	PTCH1
PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	RAF1 Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8	RARA Intron 2	RB1	RBM10	REL	RET Introns 7, 8, Exons 11, 13-16, Introns 9-11
RICTOR	RNF43	ROS1 Exons 31, 36-38, 40, Introns 31-35	RPTOR	RSP02* Intron 1	SDC4* Intron 2	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SLC34A2* Intron 4	SMAD2	SMAD4	SMARCA4	SMARCB1
SMO	SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2
STAT3	STK11	SUFU	SYK	TBX3	TEK	TERC* ncRNA	TERT* Promoter	TET2
TGFBR2	TIPARP	TMPRSS2* Introns 1-3	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3
U2AF1	VEGFA	VHL	WHSC1	WT1	XPO1	XRCC2	ZNF217	ZNF703

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status

Blood Tumor Mutational Burden (bTMB)

Tumor Fraction

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APPENDIX

About FoundationOne® Liquid CDx

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.



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 $\geq 5\%$, and bTMB is calculated based on variants with an allele frequency of $\geq 0.5\%$.
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

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APPENDIX

About FoundationOne®Liquid CDx

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. 2021. 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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APPENDIX

About FoundationOne®Liquid CDx

SELECT ABBREVIATIONS

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

MR Suite Version 5.2.0

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APPENDIX **References**

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APPENDIX **References**

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