### Companion Diagnostic (CDx) Associated Findings

<table>
<thead>
<tr>
<th>GENOMIC FINDINGS DETECTED</th>
<th>FDA-APPROVED THERAPEUTIC OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS</strong> wildtype (codons 12 &amp; 13)</td>
<td>Erbitux® (Cetuximab)</td>
</tr>
<tr>
<td><strong>KRAS/NRAS</strong> wildtype (codons 12, 13, 59, 61, 117, &amp; 146 in exons 2, 3, &amp; 4)</td>
<td>Vectibix® (Panitumumab)</td>
</tr>
</tbody>
</table>

For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be performed.

### OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See professional services section for additional information.

- **Microsatellite status**: MSI-High
- **Tumor Mutational Burden**: 35 Muts/Mb
- **ASXL1**: G645fs*58
- **ASXL1**: S1335fs*115
- **ATM**: R3047*
- **BAP1**: I191fs*2
- **CDH1**: P127fs*41
- **CDH1**: S70fs*13
- **CIC**: P1597fs*23
- **CTNNB1**: W383R
- **FAM123B**: E370fs*8
- **MLL2**: P2354fs*30
- **NTRK1**: TPM3(NM_152263)-NTRK1(NM_002529) fusion (T10*; N9)§
- **PALB2**: M296fs*1
- **RNF43**: G659fs*41
- **SUFU**: A25fs*23
- **TP53**: R273C

§ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCA1/2 alterations, LOH, MSI, or TMB results in this section.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS).

**Note**: The intended use (IU) statement and claims made on this sample report may not be up to date. For the latest version of the FoundationOne CDx claims and IU, please see the current label: [www.foundationmedicine.com/f1cdx](http://www.foundationmedicine.com/f1cdx)

**About the Test**: FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

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**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
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) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. This test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified healthcare professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

The test is also used for detection of genomic loss of heterozygosity (LOH) from FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label. The F1CDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

**TABLE 1: COMpanion DiagNostic IndICATIONS**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>BIOMARKER</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>EGFR exon 19 deletions and EGFR exon 21 L858R alterations</td>
<td>Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>EGFR exon 20 T790M alterations</td>
<td>Tagrisso® (Osimertinib)</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>ALK rearrangements</td>
<td>Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>BRAF V600E</td>
<td>Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E</td>
<td>Tafinlar® (Dabrafenib) or Ze�ora® (Vemurafenib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E and V600K</td>
<td>Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Ze�ora® (Vemurafenib)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>ERBB2 (HER2) amplification</td>
<td>Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>KRAS wild-type (absence of mutations in codons 12 and 13)</td>
<td>Erbitux® (Cetuximab)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>KRAS wild-type (absence of mutations in exons 2, 3, and 4) and NRAS wild-type (absence of mutations in exons 2, 3, and 4)</td>
<td>Vectibix® (Panitumumab)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>BRCA1/2 alterations</td>
<td>Lynparza® (Olaparib) or Rubraca® (Rucaparib)</td>
</tr>
</tbody>
</table>
**Biomarker Findings**

### Microsatellite status - MSI-High

- 10 Trials see p. 19

### Tumor Mutational Burden - 35 Muts/Mb

- 10 Trials see p. 21

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**Genomic Findings**

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

- KRAS wildtype
- NRAS wildtype
- NTRK1 TPM3-NTRK1 fusion
- ATM R3047*
- PALB2 M296fs*1
- CTNNB1 W383R
- RNF43 G659fs*41
- SUFU A25fs*23
- ASXL1 G645fs*8, S1335fs*115
- BAPT1191fs*2
- CDH1 S70fs*13, P127fs*41
- CIC P1597fs*23
- FAM123B E370fs*8
- ML2 P2354fs*30
- TP53 R273C

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

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<table>
<thead>
<tr>
<th>THERAPIES WITH CLINICAL BENEFIT (IN PATIENT’S TUMOR TYPE)</th>
<th>THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab [2A]</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Pembrolizumab [2A]</td>
<td>Avelumab</td>
</tr>
<tr>
<td></td>
<td>Cemiplimab</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td></td>
<td>Cemiplimab</td>
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<tr>
<td></td>
<td>Durvalumab</td>
</tr>
</tbody>
</table>

