

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

<b>PATIENT</b>	<b>DISEASE</b> Colon adenocarcinoma (CRC)	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN ID</b> HJL 10/25/1957
	<b>NAME</b> Li, Hsuan-Jung		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN TYPE</b> Blood
	<b>DATE OF BIRTH</b> 25 October 1957		<b>ADDITIONAL RECIPIENT</b> None		<b>DATE OF COLLECTION</b> 25 January 2022
	<b>SEX</b> Male		<b>MEDICAL FACILITY ID</b> 205872		<b>SPECIMEN RECEIVED</b> 29 January 2022
	<b>MEDICAL RECORD #</b> 21541593		<b>PATHOLOGIST</b> Not Provided		

## Biomarker Findings

**Blood Tumor Mutational Burden** - 4 Muts/Mb

**Microsatellite status** - MSI-High Not Detected

**Tumor Fraction** - Elevated Tumor Fraction Not Detected

## Genomic Findings

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

**KRAS** Q61H

**NRAS** Q61H

**APC** R876\*

**CDK12** E187fs\*11

**ASXL1** Q748\*

**RB1** splice site 2520+1G>A

**TP53** I232T

† See About the Test in appendix for details.

## Report Highlights

- Targeted therapies with potential resistance based on this patient's genomic findings: **✖ Cetuximab** (p. 11), **Panitumumab** (p. 11)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 13)
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: **ASXL1** Q748\* (p. 8)

## BIOMARKER FINDINGS

**Blood Tumor Mutational Burden** - 4 Muts/Mb

**Microsatellite status** - MSI-High Not Detected

**Tumor Fraction** - Elevated Tumor Fraction Not Detected

## GENOMIC FINDINGS

**KRAS** - Q61H VAF % 0.15%

10 Trials see p. 16

## 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).

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

**Cetuximab** ✖

**Panitumumab** ✖

### THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)

None



✖ Extensive evidence showing variant(s) in this sample may confer resistance to this therapy


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 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. · 1.888.988.3639

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GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
<b>NRAS -</b> Q61H	0.19%	<b>Cetuximab</b>  <b>Panitumumab</b> 	None
10 Trials see p. 18			
<b>APC -</b> R876*	3.6%	None	None
4 Trials see p. 13			
<b>CDK12 -</b> E187fs*11	1.5%	None	None
10 Trials see p. 14			

 Extensive evidence showing variant(s) in this sample may confer resistance to this therapy

#### 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 - Q748\*** ..... p. 8

#### 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 - Q748\*** ..... p. 8    **TP53 - I232T** ..... p. 10  
**RB1 - splice site 2520+1G>A** ..... p. 9

**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of APC, ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MEN1, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, PALB2, PMS2, POLE, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, and WT1 is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

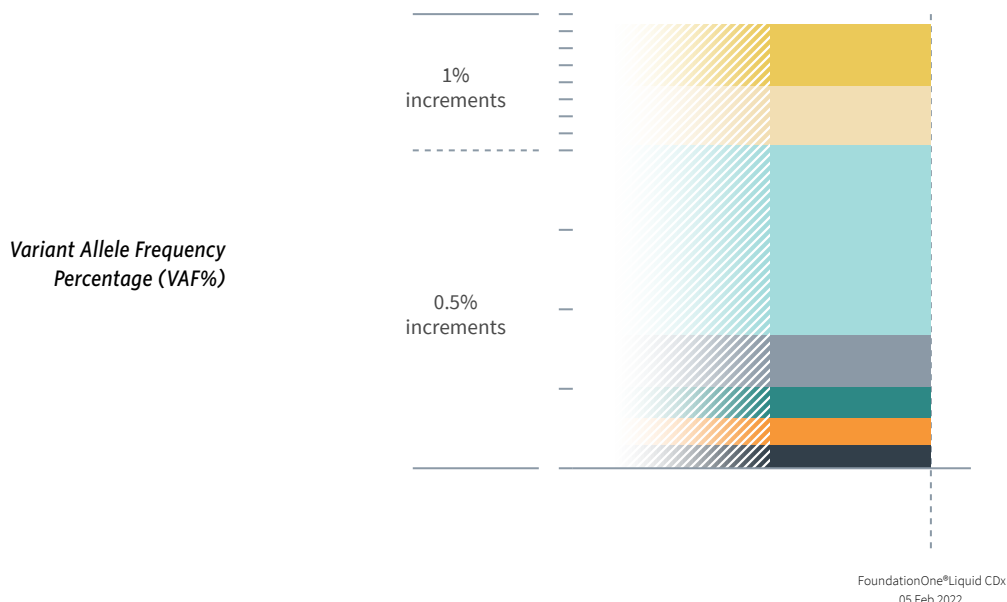
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ORDERED TEST # ORD-1290735-01



