The F1CDx assay will be performed at Foundation Medicine, Inc. RUBRACA product label.

Rubraca (rucaparib) maintenance therapy in accordance with the associated with improved progression-free survival (PFS) from tBRCA-positive and/or LOH high) in ovarian cancer patients is recombination deficiency (HRD) status (F1CDx HRD defined as (LOH) from FFPE ovarian tumor tissue. Positive homologous The test is also used for detection of genomic loss of heterozygosity therapeutic product.

not prescriptive or conclusive for labeled use of any specific professional guidelines in oncology for patients with solid neoplasms. Genomic findings other than those listed in Table 1 are 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 for qualified health care 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 3: 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 gene deletions and EGFR exon 21 L858R alterations</td>
<td>Gloitk® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)</td>
</tr>
<tr>
<td></td>
<td>EGFR exon 20 T790M alterations</td>
<td>Tagrisso® (Osimertinib)</td>
</tr>
<tr>
<td></td>
<td>AKT rearrangements</td>
<td>Alcensa® (Alpelisib), Zalaki® (Crizotinib), or Zykdaf® (Certinib)</td>
</tr>
<tr>
<td></td>
<td>BRAF v600E</td>
<td>Tafinar® (Dabrafenib) in combination with Mekeis® (Trazemblin)</td>
</tr>
<tr>
<td></td>
<td>MET single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping</td>
<td>Tabrecta® (Capmatinib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E and V600K</td>
<td>Mekinin® (Trametinib) or Cotelan® (Cobimetinib) in combination with Zeboral® (Vemurafenib)</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Breast cancer</td>
<td>EBB2 (HER2) amplification</td>
<td>Herceptin® (Trastuzumab), Kadaflya® (Ado-trastuzumab emtansine), or Perjeta® (Peruzumab)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>KRAS wild type (absence of mutations in exons 2 and 13)</td>
<td>Erbitux® (Cetuximab)</td>
</tr>
<tr>
<td></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>Vectib® (Panitumumab)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Brca1/2 alterations</td>
<td>Lynpazara® (Olaparib) or Rubraca® (Rucaparib)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>FGFR2 fusions and select rearrangements</td>
<td>Pemazyme® (Pemigatinib)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>HRR alterations</td>
<td>Lynpazara® (Olaparib)</td>
</tr>
</tbody>
</table>

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

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

**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.

**BRCA2**
- **loss**

**RAD21**
- **amplification** - equivocal

**TP53**
- R283C

† See About the Test in appendix for details.

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4 Therapies with Clinical Benefit
10 Clinical Trials
0 Therapies with Lack of Response

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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.

**RAD21**
- **amplification** - equivocal

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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
MS-Stable

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 tumor25. 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 PMS226-27. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers28-29. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins25,27,29-30.

BIOMARKER

Tumor Mutational Burden

RESULT
1 Muts/Mb

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 melanoma31-32 and cigarette smoke in lung cancer33-34, treatment with temozolomide-based chemotherapy in glioma35-36, and microsatellite instability (MSI)37-38. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types22-23.

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Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as the platinum chemotherapies cisplatin and carboplatin\(^{70-72}\).

**FREQUENCY & PROGNOSIS**

BRCA2 genomic loss has been described in 1-2% of primary and 2-3% of metastatic prostate cancer cases\(^{31,34-37}\). BRCA2 mutations have been identified in 3-6% of primary and 6-7% of metastatic prostate cancer specimens\(^{31,34-37}\), with deleterious germline BRCA2 mutations present in 5% of men with metastatic prostate cancer\(^{35}\). The positive predictive value of prostate specific antigen (PSA) levels was found to be higher in patients with BRCA1/2 mutations than in the general population\(^{37}\). BRCA2 germline mutations have been associated with attributes of aggressive prostate cancer at diagnosis, including high Gleason score, nodal involvement, advanced tumor stage, and metastatic spread\(^{38}\). Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers\(^{39}\). Following radical conventional treatment for localized prostate cancer, patients with germline BRCA1/2 mutations experienced significantly shorter metastasis-free survival (HR=2.36) and CSS (HR=2.17) than noncarriers\(^{37}\). For patients with metastatic castration-resistant prostate cancer (mCRPC), germline BRCA2 alterations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in 1 study\(^{37}\). Germline BRCA2 mutations in mCRPC were associated with relative benefit from first-line abiraterone or enzalutamide compared with taxanes (CSS 22.0 vs. 17.0 months, PFS on the second systemic therapy 18.9 vs. 8.6 months) in a large prospective cohort study\(^{78}\). Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy\(^{79-82}\).

**FINDING SUMMARY**

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage\(^{31}\). Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis\(^{82}\). BRCA2 alterations that disrupt PALB2 binding (aa 21-39)\(^{83}\), the BRCA repeats (aa 1002-2085), the DNA binding domain (aa 2479-3192), and/or the C-terminal RAD51 binding domain, as observed here, are predicted to be inactivating\(^{84-99}\). Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer\(^{100-101}\), and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >80% and 23%, respectively\(^{102}\). Elevated risk for other cancer types, including gastric, pancreatic, prostate, and colorectal, has also been identified, with an increase in risk ranging from 20 to 60%\(^ {103}\). The estimated prevalence of deleterious germline BRCA1/2 mutations in the general population is between 1:400 and 1:800, with an approximately 10-fold higher prevalence in the Ashkenazi Jewish population\(^ {104-109}\). In the appropriate clinical context, germline testing of BRCA2 is recommended.