

**ABOUT THE TEST** FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

<b>PATIENT</b>	<b>DISEASE</b> Colon adenocarcinoma (CRC)	<b>PHYSICIAN</b>	<b>ORDERING PHYSICIAN</b> Yeh, Yi-Chen	<b>SPECIMEN</b>	<b>SPECIMEN SITE</b> Colon
	<b>NAME</b> Chiang, Shu Chen		<b>MEDICAL FACILITY</b> Taipei Veterans General Hospital		<b>SPECIMEN ID</b> S111-11922 D (PF23022)
	<b>DATE OF BIRTH</b> 23 September 1966		<b>ADDITIONAL RECIPIENT</b> None		<b>SPECIMEN TYPE</b> Slide Deck
	<b>SEX</b> Female		<b>MEDICAL FACILITY ID</b> 205872		<b>DATE OF COLLECTION</b> 23 March 2022
	<b>MEDICAL RECORD #</b> 48341055		<b>PATHOLOGIST</b> Not Provided		<b>SPECIMEN RECEIVED</b> 02 March 2023

## Biomarker Findings

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 1 Muts/Mb

## Genomic Findings

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

**KRAS** wildtype

**NRAS** wildtype

**BRIP1** E1222fs\*7

**APC** R945fs\*10

**TP53** E336\*

3 Disease relevant genes with no reportable alterations: **BRAF**, **KRAS**, **NRAS**

## Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Cetuximab** (p. 8), **Panitumumab** (p. 8)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)

### BIOMARKER FINDINGS

**Microsatellite status** - MS-Stable

**Tumor Mutational Burden** - 1 Muts/Mb

### GENOMIC FINDINGS

**KRAS** - wildtype

0 Trials

**NRAS** - wildtype

0 Trials

**BRIP1** - E1222fs\*7

10 Trials see p. 12

**APC** - R945fs\*10

3 Trials see p. 11

### THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. See Biomarker Findings section

No therapies or clinical trials. See Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
Cetuximab <span>2A</span>	none
Panitumumab <span>2A</span>	
Cetuximab <span>2A</span>	none
Panitumumab <span>2A</span>	
none	Niraparib
	Olaparib
	Rucaparib
	Talazoparib
none	none

2A NCCN category

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**GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS**

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

**TP53 - E336\*** ..... **p. [7](#)**

**NOTE** Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. Neither the therapeutic agents 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.

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ORDERED TEST # ORD-1578164-01

## BIOMARKER FINDINGS

## BIOMARKER

# Microsatellite status

## RESULT

MS-Stable

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors<sup>1-3</sup>, including approved therapies nivolumab and pembrolizumab<sup>4</sup>. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%,  $p=0.001$ )<sup>5</sup>. For patients with chemotherapy-refractory microsatellite-stable (MSS) metastatic colorectal cancer (CRC), a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00);

atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)<sup>6</sup>. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)<sup>7</sup>. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months<sup>8</sup> and 5.7 months<sup>9</sup>, and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR<sup>10</sup>.

### — Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX<sup>11-12</sup> and FOLFIRI<sup>13-14</sup>. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy<sup>15-16</sup> but less likely to benefit from irinotecan chemotherapy<sup>17</sup>.

## FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases<sup>3,18-22</sup>. MSS colorectal cancers are

molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability<sup>22</sup>. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors<sup>18,23-29</sup>.

## FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor<sup>20</sup>. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2<sup>20,30-31</sup>. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers<sup>19,32-33</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>19-20,31,33</sup>.

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## BIOMARKER FINDINGS

## BIOMARKER

# Tumor Mutational Burden

## RESULT

1 Muts/Mb

## POTENTIAL TREATMENT STRATEGIES

### — Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1<sup>34-36</sup>, anti-PD-1 therapies<sup>34-37</sup>, and combination nivolumab and ipilimumab<sup>38-43</sup>. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors<sup>34-37,44-48</sup>. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB  $\geq 10$  Muts/Mb (as measured by this assay) compared with those with TMB  $< 10$  Muts/Mb in a large cohort that included multiple tumor types<sup>44</sup>; similar findings were observed in the KEYNOTE 028 and 012 trials<sup>37</sup>. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores  $\geq 10$  Muts/Mb were associated with prolonged time to treatment failure compared with scores  $< 10$  Muts/Mb (HR=0.68)<sup>48</sup>. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB  $\geq 10$  Muts/Mb independent of blood TMB at any cutpoint in matched samples<sup>49</sup>. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR

was seen in patients with TMB  $\geq 16$  Muts/Mb than those with TMB  $\geq 10$  and  $< 16$  Muts/Mb<sup>47</sup>. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as  $\geq 16-20$  Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy<sup>50</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>35</sup>. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB  $\geq 9.8$  Muts/MB compared with those with tumors with TMB  $< 9.8$  Muts/Mb (~equivalency  $< 12$  Muts/Mb as measured by this assay)<sup>34</sup>. Another retrospective study reported that a TMB  $\geq 12$  Muts/Mb cutoff identifies  $> 99\%$  of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors<sup>51</sup>.

## FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples<sup>21,52-53</sup>. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and mismatch repair deficiency (MMR-D)<sup>21,52</sup>. Increased TMB is significantly associated with MSI-H and MMR-D, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and conversely that 100% of tumors with low TMB harbor intact MMR<sup>52</sup>. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB<sup>21,52</sup>. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB<sup>21,52</sup>, whereas TMB-low tumors more frequently harbor mutations in TP53 and APC<sup>21</sup>. 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 ones<sup>54</sup>. 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 OS<sup>55</sup>. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival<sup>56</sup>. 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 therapies<sup>57</sup>. In a study for 61 patients with metastatic, 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 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 population<sup>58</sup>.

## FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma<sup>59-60</sup> and cigarette smoke in lung cancer<sup>61-62</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>63-64</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>21,65-68</sup>, and microsatellite instability (MSI)<sup>21,65,68</sup>. This sample harbors a TMB below levels that 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>34,44,51</sup>.

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**GENOMIC FINDINGS**
**GENE**  
**KRAS**
**ALTERATION**  
 wildtype

with clinical benefit of treatment with EGFR-targeting antibodies cetuximab<sup>69-72</sup> or panitumumab<sup>73-75</sup> for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC<sup>78-81,85-86</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>87-88</sup>. No alterations in KRAS were identified in this case.

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

Lack of mutations in KRAS or NRAS is associated

**FREQUENCY & PROGNOSIS**

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations<sup>76-84</sup>.

**GENE**  
**NRAS**
**ALTERATION**  
 wildtype

targeting antibodies cetuximab<sup>69-72</sup> or panitumumab<sup>73-75</sup> for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v3.2022, Rectal Cancer Guidelines, v4.2022).

frequency of metastasis<sup>84</sup> and longer survival<sup>94-95</sup> of patients with CRC.

**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>87</sup>. No alterations in NRAS were identified in this case.

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

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-

**FREQUENCY & PROGNOSIS**

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations<sup>21,84,89-94</sup>. NRAS wild-type status has been reported to be associated with decreased

**GENE**  
**BRIP1**
**ALTERATION**  
 E1222fs\*7

**TRANSCRIPT ID**  
 NM\_032043.2

**CODING SEQUENCE EFFECT**  
 3664\_3665insG

**VARIANT CHROMOSOMAL POSITION**  
 chr17:59760742

**VARIANT ALLELE FREQUENCY (% VAF)**  
 42.9%

BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

been previously reported in the context of cancer, which may indicate biological relevance.

**FREQUENCY & PROGNOSIS**

BRIP1 mutations have been reported in 3% of samples analyzed in the Colorectal Adenocarcinoma TCGA dataset<sup>21</sup>. Increased BRIP1 expression has been implicated in resistance to 5-fluorouracil treatment and increased recurrence in patients with colorectal cancer<sup>99-100</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

Germline mutations in BRIP1 are associated with increased risk of breast, ovarian, and cervical cancers<sup>104-108</sup>. Germline mutations in BRIP1 are also associated with Fanconi anemia (FA), a rare autosomal disorder that predisposes patients to a subset of cancers, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), gynecological malignancies, and head and neck tumors<sup>109-111</sup>; frequency estimates suggest an incidence of 3/1,000,000 individuals in Europe and the US, and a heterozygote carrier frequency of 1/181 to 1/300 in the US and Europe, respectively, with slightly higher rates in some populations, such as the Ashkenazi Jewish population (1/89)<sup>110,112</sup>. In the appropriate clinical context, germline testing of BRIP1 is recommended.