#### HISTORIC PATIENT FINDINGS

ORD-1290735-01  
VAF%

#### Blood Tumor Mutational Burden

4 Muts/Mb

#### Microsatellite status

MSI-High Not Detected

#### Tumor Fraction

Elevated Tumor Fraction Not Detected

<b>KRAS</b>	● Q61H	0.15%
<b>NRAS</b>	● Q61H	0.19%
<b>APC</b>	● R876*	3.6%
<b>CDK12</b>	● E187fs*11	1.5%
<b>ASXL1</b>	● Q748*	0.33%
<b>RB1</b>	● splice site 2520+1G>A	0.17%
<b>TP53</b>	● I232T	3.5%

**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

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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

4 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-L1<sup>1-2</sup> and anti-PD-1<sup>3</sup> 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/Mb<sup>1</sup>. In HNSCC, a Phase 3 trial showed that bTMB  $\geq 16$  Muts/Mb (approximate equivalency  $\geq 8$  Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor<sup>4</sup>.

### 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)<sup>5</sup>. In a study for 61 patients with metastatic, microsatellite stable (MSS) CRC treated with best standard of care, plasma TMB scores  $\geq 28$  muts/Mb (approximately 14 muts/Mb as measured by this assay) were associated with reduced OS as compared with plasma TMB scores  $< 28$  muts/Mb (3.0 vs. 5.3 months, HR 0.76,  $p=0.007$ ), whereas tissue TMB was not found to be prognostic in this population<sup>6</sup>.

### FINDING SUMMARY

Blood tumor mutational burden (bTMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma<sup>7-8</sup> and cigarette smoke in lung cancer<sup>9-10</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>11-12</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>13-17</sup>, and microsatellite instability (MSI)<sup>13,16-17</sup>. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents<sup>1-3</sup>. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

## Tumor Fraction

RESULT

Elevated Tumor Fraction Not Detected

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not

be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management<sup>18-23</sup>.

### 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)<sup>24</sup>. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer<sup>25</sup>, Ewing sarcoma and osteosarcoma<sup>26</sup>, prostate cancer<sup>21</sup>, breast cancer<sup>27</sup>, leiomyosarcoma<sup>28</sup>, esophageal cancer<sup>29</sup>, colorectal

cancer<sup>30</sup>, and gastrointestinal cancer<sup>31</sup>.

### FINDING SUMMARY

Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content<sup>32</sup>, the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy<sup>33-34</sup>.

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ORDERED TEST # ORD-1290735-01

## GENOMIC FINDINGS

## GENE

## KRAS

## ALTERATION

Q61H

## TRANSCRIPT ID

NM\_004985

## CODING SEQUENCE EFFECT

183A&gt;T

## POTENTIAL TREATMENT STRATEGIES

## — Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib<sup>35-40</sup>. However, multiple clinical trials have reported lack of efficacy of trametinib and other MEK inhibitors when used as monotherapy for treatment of patients with KRAS-mutant CRC<sup>41-45</sup>. Both clinical<sup>46-47</sup> and preclinical<sup>48-49</sup> studies suggest that combinatorial approaches including MEK inhibitors are likely to be more effective for the treatment of CRC, including strategies such as combination of MEK inhibitors with PI3K inhibitors<sup>47</sup>, RAF inhibitors<sup>48</sup>, pan-ERBB inhibitors<sup>49</sup>, or chemotherapeutic agents<sup>46</sup>. 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 myeloma<sup>50</sup>. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study<sup>51-52</sup>. Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors<sup>53-54</sup>. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations<sup>55</sup>. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer<sup>56</sup>. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors<sup>57-58</sup>. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations<sup>59-60</sup>. Preclinical and limited clinical evidence suggest that KRAS mutation may predict sensitivity to PLK1 inhibitors<sup>61</sup>. A Phase 1b/2 study of PLK1 inhibitor onvansertib in combination with FOLFIRI and bevacizumab for patients with KRAS-mutated metastatic CRC previously treated with chemotherapy reported an 87.5% (7/8; 3 PR, 4 SD) clinical benefit rate, with 1 patient going on to successful curative surgery<sup>62</sup>.

