# Companion Diagnostic (CDx) Associated Findings

## Genomic Findings Detected

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIK3CA</td>
<td>E545K</td>
</tr>
</tbody>
</table>

## FDA-Approved Therapeutic Options

- Piqray® (Alpelisib)

## 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**: MS-Stable
- **Tumor Mutational Burden**: 4 Muts/Mb
- **BRCAl**: P628fs*16
- **FANC**: FANCG (NM_004629) rearrangement intron 1

$\dagger$ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, BRCAl/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)

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FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing-based in vitro diagnostic test that uses targeted high-throughput hybridization-based capture technology 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. The 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 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 formalin-fixed, paraffin-embedded (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 is 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 exons 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), Alunbrig® (Brigatinib), Xalkori® (Crizotinib), or Zykdla® (Carfatinib)</td>
</tr>
<tr>
<td>Non-small cell lung cancer (NSCLC)</td>
<td>MET single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping</td>
<td>Tarceya® (Capmatinib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E</td>
<td>Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF V600E and V600K</td>
<td>Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>ERBB2 amplification</td>
<td>Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Colorectal cancer KRAS wild-type (absence of mutations in exons 2, 3, and 4)</td>
<td>Erbitux® (Cetuximab)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Colorectal cancer KRAS 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>
<tr>
<td>Ovarian cancer</td>
<td>Cholangiocarcinoma FGFR2 fusions and select rearrangements</td>
<td>Pemazyre® (Pemigatinib) or Truxal® (Truxal®) (Infrafibrin)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Prostate cancer Humoral Recombination Repair (HRR) gene (BRCA1, BRCA2, ATM, ATR, BARD1, BRIP1, CHEK1, CHEK2, FANC, PALB2, RAD51B, RAD51C, RAD51D and RAD54L) alterations</td>
<td>Lynparza® (Olaparib)</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>TMB &gt; 10 mutations per megabase</td>
<td>Keytruda® (Pembrolizumab)</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>NTRK1/2/3 fusions</td>
<td>Vitrakvi® (Ranotacitinib)</td>
</tr>
</tbody>
</table>
Biomarker Findings

**Microsatellite status** - MS-Stable

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

**Genomic Findings**

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

**BRCA2** P628fs*16

**PIK3CA** E545K - subclonal

**STK11** F231L - subclonal

**FANCG** rearrangement intron 11

**MAP2K4** loss

**STAG2** splice site 2674-1G>C

**TP53** C275F

2 Disease relevant genes with no reportable alterations: **BRCA1, ERBB2**

* See About the Test in appendix for details.

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**Report Highlights**

- Targeted therapies with NCCN categories of evidence in this tumor type: Alpelisib + Fulvestrant (p. 10), Olaparib (p. 11), Talazoparib (p. 12), Everolimus (p. 13)

- Variants that may inform nontargeted treatment approaches (e.g., chemotherapy) in this tumor type: **BRCA2 P628fs*16** (p. 5)

- Evidence-matched clinical trial options based on this patient’s genomic findings: (p. 15)

- Variants in select cancer susceptibility genes to consider for possible follow-up germline testing in the appropriate clinical context: **BRCA2 P628fs*16** (p. 5)

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**BIOMARKER FINDINGS**

**Microsatellite status** - MS-Stable

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

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**GENOMIC FINDINGS**

**BRCA2** - P628fs*16

10 Trials see p. 15

**PIK3CA** - E545K - subclonal

10 Trials see p. 17

**STK11** - F231L - subclonal

8 Trials see p. 19

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**THERAPY AND CLINICAL TRIAL IMPLICATIONS**

No therapies or clinical trials. see Biomarker Findings section

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**THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT’S TUMOR TYPE)**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>1</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>1</td>
</tr>
<tr>
<td>Alpelisib + Fulvestrant</td>
<td>1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niraparib</td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>2A</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

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**NCCN Category**
VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

**BRCA2** - P628fs*16 ............................................. p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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.

**FANCG** - rearrangement intron 11 ........................................ p. 7
**MAP2K4** - loss ...................................................... p. 8
**STAG2** - splice site 2674-1G>C ........................................ p. 8
**TP53** - C275F ........................................................ p. 9

**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 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 inhibitors1-3, including approved therapies nivolumab and pembrolizumab4. 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)5.