**FINDING SUMMARY**

BRIP1, also known as FANCF (Fanconi Anemia complementation group J) and BACH1, encodes a DNA helicase required for DNA repair and the maintenance of chromosomal stability<sup>101-103</sup>. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have

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

On the basis of clinical responses in ovarian cancer<sup>96</sup> and prostate cancer<sup>97</sup>, as well as clinical benefit in breast cancer<sup>98</sup>, loss or inactivation of

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**GENOMIC FINDINGS**
**GENE**
**APC**
**ALTERATION**

R945fs\*10

**TRANSCRIPT ID**

NM\_000038.4

**CODING SEQUENCE EFFECT**

2833delA

**VARIANT CHROMOSOMAL POSITION**

chr5:112174123-112174124

**VARIANT ALLELE FREQUENCY (% VAF)**

28.8%

**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>113</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>114-115</sup>. 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 days<sup>116</sup>; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer models to E7386<sup>117-118</sup>.

**FREQUENCY & PROGNOSIS**

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset<sup>21</sup>. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples<sup>119</sup>. The prognostic significance of APC mutations in sporadic CRC remains unclear<sup>120</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>121</sup>.

**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 differentiation<sup>122</sup>. Alterations such as seen here may disrupt APC function or expression<sup>123-127</sup>.

**POTENTIAL GERMLINE IMPLICATIONS**

Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)<sup>128-130</sup>. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth<sup>131</sup>, and in the appropriate clinical context germline testing of APC is recommended.

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GENOMIC FINDINGS

GENE

**TP53**

ALTERATION

E336\*

TRANSCRIPT ID

NM\_000546.4

CODING SEQUENCE EFFECT

1006G>T

VARIANT CHROMOSOMAL POSITION

chr17:7574021

VARIANT ALLELE FREQUENCY (% VAF)

28.2%

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>132-135</sup> or p53 gene therapy such as SGT53<sup>136-140</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>141</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>142</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>143</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>144</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>145</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>146</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>147</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>140</sup>. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR<sup>148</sup>. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)<sup>149</sup>.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases<sup>21,150-155</sup>. A study reported p53 expression in 49% of analyzed colorectal cancer cases<sup>156</sup>. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC<sup>157</sup>.

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>158</sup>. Alterations such as seen here may disrupt TP53 function or expression<sup>159-163</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>164-166</sup>, including sarcomas<sup>167-168</sup>. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000<sup>169</sup> to 1:20,000<sup>168</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>170</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>171-176</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>171-172</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>177</sup>. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH<sup>175,178-179</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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THERAPIES WITH CLINICAL BENEFIT

IN PATIENT'S TUMOR TYPE

## Cetuximab

*Assay findings association*
**KRAS**  
wildtype

**NRAS**  
wildtype

### 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>69-72,180-181</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines, v3.2022, NCCN Rectal Cancer Guidelines, v4.2022).

### SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFIRI, FOLFOX<sub>4</sub>, or irinotecan<sup>69-70,180-182</sup> and as monotherapy for chemotherapy-refractory patients<sup>72,183</sup>. The Phase 3 study STRATEGIC-1 reported a similar duration of disease control (DDC) for patients with unresectable metastatic CRC (mCRC) and KRAS-, NRAS-, and BRAF-wildtype status treated with mFOLFOX-bevacizumab alternated

with a cetuximab regimen in first or second line, respectively (overall DDC 22.5 vs. 23.5 months); in addition, the study reported similar OS (37.8 vs. 34.4 months) and higher numerical ORR for patients treated with cetuximab in the first line followed by mFOLFOX-bevacizumab compared with those receiving EGFR-directed antibodies in the second or third line<sup>184</sup>. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs<sup>185</sup>. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX<sub>6</sub> for patients with RAS- and BRAF-wildtype mCRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%<sup>186</sup>. In the Phase 3 ASPRECT 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>187</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>188</sup>.

## Panitumumab

*Assay findings association*
**KRAS**  
wildtype

**NRAS**  
wildtype

### 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>73,187,189</sup>; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v3.2022)(NCCN Rectal Cancers Guidelines, v4.2022).

### SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFOX<sub>4</sub>, FOLFIRI, irinotecan, or best supportive care<sup>73,190-193</sup>, and as monotherapy for chemotherapy-refractory patients<sup>153,187,189</sup>. The Phase 3 PARADIGM trial comparing panitumumab

plus mFOLFOX<sub>6</sub> versus bevacizumab plus mFOLFOX<sub>6</sub> as first-line treatment for patients with RAS-wildtype left-sided metastatic CRC demonstrated that treatment with panitumumab significantly improved median OS (mOS; 36.2 months vs. 31.3 months) compared with bevacizumab<sup>194</sup>. A Phase 2 trial reported that, for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX<sub>4</sub>, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS OF 59% vs. 49%)<sup>195</sup>. In the Phase 3 ASPRECT 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>187</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>188</sup>.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

## Niraparib

*Assay findings association*
**BRIP1**  
E1222fs\*7

### AREAS OF THERAPEUTIC USE

The PARP inhibitor niraparib is FDA approved to treat patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, with or without homologous recombination deficiency (HRD)-positive status. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence in ovarian<sup>96,196-197</sup>, breast<sup>98</sup>, endometrial<sup>198</sup>, and prostate cancer<sup>97</sup>, loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

### SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of colorectal cancer are limited (PubMed, Nov 2022). Niraparib has primarily been evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS compared with

placebo in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months), as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)<sup>199</sup>. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer experienced SD<sup>200</sup>. A Phase 1 study of the combination of niraparib and bevacizumab for patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)<sup>201</sup>. A Phase 2 study of niraparib reported 1 PR and 8 SDs, with 78% (7/9) of patients with BAP1-mutated cholangiocarcinoma, mesothelioma, uveal melanoma, or clear cell renal cell carcinoma (ccRCC) experiencing SD<sup>202</sup>. A case study reported a patient with BAP1-mutated pretreated ccRCC experienced a PR of 5 months on niraparib<sup>203</sup>.

## Olaparib

*Assay findings association*
**BRIP1**  
E1222fs\*7

### AREAS OF THERAPEUTIC USE

The PARP inhibitor olaparib is FDA approved to treat patients with epithelial ovarian, Fallopian tube, or primary peritoneal cancer, patients with deleterious or suspected deleterious gBRCA-mutated pancreatic adenocarcinoma or HER2-negative breast cancer, and patients with prostate cancer and mutations in homologous recombination repair genes. Olaparib is also approved in combination with bevacizumab to treat patients with ovarian, Fallopian tube, or primary peritoneal cancer with deleterious or suspected deleterious somatic or gBRCA mutation and/or genomic instability. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence in ovarian<sup>96,196-197</sup>, breast<sup>98</sup>, endometrial<sup>198</sup>, and prostate cancer<sup>97</sup>, loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

### SUPPORTING DATA

A Phase 2 study reported olaparib monotherapy to be ineffective for patients with genomically unselected colorectal cancer (CRC) and disease progression on prior

standard systemic therapy, regardless of microsatellite status<sup>204</sup>. Similarly, although a Phase 1 trial for patients with CRC reported 2 SDs (3-9 months, n=11) for those on continuous olaparib plus irinotecan and 7 SDs (4-13 months, n=14) for those on an intermittent regimen of the 2 agents, pronounced toxicity and overall lack of anti-tumor activity precluded further development of this combination<sup>205</sup>. However, 2 case studies reported clinical benefit from olaparib-based regimens for 2 heavily pretreated patients with CRC that harbored alterations in homologous repair deficiency genes. Olaparib monotherapy enabled a reduction in tumor volume for a patient with CRC and a germline CHEK2 R117G mutation under loss of heterozygosity<sup>206</sup>, and for a second patient whose CRC harbored 2 ATM mutations (E2977fs\*2, I1294Nfs\*8), off-label treatment with olaparib in combination with irinotecan enabled a 4-month SD, reduction in tumor markers, and symptomatic improvement<sup>207</sup>. Olaparib has been studied primarily for the treatment of ovarian cancer and has resulted in significantly higher response rates for patients with BRCA1/2 mutations than for those without<sup>208-209</sup>. Olaparib treatment has also demonstrated clinical activity for patients with breast, prostate, or pancreatic cancer and BRCA1/2 mutations<sup>208-212</sup>.