## — Potential Resistance —

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab<sup>63-66</sup> or panitumumab<sup>67-69</sup> for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

## FREQUENCY &amp; PROGNOSIS

Mutations in KRAS have been reported in approximately 35-50% of colorectal cancers (CRCs)<sup>70-78</sup>. Numerous studies have reported that KRAS mutations are associated with increased metastasis, adverse clinicopathological features, and shorter survival of patients with CRC<sup>72-75,79-80</sup>.

## 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<sup>36,81</sup>. 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<sup>36,82-104</sup>.

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**GENOMIC FINDINGS**
**GENE**

# NRAS

**ALTERATION**

Q61H

**TRANSCRIPT ID**

NM\_002524

**CODING SEQUENCE EFFECT**

183A&gt;T

combination with other therapies, may exhibit at least some activity in NRAS-mutated CRC<sup>115-116</sup>. Although the presence of a KRAS mutation in CRC has been associated with lack of efficacy to monotherapy MEK inhibitors<sup>42-45</sup>, the extent to which other alterations affecting this pathway, such as observed here, confers sensitivity to MEK inhibitors is unclear<sup>41</sup>. Preclinical data in cancer cell lines indicates that NRAS mutation predicts sensitivity to the PI3K-alpha-specific inhibitor alpelisib<sup>117</sup>.

**FREQUENCY & PROGNOSIS**

NRAS mutation, commonly at codon 61, has been observed in 2-9% of colorectal cancers<sup>118-122</sup>. For patients with CRC, NRAS mutations have been reported to be associated with increased frequency of metastasis<sup>78</sup> and shorter survival<sup>123-124</sup>.

**FINDING SUMMARY**

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways<sup>36</sup>. NRAS alterations affecting amino acids G12, G13, G60, Q61, as well as mutations I24N, T50I, T58I, and A146T have been characterized as activating and oncogenic<sup>36,84-89,91,93-95,97-98,125-128</sup>.

**POTENTIAL TREATMENT STRATEGIES**
**— Targeted Therapies —**

On the basis of clinical evidence in hematologic malignancies<sup>105-108</sup> and solid tumors<sup>105,109-110</sup> as well as preclinical evidence<sup>36,111-114</sup>, NRAS activating alterations may predict sensitivity to MEK inhibitors, such as trametinib, cobimetinib, and binimetinib. Preclinical studies have suggested that MEK inhibitors, either alone or in

**— Potential Resistance —**

Activating mutations in KRAS or NRAS are associated with lack of clinical benefit from cetuximab<sup>63-66</sup> or panitumumab<sup>67-69</sup> for patients with CRC. Therefore, activating mutations in either gene indicate against the use of cetuximab and panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

**GENE**

# APC

**ALTERATION**

R876\*

**TRANSCRIPT ID**

NM\_000038

**CODING SEQUENCE EFFECT**

2626C&gt;T

catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of -69% and response duration of 165 days<sup>132</sup>; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386<sup>133-134</sup>.

cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation<sup>138</sup>. Alterations such as seen here may disrupt APC function or expression<sup>139-143</sup>.

**FREQUENCY & PROGNOSIS**

APC alterations have been found in 77% of tumors in the Colorectal Adenocarcinoma TCGA dataset<sup>16</sup>. Inactivation of APC leads to activation of the Wnt/beta-catenin pathway, which is thought to play a role in the adenoma-carcinoma transition in some cancers, including colorectal cancer (CRC)<sup>135</sup>. The prognostic significance of APC mutations in sporadic CRC remains unclear<sup>136</sup>. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study<sup>137</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Sep 2021)<sup>144</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)<sup>145-147</sup>. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth<sup>148</sup>, and in the appropriate clinical context germline testing of APC is recommended.

**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 programs<sup>129</sup>, and potential therapeutic approaches to target this pathway include CBP/beta-catenin antagonists, which interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP<sup>130-131</sup>. In a Phase 1 trial of the CBP/beta-

**FINDING SUMMARY**

APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating

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GENOMIC FINDINGS

GENE

## CDK12

ALTERATION

E187fs\*11

TRANSCRIPT ID

NM\_016507

CODING SEQUENCE EFFECT

560\_564delAACGG

### POTENTIAL TREATMENT STRATEGIES

#### — Targeted Therapies —

CDK12 inactivation in cancer is associated with genomic instability characterized by tandem duplications<sup>149-153</sup> and has been shown to increase tumor immunogenicity in advanced prostate cancer<sup>150</sup>. On the basis of clinical and preclinical evidence in prostate cancer, CDK12 inactivation may predict benefit from immune checkpoint inhibitors<sup>150,154-155</sup>. Retrospective studies observed prostate-specific antigen (PSA) response rates of 11-50% (2/19-2/4) for patients with CDK12-mutated metastatic prostate cancer on immune checkpoint inhibitors (predominantly anti-PD-1 monotherapy)<sup>150,154-156</sup>. A prospective trial of nivolumab plus ipilimumab reported a composite response rate of 14% (1/7) in

