



# Guide to FoundationOne®CDx Reports

Use this guide to learn about the key features of the FoundationOne CDx report

## Section One: FDA-Approved Claims

Any FDA-approved claims will always appear at the beginning of the report, starting on page one.

**FOUNDATIONONE® CDx** PATIENT: Jane Sample TUMOR TYPE: Breast invasive ductal carcinoma (IDC) REPORT DATE: [Redacted] ORDERED TEST # [Redacted]

**PATIENT**  
DISEASE: Breast invasive ductal carcinoma (IDC)  
NAME: Jane Sample  
DATE OF BIRTH: [Redacted]  
SEX: [Redacted]  
MEDICAL RECORD #: [Redacted]

**PHYSICIAN**  
ORDERING PHYSICIAN: [Redacted]  
MEDICAL FACILITY: [Redacted]  
ADDITIONAL RECIPIENT: [Redacted]  
MEDICAL FACILITY ID: [Redacted]  
PATHOLOGIST: [Redacted]

**SPECIMEN**  
SPECIMEN SITE: [Redacted]  
SPECIMEN ID: [Redacted]  
SPECIMEN TYPE: [Redacted]  
DATE OF COLLECTION: [Redacted]  
SPECIMEN RECEIVED: [Redacted]

**Companion Diagnostic (CDx) Associated Findings**

**1 GENOMIC FINDINGS DETECTED**

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
<b>PIK3CA E542K</b>	Piqray® (Aplisib) [Redacted]

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

**2 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 <sup>§</sup>	PTEN splice site 253+2T>A
Tumor Mutational Burden 1 Muts/Mb <sup>§</sup>	RAD21 amplification <sup>§</sup>
MYC amplification <sup>§</sup>	TP53 V274G

<sup>§</sup> 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).

**FOUNDATIONONE® CDx (VUS) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertions and deletions (indels), and copy number alterations (CNAs) in 29 genes and other gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from FoundationOne panels 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, FCDx 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.**

**TABLE 1: COMPANION DIAGNOSTIC INDICATIONS**

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and T790M substitution	Osimertinib (Tagrisso) <sup>1</sup> , Erlotinib (Tarceva) <sup>2</sup> , or Tazemetamab (Tazmetamab) <sup>3</sup>
	EGFR exon 20 T790M alterations	Tegaserod (Dismavene) <sup>4</sup>
Breast cancer	HER2 (ERBB2) amplification	Trastuzumab (Herceptin) <sup>1</sup> , Trastuzumab emtansine (Kadcyla) <sup>2</sup> , or Pertuzumab (Perjeta) <sup>3</sup>
	PIK3CA E542K, E545K, E545Q, E545R, E545G, E545V, E545L, E545P, E545K, E545R, E545Q, E545V, E545L, E545P, E545K, E545R, E545Q, E545V, E545L, E545P	Piqray® (Aplisib) <sup>1</sup>
Colorectal cancer	KRAS wild type (absence of mutations in exons 2, 3, and 4)	Erdofitinib (Erdofitinib) <sup>1</sup>
	RAS wild type (absence of mutations in exons 2, 3, and 4)	Vandetanib (Zincifan) <sup>1</sup>
Ovarian cancer	BRCA1/2 alterations	Olaparic acid (Lynparic) <sup>1</sup> or Rubraca® (Rubraca) <sup>2</sup>

**ABOUT THE TEST** FoundationOne®CDx is the first FDA-approved broad companion diagnostic for solid tumors.

Electrically signed by Richard Huang, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director | Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141-CLIA: Z202027371  
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141-CLIA: Z202027371

FDA APPROVED CLAIMS - PAGE 3 OF 1

## Section Two: Professional Services

This section provides information about any biomarker and genomic findings.

