

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

PATIENT	DISEASE Colon adenocarcinoma (CRC)	PHYSICIAN	ORDERING PHYSICIAN Yeh, Yi-Chen	SPECIMEN	SPECIMEN ID LHL 07/14/1965
	NAME Liu, Li-Hung		MEDICAL FACILITY Taipei Veterans General Hospital		SPECIMEN TYPE Blood
	DATE OF BIRTH 14 July 1965		ADDITIONAL RECIPIENT None		DATE OF COLLECTION 27 March 2023
	SEX Male		MEDICAL FACILITY ID 205872		SPECIMEN RECEIVED 30 March 2023
	MEDICAL RECORD # 46562178		PATHOLOGIST Not Provided		

Biomarker Findings

Blood Tumor Mutational Burden - 1 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.

APC E1379*
ASXL1 P874fs*2
TP53 C275F, Q192H, H193Y

Report Highlights

- Evidence-matched clinical trial options based on this patient's genomic findings: (p. [9](#))
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **ASXL1** P874fs*2 (p. [7](#))

BIOMARKER FINDINGS

Blood Tumor Mutational Burden -
 1 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%

APC - E1379* 0.72%
 3 Trials see p. [9](#)

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 - P874fs*2 p. [7](#)

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

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 - P874fs*2..... **p. 7** **TP53 - C275F, Q192H, H193Y**..... **p. 8**

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.

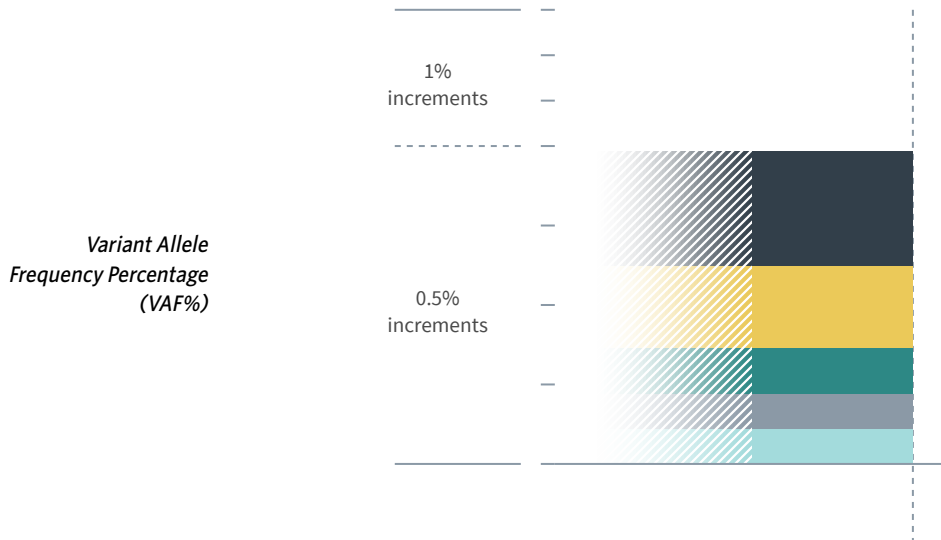
Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01



FoundationOne®Liquid CDx
07 Apr 2023

HISTORIC PATIENT FINDINGS

ORD-1599455-01
VAF%

Blood Tumor Mutational Burden

1 Muts/Mb

Microsatellite status

MSI-High Not Detected

Tumor Fraction

Elevated Tumor Fraction Not Detected

APC	● E1379*	0.72%
ASXL1	● P874fs*2	0.29%
TP53	● C275F	0.52%
	● H193Y	0.22%
	● Q192H	0.22%

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

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. Variants reported for prior time points reflect reporting practices at the time of the historical test(s). Changes in variant reporting nomenclature, classification, or handling may result in the appearance of discrepancies across time points. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

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

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

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

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

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

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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

BIOMARKER FINDINGS
BIOMARKER

Blood Tumor Mutational Burden

RESULT

1 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-L1¹⁻³, anti-PD-1³⁻⁴, anti-PD-1/CTLA4 therapies⁵⁻⁶, anti-PD-L1/CTLA4 therapies⁷⁻¹⁰. 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 inhibitor⁵. 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 inhibitor¹¹. In colorectal cancer (CRC), a Phase 2 study showed that bTMB ≥ 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 inhibitor⁷.