CDK12-mutated metastatic castration-resistant prostate cancer, with the responder also having high tumor-infiltrating lymphocytes<sup>157</sup>. Preclinical studies suggest that CDK12 truncations and inactivating mutations impair homologous recombination and sensitize cells to PARP inhibitors<sup>158-163</sup>. Preclinical data suggest CDK12 inactivating alterations may sensitize cells to PARP inhibitors<sup>158-163</sup>, and the Phase 3 PROfound study reported numerically improved PFS for patients with CDK12-altered castration-resistant prostate cancer (CRPC) treated with olaparib compared to control androgen deprivation therapy (5.1 vs. 2.2 months)<sup>164</sup>. However, multiple clinical studies have observed no radiographic responses in patients with CDK12-altered CRPC treated with PARP inhibitors<sup>165-166</sup>. A patient with ovarian cancer and a CDK12 frameshift mutation experienced a PR to rucaparib<sup>167</sup>.

#### — Nontargeted Approaches —

Cells lacking CDK12 incur spontaneous DNA damage and exhibit heightened sensitivity to DNA-damaging agents<sup>158-163</sup>.

### FREQUENCY & PROGNOSIS

CDK12 alterations are most commonly reported in prostate cancer<sup>153</sup> and are enriched in metastatic castration-resistant prostate cancer (5-7%)<sup>150,168</sup>

compared with primary disease (1-3%)<sup>150,169</sup>. A pan-cancer CDK12 alteration analysis found alterations, primarily mutations, present in 4% of vulvar/vaginal squamous cell carcinoma, 1.9% of gastric/esophageal cancer, 1.9% of ovarian cancer, 1.7% of cervical cancer, 1.7% of nonmelanoma skin cancer, 1.5% of salivary gland cancer, 1.4% of breast cancer, 1.3% of endometrial cancer, 1.1% of bladder/urothelial cancer, and 1.1% of colorectal cancer samples analyzed, with gastric/esophageal and breast cancers displaying a higher frequency of rearrangements<sup>153</sup>. In prostate cancer, CDK12 alterations are associated with high-risk features and earlier development of castration-resistant disease<sup>156,170</sup>; although published data investigating the prognostic implications of CDK12s alteration in non-prostate cancers are limited (PubMed, Mar 2021), one study correlated low expression of CDK12 in gastric cancer with advanced stage and worse overall survival<sup>171</sup>.

### FINDING SUMMARY

CDK12 encodes a cyclin-dependent kinase that interacts with cyclin K to regulate the phosphorylation of RNA polymerase II and the expression of genes involved in maintaining genomic stability, including BRCA1 and ATR<sup>172</sup>. Alterations such as seen here may disrupt CDK12 function or expression<sup>161,173-175</sup>.

GENE

## ASXL1

ALTERATION

Q748\*

TRANSCRIPT ID

NM\_015338

CODING SEQUENCE EFFECT

2242C>T

### 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 types<sup>176</sup> and are not known to act as drivers in any specific solid cancer type<sup>177</sup>. 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 smokers<sup>178</sup>.

### FINDING SUMMARY

ASXL1 regulates epigenetic marks and transcription through interaction with polycomb complex proteins and various transcription activators and repressors<sup>179-181</sup>. Alterations such as seen here may disrupt ASXL1 function or expression<sup>182-184</sup>.

### POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion<sup>185-190</sup>. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy<sup>185-186</sup>. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease<sup>191</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>189,192-193</sup>. 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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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. • 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531  
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531  
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ORDERED TEST # ORD-1290735-01

**GENOMIC FINDINGS**
**GENE**
**RB1**
**ALTERATION**

splice site 2520+1G&gt;A

**TRANSCRIPT ID**

NM\_000321

**CODING SEQUENCE EFFECT**

2520+1G&gt;A

pathway<sup>200</sup>.

**— Potential Resistance —**

Rb inactivation may predict resistance to CDK4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which act upstream of Rb<sup>201-210</sup>.

**— Nontargeted Approaches —**

Loss of Rb function has been associated with increased sensitivity to cytotoxic agents and chemotherapeutics in both preclinical studies and in patients with bladder or breast cancer<sup>211-212</sup>.