**FOUNDATIONONE® CDx** PATIENT: Jane Sample TUMOR TYPE: Breast invasive ductal carcinoma (IDC) REPORT DATE: [Redacted] ORDERED TEST # [Redacted]

**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.

**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.  
PIK3CA E542K  
PTEN splice site 253+2T>A  
MYC amplification  
RAD21 amplification - equivocal<sup>§</sup>  
TP53 V274G

**3 Disease relevant genes with no reportable alterations: BRCA1, BRCA2, ERBB2**

1 See About the Test in appendix for details.

**3 Therapies with Clinical Benefit**      **22 Clinical Trials**  
**0 Therapies with Lack of Response**

**BIOMARKER FINDINGS**

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - MS-Stable	No therapies or clinical trials. see Biomarker Findings section
Tumor Mutational Burden - 1 Muts/Mb	No therapies or clinical trials. see Biomarker Findings section

**GENOMIC FINDINGS**

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
<b>PIK3CA - E542K</b> 10 Trials see p. 12	Alpelisib [1] Everolimus [2A]	Temsirolimus
<b>PTEN - splice site 253+2T&gt;A</b> 10 Trials see p. 14	Everolimus [2A]	Temsirolimus
<b>MYC - amplification</b> 8 Trials see p. 10	none	none

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

**RAD21 - amplification - equivocal**      p. 5      **TP53 - V274G**      p. 6

<sup>§</sup> 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.

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PROFESSIONAL SERVICES - PAGE 1 OF 15

### 1 FDA-Approved CDx Claims

List of FDA-approved companion diagnostics associated with your patient's findings.

### 2 All Other Biomarkers and Genomic Signatures

All other genomic and biomarker findings, including microsatellite instability (MSI), tumor mutational burden (TMB), and Loss of heterozygosity (LOH, in ovarian cancer only), without companion diagnostic claims.

### 3 Pertinent Negatives

Identifies important negative results that can be used for patient management.

### 4 Therapies with Clinical Benefit

Therapies for each associated genomic finding are listed in alphabetic order. On the left are therapies within your patient's tumor type, and on the right are those with proven clinical benefit in other tumor types.

### 5 NCCN Categories of Evidence and Consensus

Associated NCCN Category that has been assigned to the therapy listed within your patient's tumor type.

### 6 Clinical Trials

Identifies trials based on your patient's unique genomic profile with page number for quick reference.

Note: The images shown on this piece are of a sample report and do not represent actual test results. This piece is intended to educate healthcare providers on the FoundationOne®CDx report and should not be used for patient diagnosis or treatment decisions.

Sample report images last updated April 2020.

# Professional Services Continued

## Detailed Information on Biomarker and Genomic Findings

Following the initial pages of the report, the professional services section goes into more detail about your patient's findings. Detailed information about their biomarker findings will appear first, followed by their genomic findings.