FREQUENCY & PROGNOSIS

In 1 study, the median plasma TMB for 163 patients with metastatic CRC was 16.3 muts/Mb (approximately 8 muts/Mb as measured by this assay)¹². The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones¹³. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS¹⁴. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival¹⁵. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies¹⁶. In a study for

61 patients with metastatic, MSS CRC treated with best standard of care, plasma TMB scores ≥ 28 Muts/Mb (approximately 14 Muts/Mb as measured by this assay) were associated with reduced OS compared with plasma TMB scores < 28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, p=0.007), whereas tTMB was not found to be prognostic in this population⁷.

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 melanoma¹⁷⁻¹⁸ and cigarette smoke in lung cancer¹⁹⁻²⁰, treatment with temozolomide-based chemotherapy in glioma²¹⁻²², mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes²³⁻²⁷, and microsatellite instability (MSI)^{23,26-27}. 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 agents¹⁻²⁴. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

BIOMARKER FINDINGS
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 management²⁸⁻³³.

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)³⁴. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer³⁵, Ewing sarcoma and osteosarcoma³⁶, prostate cancer³¹, breast cancer³⁷, leiomyosarcoma³⁸, esophageal cancer³⁹, colorectal

cancer⁴⁰, and gastrointestinal cancer⁴¹.

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 content⁴², 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 therapy⁴³⁻⁴⁴.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

GENOMIC FINDINGS

GENE

APC

ALTERATION

E1379*

HGVS VARIANT

NM_000038.4: c.4135G>T (p.E1379*)

VARIANT CHROMOSOMAL POSITION

chr5:112175426

which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP⁴⁶⁻⁴⁷. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of ~69% and response duration of 165 days⁴⁸; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386⁴⁹⁻⁵⁰.

study⁵³.

FINDING SUMMARY

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation⁵⁴. Alterations such as seen here may disrupt APC function or expression⁵⁵⁻⁵⁹.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to accumulation of beta-catenin and upregulation of WNT pathway transcription programs⁴⁵, and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists,

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset²⁶. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples⁵¹. The prognostic significance of APC mutations in sporadic CRC remains unclear⁵². Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)⁶⁰⁻⁶². The prevalence for FAP in the general population is estimated to be 1:8,300 from birth⁶³, and in the appropriate clinical context germline testing of APC is recommended.

GENE

ASXL1

ALTERATION

P874fs*2

HGVS VARIANT

NM_015338.5: c.2619del (p.P874Lfs*2)

VARIANT CHROMOSOMAL POSITION

chr20:31023133-31023134

various solid tumor types⁶⁴ and are not known to act as drivers in any specific solid cancer type⁶⁵. Published data investigating the prognostic implications of ASXL1 alterations in solid tumors are limited (PubMed, May 2022). In the context of clonal hematopoiesis, ASXL1 mutations are significantly enriched in current or former smokers⁶⁶.

FINDING SUMMARY

ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors⁶⁷⁻⁶⁹. Alterations such as seen here may disrupt ASXL1 function or expression⁷⁰⁻⁷².

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 expansion⁷³⁻⁷⁸. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy⁷³⁻⁷⁴. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease⁷⁹. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{77,80-81}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

ASXL1 alterations occur infrequently across

ORDERED TEST # ORD-1599455-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

C275F, Q192H, H193Y

HGVS VARIANT

NM_000546.4: c.824G>T (p.C275F),

NM_000546.4: c.576G>T (p.Q192H),

NM_000546.4: c.577C>T (p.H193Y)

VARIANT CHROMOSOMAL POSITION

chr17:7577114, chr17:7578273, chr17:7578272

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 adavosertib⁸²⁻⁸⁵ or p53 gene therapy such as SGT53⁸⁶⁻⁹⁰. 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 wildtype⁹¹. 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 cancer⁹². 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 cancer⁹³. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone⁹⁴. 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 paclitaxel⁹⁵. 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 alterations⁹⁶. 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 monitoring⁹⁷. 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 shrinkage⁹⁰. 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% DCR⁹⁸. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)⁹⁹.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases^{26,100-105}. A study reported p53 expression in 49% of analyzed colorectal cancer cases¹⁰⁶. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC¹⁰⁷.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers¹⁰⁸. Alterations such as seen here may disrupt TP53 function or

expression¹⁰⁹⁻¹¹³.