**FREQUENCY & PROGNOSIS**

In TCGA dataset, mutation of RB1 has been found in 2.2% of colorectal adenocarcinoma cases<sup>16</sup>. Although RB1 loss is frequent in many types of cancer, RB1 amplification and/or overexpression has been reported in colorectal cancer, with RB1 mRNA overexpression detected in 37.5% of colorectal tumors and RB1 protein expression found in 83-88% of cases<sup>213-216</sup>. Published data investigating the prognostic implications of RB1 alterations in colorectal carcinoma are limited (PubMed, Sep 2021).

**FINDING SUMMARY**

RB1 encodes the retinoblastoma protein (Rb), a tumor suppressor and negative regulator of the cell cycle<sup>212,217</sup>. Alterations such as seen here may disrupt RB1 function or expression<sup>218-224</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

One or more of the RB1 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 retinoblastoma (ClinVar, Sep 2021)<sup>144</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Mutations in RB1 underlie the development of retinoblastoma (RB), a rare tumor that arises at a rate of approximately 1:20,000 live births, with nearly 5,000 new cases worldwide per year<sup>225</sup>. Germline mutations in RB1 account for approximately 40% of RB tumors<sup>226</sup> and are associated with an increased risk of developing secondary malignancies that include soft tissue and bone sarcoma and malignant melanoma<sup>227-228</sup>. In the appropriate clinical context, germline testing of RB1 is recommended.

**POTENTIAL TREATMENT STRATEGIES**
**— Targeted Therapies —**

On the basis of limited clinical data<sup>194</sup> and strong preclinical data<sup>195-197</sup>, RB1 inactivation may be associated with sensitivity to inhibitors of Aurora kinase A, particularly in small cell lung cancer. It should be noted that a trial of the Aurora kinase A inhibitor alisertib in advanced prostate cancer did not find an association between RB1 deletion and clinical benefit<sup>198</sup>. Other approaches to target RB1 inactivation under investigation in preclinical studies include inhibitors of BCL-2 family members<sup>199</sup> and activation of the NOTCH

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ORDERED TEST # ORD-1290735-01

GENOMIC FINDINGS

GENE

TP53

ALTERATION

I232T

TRANSCRIPT ID

NM\_000546

CODING SEQUENCE EFFECT

695T>C

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib<sup>229-232</sup>, or p53 gene therapy and immunotherapeutics such as SGT-53<sup>233-237</sup> and ALT-801<sup>238</sup>. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype<sup>239</sup>. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer<sup>240</sup>. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer<sup>241</sup>. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone<sup>242</sup>. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with

adavosertib combined with paclitaxel<sup>243</sup>. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations<sup>244</sup>. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring<sup>245</sup>. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage<sup>237</sup>. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutated p53 such as APR-246<sup>246-248</sup>. 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% DCR<sup>249</sup>. 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 studies<sup>250-251</sup>; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies<sup>252-253</sup>. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 60% of colorectal cancer cases<sup>16,254-259</sup>. A study reported p53 expression in 49% of analyzed colorectal cancer cases<sup>260</sup>. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC<sup>261</sup>.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>262</sup>. Alterations such as seen here may disrupt TP53 function or expression<sup>263-267</sup>.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers<sup>268-270</sup>, including sarcomas<sup>271-272</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>273</sup> to 1:20,000<sup>272</sup>. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30<sup>274</sup>. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion<sup>185-190</sup>. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy<sup>185-186</sup>. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease<sup>191</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>189,192-193</sup>. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

ORDERED TEST # ORD-1290735-01

THERAPIES ASSOCIATED WITH RESISTANCE

IN PATIENT'S TUMOR TYPE

## Cetuximab

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS  
Q61H

NRAS  
Q61H

### AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC<sup>63-66,275-276</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS<sup>63-66</sup> or NRAS<sup>121,259</sup>, which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Guidelines v3.2021). Activating mutations in either KRAS<sup>63-66</sup> or NRAS<sup>121,259</sup>, which function downstream of EGFR, are associated with lack of benefit of cetuximab for patients with CRC and indicate against the use of cetuximab (NCCN Colon Cancer Guidelines v3.2021).

### SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and

response rate for patients with KRAS-wild-type CRC, both as first-line combination therapy with FOLFIRI or FOLFOX<sub>4</sub><sup>63-64,276</sup> and as monotherapy or combination therapy with irinotecan for chemotherapy-refractory patients<sup>65-66,275</sup>. A prospective study of first-line cetuximab for patients with KRAS/NRAS/BRAF mutation-negative metastatic CRC resulted in limited efficacy, with 10.5% (2/19) of participants experiencing PRs and 57.9% (11/19) experiencing SDs<sup>277</sup>. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wild-type metastatic CRC resulted in an ORR of 79.5% (6 CR and 25 PRs, n=39) and a DCR of 92.3%<sup>278</sup>. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)<sup>279</sup>. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)<sup>280</sup>.

## Panitumumab

✗ Resistance of variant(s) to associated therapy is likely

Assay findings association

KRAS  
Q61H

NRAS  
Q61H

### AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC<sup>67,279,281</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2021). Activating mutations in either KRAS<sup>67-69</sup> or NRAS<sup>68,257</sup>, which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Guidelines v3.2021). Activating mutations in either KRAS<sup>67-69</sup> or NRAS<sup>68,257</sup>, which function downstream of EGFR, are associated with lack of benefit of panitumumab for patients with CRC and indicate against the use of panitumumab (NCCN Colon Cancer Guidelines, v3.2021).

### SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS wild-type CRC, both as first-line combination therapy with FOLFOX<sub>4</sub><sup>67</sup> and as monotherapy for chemotherapy-refractory patients<sup>279,281</sup>. An open-label, randomized Phase 2 trial reported that for patients with unresectable RAS-wild-type colorectal adenocarcinoma treated with first-line panitumumab plus FOLFOX<sub>4</sub>, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS 59% vs. 49%)<sup>282</sup>. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)<sup>279</sup>. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)<sup>280</sup>.

**NOTE** Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies

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Electronically signed by Amanda Hemmerich, M.D. | 05 February 2022  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. · 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531  
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**ORDERED TEST #** ORD-1290735-01

**THERAPIES ASSOCIATED WITH RESISTANCE**
**IN PATIENT'S TUMOR TYPE**

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

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**CLINICAL TRIALS**

ORDERED TEST # ORD-1290735-01

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

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

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

**GENE**  
**APC**
**ALTERATION**  
**R876\***

**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:** Tokyo (Japan)

**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:** Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

**NCT03833700**
**PHASE 1**

A Study of E7386 in Participants With Advanced Solid Tumor Including Colorectal Cancer (CRC)

**TARGETS**  
 CBP, Beta-catenin

**LOCATIONS:** Chuo Ku (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), Sutton (United Kingdom)

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ORDERED TEST # ORD-1290735-01

**CLINICAL TRIALS**
**GENE**
**CDK12**
**RATIONALE**

Preclinical and clinical data suggest that tumors with CDK12 mutation or loss may be sensitive to

PARP inhibitors.

**ALTERATION**

E187fs\*11

**NCT04456699**
**PHASE 3**

Efficacy and Safety of Olaparib, Olaparib + Bevacizumab Compared to Bevacizumab + 5-Fluorouracil (FU)

**TARGETS**  
 VEGFA, PARP

**LOCATIONS:** Fukuoka (Japan), Daegu (Korea, Republic of), Matsuyama (Japan), Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Nagoya (Japan), Sunto-gun (Japan), Kawasaki (Japan), Tokyo (Japan), Kitaadachi-gun (Japan)

**NCT04123366**
**PHASE 2**

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

**TARGETS**  
 PARP, PD-1

**LOCATIONS:** Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

**NCT03742895**
**PHASE 2**

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

**TARGETS**  
 PARP

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Ryazan (Russian Federation), Darlinghurst (Australia), Moscow (Russian Federation)

**NCT02264678**
**PHASE 1/2**

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

**TARGETS**  
 ATR, PARP, PD-L1

**LOCATIONS:** Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), London (United Kingdom), Sutton (United Kingdom), Villejuif (France), Saint Herblain (France), California

**NCT05035745**
**PHASE 1/2**

Selinexor &amp; Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

**TARGETS**  
 XPO1, PARP

**LOCATIONS:** Singapore (Singapore)

**NCT03772561**
**PHASE 1**

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

**TARGETS**  
 PARP, AKTs, PD-L1

**LOCATIONS:** Singapore (Singapore)

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ORDERED TEST # ORD-1290735-01

**CLINICAL TRIALS**
**NCT04801966**
**PHASE NULL**

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

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

**LOCATIONS:** Melbourne (Australia)

**NCT03150810**
**PHASE 1/2**

Study to Assess Safety, Tolerability and Clinical Activity of BGB-290 in Combination With Temozolomide (TMZ) in Subjects With Locally Advanced or Metastatic Solid Tumors