FOUNDATIONONE® CDx		PATIENT Jane Sample	TUMOR TYPE Breast invasive ductal carcinoma (IDC)	REPORT DATE
ORDERED TEST #		<b>BIOMARKER FINDINGS</b>		
<p><b>BIOMARKER</b></p> <p><b>Microsatellite status</b></p> <p><b>RESULT</b> MS-Stable</p> <p><b>POTENTIAL TREATMENT STRATEGIES</b> 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>1,2</sup>, including approved therapies nivolumab and pembrolizumab<sup>3</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=0.0004).</p> <p><b>FREQUENCY &amp; PROGNOSIS</b> No MSI was observed in two large sets of breast cancer samples<sup>4,5</sup>. However, a syndrome-related breast cancer, MSI-H reported in 20-85% of cases<sup>6,7</sup>. A pros study observed increased MSI following chemotherapy treatment, and MSI is a marker of incidence of secondary tumors<sup>8,9</sup>.</p> <p><b>FINDING SUMMARY</b> Microsatellite instability (MSI) is a con</p>				
ORDERED TEST #		<b>GENOMIC FINDINGS</b>		
<p><b>GENE</b></p> <p><b>PTEN</b></p> <p><b>ALTERATION</b> splice site 253&gt;27-A</p> <p><b>TRANSSCRIPT NUMBER</b> NM_000318</p> <p><b>CODING SEQUENCE EFFECT</b> 253&gt;27-A</p> <p><b>POTENTIAL TREATMENT STRATEGIES</b> PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway<sup>10-12</sup> and may predict sensitivity to inhibitors of this pathway<sup>13-15</sup> such as the mTOR inhibitors temsirolimus and everolimus or the PI3K inhibitor copanlisib. Preclinical studies suggest that PTEN-deficient cancers, in the absence of other oncogenic mutations, depend primarily on the beta isoform of PI3K (PI3K-beta)<sup>16,17</sup> and PI3K-beta-selective inhibitors are in clinical trials for PTEN-deficient tumors. However, the NCI-MATCH Phase 2 study observed limited activity of the PI3K-beta-selective inhibitor GSK697711 as monotherapy in PTEN-deficient cancers, with a median PFS of 1.8 months. The best outcomes were 1 PR (1/2), prostate cancer; SD (1/22) for patients with PTEN deletion/mutation, and SD (0/4) for patients with PTEN protein loss<sup>18</sup>. Clinical data in breast<sup>19,20</sup> and prostate cancer<sup>21,22</sup> suggest that PTEN alterations may predict sensitivity to pan-AKT inhibitors such as ipatasertib or capivasertib. Phase 2 studies have reported improved PFS from the addition of either ipatasertib (9.0 vs. 4.9 months, HR=0.44) or capivasertib (6.3 vs. 3.7 months, HR=0.30) to paclitaxel compared with paclitaxel and placebo, for patients with metastatic triple-negative breast cancer harboring PI3K/AKT1/PTEN alterations<sup>23</sup>. Emerging clinical and preclinical data suggest that PTEN alterations may predict sensitivity to PARP inhibitors. Four patients with tumors harboring PTEN mutation or loss but no detected BRCA1/2 alterations experienced clinical benefit from PARP inhibition by olaparic or niraparib<sup>24,25</sup>. However, although multiple preclinical studies have demonstrated sensitivity of PTEN-mutant cell lines to various PARP inhibitors<sup>26,27,28</sup>, other studies have observed a lack of association between PTEN mutation and PARP inhibitor sensitivity<sup>29,30</sup>. PTEN alterations may predict a lack of response to anti-PD-1 therapy. In a retrospective analysis of 66 patients with glioblastoma (GBM), tumors from nivolumab or pembrolizumab non-responders were significantly enriched for PTEN mutations<sup>31</sup>. In a patient with uterine leiomyosarcoma treated with pembrolizumab monotherapy, a treatment-resistant tumor arose that harbored PTEN loss<sup>32</sup>. A patient with NCLC whose tumor harbored PTEN alteration exhibited a lack of response to nivolumab and pembrolizumab<sup>33</sup>. In an analysis of 30 patients with metastatic melanoma treated with pembrolizumab or nivolumab, patients with PTEN-expressing tumors achieved significantly greater reduction of tumor size than those with reduction or loss of PTEN expression<sup>34</sup>. In the context of concurrent PI3K/AKT/mTOR, PTEN loss or mutation may predict resistance to PI3K-alpha-specific inhibitors<sup>35,36</sup>.</p> <p><b>FREQUENCY &amp; PROGNOSIS</b> In the TCGA dataset, PTEN mutation has been reported in 4% of breast invasive carcinomas, while pathologic homozygous deletion of PTEN has been reported in 2% of cases<sup>37</sup>. PTEN mutation has also been observed in 53% (1/19) of metastatic breast cancers<sup>38</sup> and 2% of invasive lobular carcinoma tumors analyzed<sup>39</sup>. PTEN mutations are associated more frequently with triple-negative breast cancer than with HER2- or hormone-positive breast cancer<sup>40,41</sup>. Loss or reduction of PTEN expression has been observed in 28% of invasive ductal breast carcinomas and has been correlated with metastasis and poor patient prognosis, including decreased 2-year disease-free survival<sup>42,43</sup>.</p> <p><b>FINDING SUMMARY</b> PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway. Loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis<sup>44</sup>. PTEN alterations that disrupt the N-terminal PP2A binding motif<sup>45</sup>, the phosphatase domain (amino acids 14-185)<sup>46,47</sup>, the C-terminal region<sup>48,49</sup>, and/or PTEN localization, such as observed here, are predicted to cause a loss of function. One or more of the PTEN variants observed here has been described in the ClinVar database as a pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hamantoma tumor syndrome (ClinVar, Nov 2019)<sup>50</sup>. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. PTEN mutations underlie several inherited disorders, collectively termed PTEN hamantoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Li-Fraumeni-Duclos disease (LD), Bannayan-Riley-Ravulaca syndrome (BRRS), PTEN-related Patau syndrome (PS), and Proteus-like syndrome<sup>51,52</sup>. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients<sup>53,54</sup>. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder<sup>55</sup>. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.</p>				
ORDERED TEST #		<p><b>BIOMARKER</b></p> <p><b>Tumor Mutational Burden</b></p> <p><b>RESULT</b> 1 Mut/Mb</p> <p><b>POTENTIAL TREATMENT STRATEGIES</b> On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-1<sup>56,57</sup> and anti-PD-1 therapies<sup>58</sup>. Higher TMB has corresponded with increased ORR and OS from treatment with immune checkpoint inhibitors in phase 2 studies<sup>59,60</sup>. Analyses across several solid tumor types have identified that patients with higher TMBs (≥10 Mut/Mb) achieved greater clinical benefit using PD-1/PD-L1 monotherapy, compared with patients treated with chemotherapy<sup>61</sup> or those with lower TMBs<sup>62</sup>. Additionally, higher TMB is significantly associated with improved OS with immune checkpoint inhibitor treatment for patients with advanced cancer across 9 solid tumor types<sup>63</sup>.</p> <p><b>FREQUENCY &amp; PROGNOSIS</b> Invasive breast ductal carcinoma harbors TMB of 3.6 mutations per megabase (p and 4.4% of cases have high TMB (≥20 Mut/Mb). The Breast Invasive Carcinoma analysis reported an average (non-silenced) of 0.63 mut/Mb for luminal A-H1 mut/Mb, 0.91 mut/Mb for luminal B tumors, 2.57 HER2-enriched tumors, and 4.08 mut/Mb basal-like tumors<sup>64</sup>. In breast cancer, TMBs (≥10 Mut/Mb) have also been reported in metastatic invasive lobular carcinoma compared to metastatic invasive ductal (1.6/0.9). In estrogen receptor-positive cancer, increased mutation load (≥ 6 me</p>		