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)¹¹⁴. 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 cancers¹¹⁵⁻¹¹⁷, including sarcomas¹¹⁸⁻¹¹⁹. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000¹²⁰ to 1:20,000¹¹⁹. 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 30¹²¹. 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 expansion⁷³⁻⁷⁸. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy⁷³⁻⁷⁴. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease⁷⁹. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH^{77,80-81}. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

CLINICAL TRIALS

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

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

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

GENE
APC
ALTERATION
E1379*
RATIONALE

Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT05091346
PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

TARGETS

CBP, Beta-catenin, PD-1

LOCATIONS: Fukuoka (Japan), Osaka (Japan), Shizouka (Japan), Tokyo (Japan), Chiba-shi (Japan), Kashiwa (Japan), Sapporo shi (Japan), Glasgow (United Kingdom), Manchester (United Kingdom), London (United Kingdom)

NCT04008797
PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS

CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Kurume (Japan), Matsuyama (Japan), Seodaemun (Korea, Republic of), Osakasayama (Japan), Nagoya (Japan), Kawasaki (Japan), Chuo-Ku (Japan), Koto-ku (Japan), Chiba (Japan), Kashiwa (Japan)

NCT03264664
PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS

CBP, Beta-catenin

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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

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.

ALK

 NM_004304.4: c.1528C>T
 (p.R510W)
 chr2:29543635

CDKN2A/B

 NM_000077.4: c.35C>T
 (p.S12L)
 chr9:21974792

PRKN (PARK2)

 NM_004562.2: c.1034C>G
 (p.P345R)
 chr6:161969935

APC

 NM_000038.4: c.3941G>T
 (p.R1314M)
 chr5:112175232

DDR1

 NM_001954.4: c.481G>A
 (p.A161T)
 chr6:30858813

SETD2

 NM_014159.6: c.922A>G
 (p.K308E)
 chr3:47165204

ASXL1

 NM_015338.5: c.200_202del
 (p.G67del)
 chr20:30956867-30956870

ERBB3

 NM_001982.3: c.2900G>A
 (p.R967K)
 chr12:56493492

TBX3

 NM_016569.3: c.1685C>T
 (p.A562V)
 chr12:115112055

CD274 (PD-L1)

 NM_014143.3: c.518A>C
 (p.Q173P)
 chr9:5462957

KMT2D (MLL2)

 NM_003482.4: c.13481A>C
 (p.K4494T)
 chr12:49425007

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

 Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

APPENDIX
Genes assayed in FoundationOne® Liquid CDx

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

ABL1 Exons 4-9	ACVR1B	AKT1 Exon 3	AKT2	AKT3	ALK Exons 20-29, Introns 18, 19	ALOX12B	AMER1 (FAM123B or WTX)	APC
AR	ARAF Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	BRAF Exons 11-18, Introns 7-10	BRCA1 Introns 2, 7, 8, 12, 16, 19, 20	BRCA2 Intron 2	BRD4	BRIP1	BTG1
BTG2	BTK Exons 2, 15	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B	CD274 (PD-L1)	CDC73
CDH1	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B
CDKN2C	CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R
CTCF	CTNNA1	CTNNB1 Exon 3	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2 Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	EGFR Introns 7, 15, 24-27	EMSY (C11orf30)	EP300	EPHA3
EPHB1	EPHB4	ERBB2	ERBB3 Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	ERRF1	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	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)	KRAS

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

ORDERED TEST # ORD-1599455-01

APPENDIX

Genes assayed in FoundationOne®Liquid CDx

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

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 9, 11
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	RSP02* 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

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

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, Ciplastraat 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 to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*,

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

APPENDIX
About FoundationOne® Liquid CDx

KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, TP53, and U2AF1.

