

**PATIENT**

 DISEASE Prostate acinar adenocarcinoma  
 NAME  
 DATE OF BIRTH  
 SEX  
 MEDICAL RECORD #

**PHYSICIAN**

 ORDERING PHYSICIAN  
 MEDICAL FACILITY  
 ADDITIONAL RECIPIENT  
 MEDICAL FACILITY ID  
 PATHOLOGIST

**SPECIMEN**

 SPECIMEN SITE  
 SPECIMEN ID  
 SPECIMEN TYPE  
 DATE OF COLLECTION  
 SPECIMEN RECEIVED

**Companion Diagnostic (CDx) Associated Findings**
**GENOMIC FINDINGS DETECTED**
**BRCA2** loss

**FDA-APPROVED THERAPEUTIC OPTIONS**

Lynparza® (Olaparib)

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** MS-Stable<sup>§</sup>
**Tumor Mutational Burden** 1 Muts/Mb<sup>§</sup>
**RAD21** amplification<sup>§</sup>
**TP53** R283C

<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 (FICDx) 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. 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, FICDx 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 FFPE ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (FICDx 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 FICDx assay will be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	EGFR exon 19 deletions and EGFR exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	EGFR exon 20 T790M alterations	Tagrisso® (Osimertinib)
	ALK rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	MET single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping	Tabrecta™ (Capmatinib)
	BRAF V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
Breast cancer	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotelllic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
	ERBB2 (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
	KRAS wild-type (absence of mutations in codons 12 and 13)	Erbix® (Cetuximab)
Ovarian cancer	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)	Vectibix® (Panitumumab)
	BRCA1/2 alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	FGFR2 fusions and select rearrangements	Pemazyre™ (Pemigatinib)
Prostate Cancer	HRR alterations	Lynparza® (Olaparib)

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

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**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.

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

**BIOMARKER FINDINGS**

**Microsatellite status** - MS-Stable

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

**GENOMIC FINDINGS**

**BRCA2** - loss

10 Trials *see p. 8*

**ACTIONABILITY**

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

**THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)**

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

Olaparib	1
Rucaparib	2A

Niraparib
Talazoparib

NCCN category

**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 ..... p. 4    **TP53** - R283C ..... p. 5

**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.

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BIOMARKER FINDINGS

BIOMARKER

# Microsatellite status

RESULT  
MS-Stable

**POTENTIAL TREATMENT STRATEGIES**

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>.

**FREQUENCY & PROGNOSIS**

MSI has been reported in 3.1-14.6% of prostate cancer samples<sup>6-10</sup>. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases<sup>11-13</sup>. For patients with advanced prostate cancer, dMMR/MSI status was associated with shorter median OS compared with patients with proficient MMR (3.8 vs. 7.0 years) by univariate and multivariate analysis (adjusted HR=4.09; P=0.005)<sup>14</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>15</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>15-17</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>18-20</sup>. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins<sup>15,17,19-20</sup>.

BIOMARKER

# Tumor Mutational Burden

RESULT  
1 Muts/Mb

**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-L1<sup>21-23</sup> and anti-PD-1 therapies<sup>21-24</sup>. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors<sup>21-24</sup>. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors<sup>21</sup>. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥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>25</sup> or those with lower TMB treated with PD-1 or PD-L1-targeting agents<sup>22</sup>. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in patients with TMB ≥10 Muts/Mb 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 012 trials<sup>24</sup>. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

**FREQUENCY & PROGNOSIS**

Prostate acinar adenocarcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 3.4% of cases have high TMB (>20 muts/Mb)<sup>26</sup>. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors<sup>27-28</sup>, with approximately 0.5-1.5 (muts/Mb) in localized tumor samples<sup>29-31</sup>, and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples<sup>32-34</sup>. One study reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 muts/Mb), which was due to defects in mismatch repair genes

MLH1 and MSH2 in 3 of the 4 cases<sup>34</sup>. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2020).

**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>35-36</sup> and cigarette smoke in lung cancer<sup>37-38</sup>, treatment with temozolomide-based chemotherapy in glioma<sup>39-40</sup>, mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes<sup>41-45</sup>, and microsatellite instability (MSI)<sup>41,44-45</sup>. 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 types<sup>22-23</sup>.

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ORDERED TEST #

GENOMIC FINDINGS

GENE  
**BRCA2**

ALTERATION  
loss

**POTENTIAL TREATMENT STRATEGIES**

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors<sup>46-63</sup> or to ATR inhibitors<sup>64-65</sup>. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations<sup>47,52,55,62-63</sup> and for patients with platinum-resistant or -refractory disease<sup>46,51,58,61</sup>. In a case study, a patient with therapy-induced neuroendocrine prostate cancer and an inactivating BRCA2 rearrangement experienced a CR ongoing for 20 months to the ATR inhibitor berzosertib<sup>65</sup>. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)<sup>66</sup>, ovarian carcinoma<sup>67</sup>, and triple-negative breast cancer (TNBC)<sup>68</sup> showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA2-deficient cells to ATR inhibitors. The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (CRPC) who had progressed on a new hormonal agent reported improved radiographic PFS with olaparib compared with physician's choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations (7.4 vs. 3.6 mo., HR=0.34)<sup>69</sup>.

Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as the platinum chemotherapies cisplatin and carboplatin<sup>70-72</sup>.

**FREQUENCY & PROGNOSIS**

BRCA2 genomic loss has been described in 1-2% of primary and 2-3% of metastatic prostate cancer cases<sup>31,34,73</sup>. BRCA2 mutations have been identified in 3-6% of primary and 6-7% of metastatic prostate cancer specimens<sup>31,34,73</sup>, with deleterious germline BRCA2 mutations present in 5% of men with metastatic prostate cancer<sup>74</sup>. 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<sup>75</sup>. 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<sup>76</sup>. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers<sup>76</sup>. 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<sup>77</sup>. For patients with metastatic castration-resistant prostate cancer (mCRPC), germline BRCA2 mutations were an independent marker of poor prognosis (CSS 17.4 vs. 33.2 months, HR=2.11) in a study<sup>78</sup>. Germline BRCA2 mutations in mCRPC were associated with relative benefit from first-line abiraterone or enzalutamide compared with taxanes (CSS 24.0 vs. 17.0 months, PFS on the

second systemic therapy 18.9 vs. 8.6 months) in a large prospective cohort study<sup>78</sup>. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy<sup>79-80</sup>.

**FINDING SUMMARY**

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage<sup>81</sup>. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis<sup>82</sup>. BRCA2 alterations that disrupt PALB2 binding (aa 21-39)<sup>83</sup>, the BRC 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<sup>81,84-99</sup>. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer<sup>100-101</sup>, 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<sup>102</sup>. 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%<sup>103</sup>. 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<sup>102,104-109</sup>. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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ORDERED TEST #

**GENOMIC FINDINGS**
**GENE**

# RAD21

**ALTERATION**

amplification - equivocal

**POTENTIAL TREATMENT STRATEGIES**

There are no therapies to target alterations in this gene.

**FREQUENCY & PROGNOSIS**

RAD21 amplifications, point mutations, and truncating mutations have been reported in various cancers<sup>110</sup>. In the context of breast cancer, increased RAD21 expression has been correlated with poor prognosis in multiple subtypes<sup>111-112</sup>, including sporadic Grade 3 but not Grade 1 cancers<sup>111</sup>, as well as hereditary BRCA2-mutant and hereditary BRCA-wild-type but not hereditary BRCA1-mutant cancers<sup>111</sup>. Furthermore, SNPs in or

near RAD21 have been linked with risk of breast cancer development<sup>113-114</sup>. RAD21 overexpression has also been correlated with poor prognosis in endometrial cancer<sup>115</sup> and in colorectal cancer (CRC), especially in KRAS-mutant CRC<sup>116</sup>. Heterogeneity of RAD21 expression also correlated with aggressive tumor behavior and shorter survival in endometrial cancer<sup>117</sup>. RAD21 amplification has been more frequently reported in hormone-refractory than in treatment-naïve prostate cancer, but RAD21 amplification did not correlate with expression<sup>118</sup>. In the context of ovarian cancer, both RAD21 overexpression and downregulation have been observed, but RAD21 expression was not prognostic<sup>119</sup>. Downregulation of RAD21 expression resulted in sensitization of cultured breast<sup>112,120</sup> and CRC<sup>116</sup> cells to chemotherapy, thereby suggesting that RAD21 overexpression confers resistance to chemotherapy.

**FINDING SUMMARY**

RAD21 encodes a protein involved in DNA double-strand break repair and sister chromatid cohesion as a part of the cohesin complex<sup>121-124</sup>. In preclinical studies, downregulation of RAD21 or other cohesin components leads to loss of expression from amplified genes, as well as amplifications themselves upon cell passaging<sup>125</sup>, but also leads to an increase in deletions, insertions, and other rearrangements<sup>126</sup>. High RAD21 expression has also been associated with increased genomic instability<sup>111</sup>. Cohesin complex also organizes chromatin domains and regulates gene expression<sup>127-128</sup>. Both overexpression and reduction of expression of RAD21 has been reported to alter gene expression<sup>129</sup>. RAD21 amplification has been correlated with increased expression in breast<sup>111-112,130</sup> and endometrial<sup>115</sup> cancers. Other RAD21 alterations, including truncating and point mutations, have been reported in the context of cancer, but the majority have not been characterized.