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THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

## Rucaparib

Assay findings association

**BRIP1**  
E1222fs\*7

### AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence in ovarian<sup>96,196-197</sup>, breast<sup>98</sup>, endometrial<sup>198</sup>, and prostate cancer<sup>97</sup>, loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

### SUPPORTING DATA

Clinical data on the efficacy of rucaparib for the treatment of colorectal cancer are limited (PubMed, Nov 2022). Rucaparib has primarily been evaluated in the context of ovarian carcinoma, breast carcinoma, pancreatic carcinoma, and melanoma. In a Phase 2 study of rucaparib for recurrent, platinum-sensitive ovarian, peritoneal, or fallopian tube carcinoma, median PFS was significantly longer in patients with BRCA1/2 mutations (12.8 months) or high loss of heterozygosity (LOH; 5.7 months) compared to patients with low LOH (5.2 months). Objective responses were observed for 80% (32/40) of patients with BRCA1/2 mutations, for 29% (24/82) with high LOH, and

for 10% (7/10) with low LOH<sup>96</sup>. In heavily pretreated patients with a germline BRCA1/2 mutation who had received 2-4 prior chemotherapy treatments and had a progression free interval of greater than 6 months, 65% (17/26) of patients achieved an objective response with rucaparib treatment<sup>142</sup>. In a Phase 2 study evaluating rucaparib for patients with advanced breast or ovarian cancer and germline BRCA1/2 mutations, disease control was observed in 92% (12/13) of patients with ovarian cancer treated with oral rucaparib dosed continuously, but no objective responses were reported in breast cancer patients (n=23). However, 39% (9/23) of evaluable patients with breast cancer achieved SD lasting 12 weeks or more<sup>213</sup>. In a Phase 1 study of rucaparib treatment in patients with solid tumors, 3/4 patients with ovarian cancer and 1/1 patient with breast cancer given the recommended Phase 2 dose reported objective responses; all responders harbored BRCA1/2 mutations<sup>214</sup>. A Phase 2 study of rucaparib treatment for patients with relapsed pancreatic cancer reported 1/19 CR, 2/19 PR (one unconfirmed) and 4/19 SD. Of the 19 patients treated in the study, 15 (79%) had a BRCA2 mutation<sup>215</sup>. In a Phase 2 study of intravenous rucaparib in combination with temozolomide for patients with metastatic melanoma, 8/46 patients achieved a PR and 8/46 had SD<sup>216</sup>; a Phase 1 study reported 1 CR, 1 PR, and 4 SD lasting six months or longer in patients with metastatic melanoma<sup>217</sup>. A Phase 1 study of intravenous and oral rucaparib in combination with chemotherapy for the treatment of advanced solid tumors reported a disease control rate of 68.8% (53/77), including 1 CR and 9 PRs<sup>218</sup>.

## Talazoparib

Assay findings association

**BRIP1**  
E1222fs\*7

### AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

### GENE ASSOCIATION

On the basis of clinical evidence in ovarian<sup>96,196-197</sup>, breast<sup>98</sup>, endometrial<sup>198</sup>, and prostate cancer<sup>97</sup>, loss or inactivation of BRIP1 may confer sensitivity to PARP inhibitors. It is not known whether this therapeutic approach would be relevant in the context of alterations that have not been fully characterized, as seen here.

### SUPPORTING DATA

Clinical data on the efficacy of talazoparib for the treatment of colorectal cancer are limited (PubMed, Nov

2022). Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study<sup>219-220</sup>. In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration<sup>221</sup>. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer<sup>222-225</sup>.

**NOTE** Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied evidence in the patient's tumor type.

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**CLINICAL TRIALS**

**NOTE** 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. 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 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://www.clinicaltrials.gov). Or, visit <https://www.foundationmedicine.com/genomic-testing#support-services>.

**GENE**
**APC**
**ALTERATION**
**R945fs\*10**
**RATIONALE**

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

**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)

**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)

**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)

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CLINICAL TRIALS

GENE

**BRIP1**

ALTERATION

E1222fs\*7

RATIONALE

BRIP1 inactivation may predict sensitivity to inhibitors of other DNA repair pathways, including inhibitors of PARP. It is not known

whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

**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), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

**NCT02264678**

PHASE 1/2

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

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

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

**NCT05035745**

PHASE 1/2

Selinexor & 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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**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)

**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), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

**NCT03297606**
**PHASE 2**

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

**NCT04991480**
**PHASE 1/2**

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

**TARGETS**  
 PARP, Pol theta

**LOCATIONS:** London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

**NCT04972110**
**PHASE 1/2**

Study of RP-3500 With Niraparib or Olaparib in Advanced Solid Tumors

**TARGETS**  
 PARP, ATR

**LOCATIONS:** Utah, Minnesota, Michigan, Connecticut, New York, Maryland, 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.