**TARGETS**  
 PARP

**LOCATIONS:** North Lakes (Australia), Chermshire (Australia), Auchenflower (Australia), South Brisbane (Australia), Southport (Australia), Darlinghurst (Australia), Melbourne (Australia), Newcastle (United Kingdom), Glasgow (United Kingdom), London (United Kingdom)

**NCT04497116**
**PHASE 1/2**

Study of RP-3500 in Advanced Solid Tumors

**TARGETS**  
 ATR, PARP

**LOCATIONS:** Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee, Texas

**NCT03127215**
**PHASE 2**

Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors

**TARGETS**  
 FUS-DDIT3, PARP

**LOCATIONS:** Dresden (Germany), München (Germany), Frankfurt (Germany), Essen (Germany), Mainz (Germany), Heidelberg (Germany), Stuttgart (Germany), Tuebingen (Germany), Freiburg (Germany)

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 Electronically signed by Amanda Hemmerich, M.D. | 05 February 2022  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
 Foundation Medicine, Inc. · 1.888.988.3639

 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-1290735-01

**CLINICAL TRIALS**
**GENE**
**KRAS**
**ALTERATION**
**Q61H**
**RATIONALE**

KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. KRAS mutation may predict sensitivity to PLK1 inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity

to MEK-pan-RAF dual inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant colorectal cancer; combination therapies may be more effective.

**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)

**NCT04303403**
**PHASE 1**

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

**TARGETS**  
 JAK2, JAK1, MEK

**LOCATIONS:** Singapore (Singapore)

**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)

**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

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**CLINICAL TRIALS**
**NCT03829410**
**PHASE 1/2**

Onvansertib in Combination With FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer Patients With a Kras Mutation

**TARGETS**  
 PLK1, VEGFA

**LOCATIONS:** California, Arizona, Minnesota, Kansas, Arkansas, Virginia, Florida

**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)

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ORDERED TEST # ORD-1290735-01

**CLINICAL TRIALS**
**GENE**  
**NRAS**
**ALTERATION**  
 Q61H

**RATIONALE**  
 Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways.

NRAS activating mutations or amplification may therefore sensitize tumors to inhibitors of these downstream pathways.

**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)

**NCT04303403**
**PHASE 1**

Study of Trametinib and Ruxolitinib in Colorectal Cancer and Pancreatic Adenocarcinoma

**TARGETS**  
 JAK2, JAK1, MEK

**LOCATIONS:** Singapore (Singapore)

**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)

**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

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ORDERED TEST # ORD-1290735-01

**CLINICAL TRIALS**
**NCT03377361**
**PHASE 1/2**

An Investigational Immuno-therapy Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Patients With Previously Treated Cancer of the Colon or Rectum That Has Spread

**TARGETS**  
 PD-1, MEK, CTLA-4, BRAF, VEGFRs, RET, KIT

**LOCATIONS:** Brussels (Belgium)

**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

**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.

**CDK12**  
G1460E

**CIC**  
P1551T

**ERCC4**  
R726C

**FAM123B**  
Q647R

**IRF2**  
G276C

**MITF**  
S279F

**MSH2**  
R534L

**MSH6**  
K1358fs\*2

**MTOR**  
T1834\_T1837del

**SRC**  
A141V

**ZNF217**  
I211V

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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.