35 Trials see p. 19

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About the Test

FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

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## Genomic Findings

<table>
<thead>
<tr>
<th>Genomic Alteration</th>
<th>Tumor Type</th>
<th>Trials</th>
<th>Therapies with Clinical Benefit (In Patient's Tumor Type)</th>
<th>Therapies with Clinical Benefit (In Other Tumor Type)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS - wildtype</td>
<td></td>
<td>0</td>
<td>Cetuximab 2A, Panitumumab 2A</td>
<td>none</td>
</tr>
<tr>
<td>NRAS - wildtype</td>
<td></td>
<td>0</td>
<td>Cetuximab 2A, Panitumumab 2A</td>
<td>none</td>
</tr>
<tr>
<td>NTRK1 - TPM3-NTRK1 fusion</td>
<td></td>
<td>6</td>
<td>Entrectinib 2A, Larotrectinib 2A</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>ATM - R3047*</td>
<td></td>
<td>10</td>
<td>none</td>
<td>Niraparib, Olaparib, Rucaparib, Talazoparib</td>
</tr>
<tr>
<td>PALB2 - M296fs*1</td>
<td></td>
<td>10</td>
<td>none</td>
<td>Niraparib, Olaparib, Rucaparib, Talazoparib</td>
</tr>
<tr>
<td>CTNNB1 - W383R</td>
<td></td>
<td>10</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>RNF43 - G659fs*41</td>
<td></td>
<td>2</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>SUFU - A25fs*23</td>
<td></td>
<td>5</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

### 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.

### Therapies with Clinical Benefit

- **ASXL1 - G645fs*58, S1335fs*115**
  - p. 8
- **BAPI - I191fs*2**
  - p. 9
- **CDH1 - S70fs*13, P127fs*41**
  - p. 9
- **CIC - P1597fs*23**
  - p. 9
- **FAM123B - E370fs*8**
  - p. 10
- **MLL2 - P2354fs*30**
  - p. 10
- **TP53 - R273C**
  - p. 11

### Note

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

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.
**Biomarker**

**Microsatellite status**

**RESULT**

MSI-High

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**Potential Treatment Strategies**

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors, including the approved therapies nivolumab, pembrolizumab, avelumab, and durvalumab. Pembrolizumab therapy resulted in a significantly higher objective response rate in patients with MSI-H colorectal cancer (CRC) compared with MSS CRC (40% vs. 0%). Similarly, a clinical study of nivolumab, alone or in combination with ipilimumab, in patients with CRC reported a significantly higher response rate in patients with high MSI than those without. An earlier case study reported that nivolumab therapy resulted in a complete response in a patient with MSI-H CRC. A Phase 1b trial of atezolizumab combined with bevacizumab reported PRs for 40% (4/10) of patients with MSI-H CRC. MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFIRI and FOLFOX. MSI and deficient MMR are associated with lack of benefit of postsurgical fluorouracil (FU)-based adjuvant therapy in colon cancer, but may predict benefit from irinotecan chemotherapy.

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**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. 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. This sample has a high level of MSI, equivalent to the clinical definition of an MSI-high (MSI-H) tumor. MSI-H colorectal cancers (CRCs) make up 10–15% of 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.

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**Biomarker**

**Tumor Mutational Burden**

**RESULT**

35 Muts/Mb

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**Potential Treatment Strategies**

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-1 and anti-PD-L1 therapies. A large-scale retrospective analysis of immune checkpoint inhibitor efficacy in CRC reported significantly improved OS for patients with tumors harboring TMB ≥ 12 Muts/Mb compared to those with tumors with TMB < 12 Muts/Mb. Another study reported that a TMB ≥ 12 Muts/Mb cutoff identifies 59% of MSI-H CRC cases but only 3% of MSS cases, indicating the potential for improved predictive biomarker identification with other agents.

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**Finding Summary**

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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 and cigarette smoke in lung cancer. Mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes and cigarette smoke in lung cancer. Mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes and microsatellite instability (MSI) are associated with a higher risk of colorectal, endometrial, gastric, and other cancers. MSI is defined by mutations in >30% of microsatellite repeats. This sample harbors a TMB level that may be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents.

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Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab\textsuperscript{54-57} or panitumumab\textsuperscript{58-60} in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

**FREQUENCY & PROGNOSIS**
Approximately 50-65\% of colorectal cancers (CRCs) have been reported to lack KRAS mutations\textsuperscript{61-65}. Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC\textsuperscript{63-66,70-71}.

**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\textsuperscript{72-73}. No alterations in KRAS were identified in this case.

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab\textsuperscript{54-57} or panitumumab\textsuperscript{58-60} in patients with CRC. Therefore, these agents are indicated for treatment of patients with CRC lacking such mutations (NCCN Guidelines v2.2019).

**FREQUENCY & PROGNOSIS**
The majority of colorectal cancers (CRCs) (91-98\%) have been reported to lack NRAS mutations\textsuperscript{21,69,74-79}. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis\textsuperscript{69} and longer survival\textsuperscript{79-80} 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\textsuperscript{72}. No alterations in NRAS were identified in this case.