FREQUENCY & PROGNOSIS

MSI is extremely rare in breast cancer, reported in 0-1% of cases across studies6-11. The incidence of MSI is increased in triple-negative breast cancer9-11 and in tumors with homologous recombination defects, such as mutations in BRCA1/29,10. Notably, in Lynch syndrome-related breast cancer, MSI has been reported in 51-85% of cases9,10,11. A prospective study of 123 patients with breast cancer treated with chemotherapy reported an increase in the incidence of MSI-H following chemotherapy treatment (from 0% pre-treatment to 19% post-treatment) and a significant association between MSI and tumor recurrence12.

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 tumor19. 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 PMS219-21. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers22-24. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins19,21,22-24.
**Tumor Mutational Burden**

**RESULT**

4 Muts/Mb

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**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, anti-PD-1 therapies, and combination nivolumab and ipilimumab. Higher TMB was found to be significantly associated with improved OS from treatment with immune checkpoint inhibitors. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with tumors with TMB >20 Muts/Mb. Analyses across several solid tumor types reported that patients with TMB >20 Muts/Mb achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with lower TMB treated with chemotherapy or those with lower TMB treated with PD-1 or PD-L1-targeting agents. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB >20 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types.

Similar findings were observed in the KEYNOTE-028 and KEYNOTE-122 trials. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

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**FREQUENCY & PROGNOSIS**

One study reported that invasive ductal carcinoma (IDC) of the breast has a median TMB of 3.6 mutations per megabase (Muts/Mb), with 1.4% of cases harboring TMB ≥20 Muts/Mb. Another study found that 4% of breast IDC cases have TMB ≥10 Muts/Mb, with a higher frequency of such elevated TMB (7.8%) in metastatic samples. A study of 3,969 patients with breast cancer reported a median TMB of 2.63 mutations per megabase (Muts/Mb), with 5% of cases harboring TMB ≥10 Muts/Mb; median TMB was significantly higher in hormone receptor (HR)-negative and HER2-negative tumors than HR-positive or HER2-positive tumors. The Breast Invasive Carcinoma TCGA analysis reported an average (non-silent) mutation load of 0.84 Muts/Mb for luminal A tumors, 1.58 Muts/Mb for luminal B tumors, 2.05 Muts/Mb for HER2-enriched tumors, and 1.68 Muts/Mb for basal-like tumors. In breast cancer, TMB is significantly higher in recurrent versus primary tumors, metastatic versus localized cancers, triple-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors. Among metastatic tumors, TMB-high samples have been reported more frequently in invasive lobular carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive ductal carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma. Breast carcinoma harbors a median TMB of 3.8 Muts/Mb, and 3.1% of cases have high TMB (>20 Muts/Mb). In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data.

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**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 and cigarette smoke in lung cancer, treatment with temozolomide-based chemotherapy in glioma, and microsatellite instability (MSI) mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes, and mutations in the TPSA and TPSB genes. In breast cancer, TMB is significantly higher in HER2-negative versus HR-positive tumors, and CDH1-mutated versus CDH1-wildtype tumors. TMB-high samples have been reported more frequently in invasive ductal carcinoma (9-17% of cases, depending on the TMB cutoff to designate TMB-high) than in invasive lobular carcinoma (2-8% of cases, depending on the cutoff), and TMB-high (at either cutoff) has not been observed in papillary carcinoma. Breast carcinoma harbors a median TMB of 3.8 Muts/Mb, and 3.1% of cases have high TMB (>20 Muts/Mb). In a large study of patients with breast cancer, hypermutation was more frequently observed in metastatic tumors than in primary tumors. In a study of 14,867 patients with breast cancer, high TMB was associated with older age and metastatic disease but was not significantly associated with PD-L1 positivity using the TMB cutoff of ≥10 Muts/Mb. In estrogen receptor-positive breast cancer, increased TMB in tissue samples (mean of 1.25 Muts/Mb) associated with shorter OS (HR=2.02) in an analysis of the TCGA data.