### Report Interpretation Services

For providers who have access to the Foundation Medicine portal, select the "Ask An Expert" button for additional help with report interpretation.

\* The list of genes is based on professional guidelines from ACMG (Kalia et al., 2017; 27854360) and ESMO (Mandelker et al., 2019; 31050713). Gene list includes the following: APC, BRCA1, BRCA2, BRIP1, MEN1, MLH1, MSH2, MSH6, MUTYH, NF2, PALB2, PMS2, PTEN, RAD51, RAD51D, RB1, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TGFBR2, TP53, TSC1, TSC2, VHL, WT1.

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FoundationOne®CDx is a next-generation sequencing based *in vitro* test intended for use by healthcare professionals for advanced cancer patients with solid tumors. The test analyzes 324 genes as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) and is FDA-approved as a companion diagnostic to identify patients who may benefit from treatment with a specific list of therapies (listed in Table 1 in the Technical Information at <http://www.foundationmedicine.com/flcdx>) in accordance with the approved therapeutic product labeling. Additional genomic findings, other than those listed in Table 1, may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the test does not guarantee a patient will be matched to a treatment or clinical trial option, or that all relevant alterations will be detected. Some patients may require a biopsy. For the complete label, including important risk information, please visit <http://www.foundationmedicine.com/flcdx>.