<b>ABL1</b> Exons 4-9	ACVR1B	<b>AKT1</b> Exon 3	AKT2	AKT3	<b>ALK</b> Exons 20-29, Introns 18, 19	ALOX12B	AMER1 (FAM123B)	<b>APC</b>
<b>AR</b>	<b>ARAF</b> Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	<b>ATM</b>	<b>ATR</b>	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	<b>BRAF</b> Exons 11-18, Introns 7-10	<b>BRCA1</b> Introns 2, 7, 8, 12, 16, 19, 20	<b>BRCA2</b> Intron 2	BRD4	BRIP1	BTG1
BTG2	<b>BTK</b> Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL
<b>CCND1</b>	CCND2	CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B
<b>CD274</b> (PD-L1)	CDC73	<b>CDH1</b>	<b>CDK12</b>	<b>CDK4</b>	<b>CDK6</b>	CDK8	CDKN1A	CDKN1B
<b>CDKN2A</b>	CDKN2B	CDKN2C	CEBPA	CHEK1	<b>CHEK2</b>	CIC	CREBBP	<b>CRKL</b>
CSF1R	CSF3R	CTCF	CTNNA1	<b>CTNNB1</b> Exon 3	CUL3	CUL4A	CXCR4	CYP17A1
DAXX	DDR1	<b>DDR2</b> Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	<b>EGFR</b> Introns 7, 15, 24-27	EP300
EPHA3	EPHB1	EPHB4	<b>ERBB2</b>	<b>ERBB3</b> Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	<b>ERRFI1</b>
<b>ESR1</b> Exons 4-8	ETV4* Intron 8	ETV5* Introns 6, 7	<b>ETV6*</b> Introns 5, 6	EWSR1* Introns 7-13	<b>EZH2</b> Exons 4, 16, 17, 18	EZR* Introns 9-11	FAM46C	FANCA
FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14	FGF19
FGF23	FGF3	FGF4	FGF6	<b>FGFR1</b> Introns 1, 5, Intron 17	<b>FGFR2</b> Intron 1, Intron 17	<b>FGFR3</b> Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17	FGFR4	FH
FLCN	FLT1	<b>FLT3</b> Exons 14, 15, 20	<b>FOXL2</b>	FUBP1	GABRA6	GATA3	GATA4	GATA6
<b>GNA11</b> Exons 4, 5	GNA13	<b>GNAQ</b> Exons 4, 5	<b>GNAS</b> Exons 1, 8	GRM3	GSK3B	H3F3A	HDAC1	HGF
HNFI1A	<b>HRAS</b> Exons 2, 3	HSD3B1	ID3	<b>IDH1</b> Exon 4	<b>IDH2</b> Exon 4	IGF1R	IKBKE	IKZF1
INPP4B	IRF2	IRF4	IRS2	JAK1	<b>JAK2</b> Exon 14	<b>JAK3</b> Exons 5, 11, 12, 13, 15, 16	JUN	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KEL	<b>KIT</b> Exons 8, 9, 11, 12, 13, 17, Intron 16	KLHL6	KMT2A (MLL) Introns 6, 8-11, Intron 7	KMT2D (MLL2)

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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.

<b>KRAS</b>	LTK	LYN	MAF	<b>MAP2K1</b> (MEK1) Exons 2, 3	<b>MAP2K2</b> (MEK2) Exons 2-4, 6, 7	MAP2K4	MAP3K1	MAP3K13
MAPK1	MCL1	<b>MDM2</b>	MDM4	MED12	MEF2B	MEN1	MERTK	<b>MET</b>
MITF	MKNK1	MLH1	<b>MPL</b> Exon 10	MRE11A	MSH2 Intron 5	MSH3	MSH6	MST1R
MTAP	<b>MTOR</b> Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56	MUTYH	MYB* Intron 14	<b>MYC</b> Intron 1	MYCL (MYCL1)	<b>MYCN</b>	<b>MYD88</b> Exon 4	NBN
<b>NF1</b>	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2 Intron 26	NOTCH3	<b>NPM1</b> Exons 4-6, 8, 10
<b>NRAS</b> Exons 2, 3	NSD3 (WHSC1L1)	NTSC2	<b>NTRK1</b> Exons 14, 15, Introns 8-11	NTRK2 Intron 12	<b>NTRK3</b> Exons 16, 17	NUTM1* Intron 1	P2RY8	<b>PALB2</b>
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	<b>PDCD1LG2</b> (PD-L2)	<b>PDGFRA</b> Exons 12, 18, Introns 7, 9, 11
<b>PDGFRB</b> Exons 12-21, 23	PDK1	PIK3C2B	PIK3C2G	<b>PIK3CA</b> 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
<b>PTEN</b>	<b>PTPN11</b>	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B	RAD51C
RAD51D	RAD52	RAD54L	<b>RAF1</b> Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8	RARA Intron 2	<b>RB1</b>	RBM10	REL	<b>RET</b> Introns 7, 8, Exons 11, 13-16, Introns 9-11
RICTOR	RNF43	<b>ROS1</b> 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
<b>SMO</b>	SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2
STAT3	<b>STK11</b>	SUFU	SYK	TBX3	TEK	TERC* ncRNA	<b>TERT*</b> Promoter	TET2
TGFBR2	TIPARP	<b>TMPRSS2*</b> Introns 1-3	TNFAIP3	TNFRSF14	<b>TP53</b>	TSC1	TSC2	TYRO3
U2AF1	<b>VEGFA</b>	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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Electronically signed by Amanda Hemmerich, M.D. | 05 February 2022  
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
Foundation Medicine, Inc. · 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531  
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531  
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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](http://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](http://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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Electronically signed by Amanda Hemmerich, M.D. | 05 February 2022  
 Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531  
 Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309  
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Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531  
 Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531  
 Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D2027531