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

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2, and VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2, and U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This report makes no promises or guarantees that a particular drug will be effective in the treatment of

disease in any patient. This report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this test or the information contained in this report.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

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

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) 7.7.0

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
 Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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

ORDERED TEST # ORD-1599455-01

APPENDIX
References

1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
4. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
5. Schenker et al., 2022; AACR Abstract CT022
6. Saori et al., 2021; ESMO Abstract 80P
7. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
8. Rizvi NA, et al. JAMA Oncol (2020) pmid: 32271377
9. Si H, et al. Clin Cancer Res (2021) pmid: 33355200
10. Leighl NB, et al. J Thorac Oncol (2022) pmid: 34800700
11. Li et al., 2020; ASCO Abstract 6511
12. Loree et al., 2021; ASCO GI Abstract 61
13. Schwartz et al., 2018; ASCO Abstract 572
14. Innocenti F, et al. J Clin Oncol (2019) pmid: 30865548
15. Lee DW, et al. Clin Cancer Res (2019) pmid: 31285374
16. Randon G, et al. Eur J Cancer (2022) pmid: 34933155
17. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
18. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
19. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
20. Rizvi NA, et al. Science (2015) pmid: 25765070
21. Johnson BE, et al. Science (2014) pmid: 24336570
22. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
23. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
24. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
25. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
26. Nature (2012) pmid: 22810696
27. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
28. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
29. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
30. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
31. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
32. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
33. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
34. Bettgowda C, et al. Sci Transl Med (2014) pmid: 24553385
35. Lapin M, et al. J Transl Med (2018) pmid: 30400802
36. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
37. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
38. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
39. Egvud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
40. Fan G, et al. PLoS ONE (2017) pmid: 28187169
41. Vu et al., 2020; DOI: 10.1200/PO.19.00204
42. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
43. Zhang EW, et al. Cancer (2020) pmid: 32757294
44. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
45. Zhan T, et al. Oncogene (2017) pmid: 27617575
46. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
47. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
48. Kawazoe et al., 2021; ESMO Abstract 473P
49. Yamada K, et al. Cancer Res (2021) pmid: 33408116
50. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
51. Christie M, et al. Oncogene (2013) pmid: 23085758
52. Quyn AJ, et al. Surgeon (2008) pmid: 19110823
53. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
54. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
55. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
56. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
57. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
58. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
59. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
60. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
61. Ann Rev Pathol (2011) pmid: 21090969
62. Kastiris E, et al. Int. J. Cancer (2009) pmid: 18844223
63. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
64. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
65. Bailey MH, et al. Cell (2018) pmid: 29625053
66. Bolton KL, et al. Nat Genet (2020) pmid: 33106634
67. Scheuermann JC, et al. Nature (2010) pmid: 20436459
68. Cho YS, et al. J. Biol. Chem. (2006) pmid: 16606617
69. Park UH, et al. J. Biol. Chem. (2011) pmid: 21047783
70. Inoue D, et al. J. Clin. Invest. (2013) pmid: 24216483
71. Abdel-Wahab O, et al. Cancer Cell (2012) pmid: 22897849
72. Br. J. Cancer (2013) pmid: 23736028
73. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
74. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
75. Xie M, et al. Nat. Med. (2014) pmid: 25326804
76. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
77. Severson EA, et al. Blood (2018) pmid: 29678827
78. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
79. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
80. Chabon JJ, et al. Nature (2020) pmid: 32269342
81. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
82. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
83. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
84. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
85. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
86. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
87. Xu L, et al. Mol. Med. (2001) pmid: 11713371
88. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
89. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
90. Pirolo KF, et al. Mol. Ther. (2016) pmid: 27357628
91. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
92. Moore et al., 2019; ASCO Abstract 5513
93. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
94. Oza et al., 2015; ASCO Abstract 5506
95. Lee J, et al. Cancer Discov (2019) pmid: 31315834
96. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
97. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
98. Gourley et al., 2016; ASCO Abstract 5571
99. Park H, et al. ESMO Open (2022) pmid: 36084396
100. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
101. Berg M, et al. PLoS ONE (2010) pmid: 21103049
102. Han SW, et al. PLoS ONE (2013) pmid: 23700467
103. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582
104. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
105. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
106. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
107. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
108. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
109. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
110. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
111. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
112. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
113. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
114. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
115. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
116. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
117. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
118. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
119. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
120. Laloo F, et al. Lancet (2003) pmid: 12672316
121. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713

Disclaimer: Foundation Medicine Inc. only provides PDF report as an official issuance of the test result. Any other transformed format is not an "official / formal solution" and not guarantee the accuracy of this conversion. It is suggested the hospital to verify the outputs and validate the suitability of use.

© 2023 Foundation Medicine, Inc. All rights reserved.

Electronically signed by Jo-Anne Vergilio, M.D. | 06 April 2023
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | www.rochefoundationmedicine.com

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