**ARID1A**

Q1334\_R1335insQQ

**BRAF**

R384G

**BRCA2**

K1533N

**CD22**

A581V

**MSH6**

K1358fs\*2

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**APPENDIX**

Genes Assayed in FoundationOne®CDx

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

**DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS**

ABL1	ACVR1B	AKT1	AKT2	AKT3	ALK	ALOX12B	AMER1 (FAM123B or WTX)	
APC	AR	ARAF	ARFRP1	ARID1A	ASXL1	ATM	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2
BCL6	BCOR	BCORL1	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1
BTG2	BTK	CALR	CARD11	CASP8	CBFB	CBL	CCND1	CCND2
CCND3	CCNE1	CD22	CD274 (PD-L1)	CD70	CD79A	CD79B	CDC73	CDH1
CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C
CEBPA	CHEK1	CHEK2	CIC	CREBBP	CRKL	CSF1R	CSF3R	CTCF
CTNNA1	CTNNB1	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1	DDR2
DIS3	DNMT3A	DOT1L	EED	EGFR	EMSY (C11orf30)	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14
FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FOXL2	FUBP1	GABRA6	GATA3	GATA4
GATA6	GID4 (C17orf39)	GNA11	GNA13	GNAS	GNAS	GRM3	GSK3B	H3-3A (H3F3A)
HDAC1	HGF	HNFA1	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	KIT	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	KRAS	LTK	LYN	MAF	MAP2K1 (MEK1)	MAP2K2 (MEK2)	MAP2K4
MAP3K1	MAP3K13	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1
MERTK	MET	MITF	MKNK1	MLH1	MPL	MRE11 (MRE11A)	MSH2	MSH3
MSH6	MST1R	MTAP	MTOR	MUTYH	MYC	MYCL (MYCL1)	MYCN	MYD88
NBN	NF1	NF2	NFE2L2	NFKBIA	NKX2-1	NOTCH1	NOTCH2	NOTCH3
NPM1	NRAS	NSD2 (WHSC1 or MMSET)	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	NTRK3
P2RY8	PALB2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCC1 (PD-1)	PDCC1LG2 (PD-L2)
PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	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	RARA	RB1	RBM10
REL	RET	RICTOR	RNF43	ROS1	RPTOR	SDHA	SDHB	SDHC
SDHD	SETD2	SF3B1	SGK1	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO
SNCAIP	SOC1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3
STK11	SUFU	SYK	TBX3	TEK	TENT5C (FAM46C)	TET2	TET2	TGFB2
TIPARP	TNFAIP3	TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA
VHL	WT1	XPO1	XRCC2	ZNF217	ZNF703			

**DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS**

ALK	BCL2	BCR	BRAF	BRCA1	BRCA2	CD74	EGFR	ETV4
ETV5	ETV6	EWSR1	EZR	FGFR1	FGFR2	FGFR3	KIT	KMT2A (MLL)
MSH2	MYB	MYC	NOTCH2	NTRK1	NTRK2	NUTM1	PDGFRA	RAF1
RARA	RET	ROS1	RSP02	SDC4	SLC34A2	TERC*	TERT**	TPRSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated


**ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS**

Homologous Recombination status  
Loss of Heterozygosity (LOH) score  
Microsatellite (MS) status  
Tumor Mutational Burden (TMB)

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**APPENDIX**
**About FoundationOne®CDx**

FoundationOne 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, Ciplstraat 3, 2440 Geel, Belgium. 

**ABOUT FOUNDATIONONE CDx**

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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:  
[www.rochefoundationmedicine.com/f1cdxtech](http://www.rochefoundationmedicine.com/f1cdxtech).

**INTENDED USE**

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx 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 solid malignant neoplasms.

**TEST PRINCIPLE**

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes

detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture-selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g. gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

**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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

**Diagnostic Significance**

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

**Qualified Alteration Calls (Equivocal and Subclonal)**

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical

methodology has identified as being present in <10% of the assayed tumor DNA.

**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.

**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. 2023. 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.

**Limitations**

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by

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## APPENDIX

## About FoundationOne®CDx

- analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.
- TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation [https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/P170019B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf). The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
  - Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score  $\geq 16\%$  will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
  - The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and

- extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
  - Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
  - Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in <https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/> report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

### 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.

### VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	%CV*
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

\*Interquartile Range = 1st Quartile to 3rd Quartile

### 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 >10%, 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

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**APPENDIX**

About FoundationOne®CDx

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*, *CBL*, *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.

**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 CDx.

**TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

**SELECT ABBREVIATIONS**

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
mut/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) 7.6.0

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**APPENDIX**
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