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**GENOMIC FINDINGS**
**GENE**
**TP53**
**ALTERATION**

R283C

**TRANSCRIPT NUMBER**

NM\_000546

**CODING SEQUENCE EFFECT**

847C&gt;T

**POTENTIAL TREATMENT STRATEGIES**

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>131-134</sup>, or p53 gene therapy and immunotherapeutics such as SGT-53<sup>135-139</sup> and ALT-801<sup>140</sup>. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type<sup>141</sup>. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in 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 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer<sup>143</sup>. The combination of adavosertib with paclitaxel and carboplatin in 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 24.0% (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 71.4% (5/7) response rate for patients with TP53 alterations<sup>146</sup>. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (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>139</sup>. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model<sup>147</sup>. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246<sup>148-150</sup>. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR<sup>151</sup>. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies<sup>152-153</sup>; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies<sup>154-155</sup>. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to

ATR inhibition.

**FREQUENCY & PROGNOSIS**

TP53 mutations have been reported in 18-40% of prostate cancers<sup>156-157</sup>. Overexpression of p53, which is indicative of TP53 dysregulation, has been reported to be significantly more common in late-stage and hormone-refractory prostate cancers and has been found to be associated with prostate-specific antigen (PSA) recurrence in low- and intermediate-grade prostate cancer<sup>158</sup>. TP53 loss has been found to be associated with prostate cancer-specific mortality in univariate analysis<sup>159</sup>.

**FINDING SUMMARY**

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers<sup>160</sup>. Any alteration that results in the disruption or partial or complete loss of the region encoding the TP53 DNA-binding domain (DBD, aa 100-292) or the tetramerization domain (aa 325-356), such as observed here, is thought to dysregulate the transactivation of p53-dependent genes and is predicted to promote tumorigenesis<sup>161-163</sup>. 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.

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**THERAPIES WITH CLINICAL BENEFIT**    **IN PATIENT'S TUMOR TYPE**

## Olaparib

Assay findings association

**BRCA2**  
loss

### 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 extensive clinical evidence in ovarian cancer<sup>56-60</sup> as well as strong clinical evidence in multiple other cancer types<sup>46-48,56,59,63,171</sup>, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

### SUPPORTING DATA

The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (mCRPC) reported improved radiographic PFS with olaparib compared with physician's choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations (7.4 vs. 3.6 months, HR=0.34) as well as for the overall study population of patients with homologous recombination repair (HRR) gene alterations (5.8 vs. 3.5 months, HR=0.49)<sup>172</sup>. PROfound patients with BRCA1/2 or ATM alterations also had improved OS (18.5 vs. 15.1 months, HR=0.64), and ORR (33.3% [28/84] vs. 2.3% [1/43], p<0.001) with olaparib compared with physician's choice of enzalutamide or abiraterone/prednisone<sup>172</sup>. A

Phase 2 trial of olaparib for patients with germline BRCA1/2 mutation reported 50% (4/8) PRs and 25% (2/8) SDs for patients with previously treated prostate cancer<sup>46</sup>. In the Phase 2 TOPARP-A study, 32.7% (16/49) of patients with metastatic castration-resistant prostate cancer (mCRPC), including 87.5% (14/16) of patients with a mutation in 1 or more genes affecting homologous recombination, benefited (PR, SD, and/or decline in prostate-specific antigen [PSA] levels) from olaparib treatment<sup>47</sup>. Other Phase 2 studies of recurrent or metastatic prostate cancer have observed increased clinical benefit from olaparib for patients with BRCA1/2 alterations compared with patients with alterations in other homologous recombination repair (HRR) genes<sup>173-174</sup>. The Phase 2 TOPARP-B study for patients with mCRPC reported a 52.4% (11/21) ORR and 8.3-month median PFS for patients with BRCA1/2 alterations, with numerically lower ORR and PFS reported in patients with alterations in ATM (8.3% [1/12], 5.8 months) or PALB2 (33.3% [2/6], 5.3 months)<sup>174</sup>. A Phase 2 trial of olaparib combined with abiraterone for genomically unselected patients with mCRPC reported improved median radiographic PFS (rPFS) with the combination, compared with abiraterone with placebo (13.8 vs. 8.2 months, HR=0.65)<sup>175</sup>. A Phase 1/2 trial combining olaparib with durvalumab for patients with previously treated mCRPC reported a PSA decrease of 50% or greater (PSA50) for 52.9% (9/17) of patients; 66.7% (6/9) of responders had biallelic BRCA2 alterations<sup>176</sup>. A Phase 1 trial of combination pembrolizumab and the PARP inhibitor olaparib for docetaxel-pretreated patients with mCRPC observed an ORR of 8.3% (2/24 PRs), PSA50 of 8.5% (7/82), median rPFS of 4.3 months, and median OS (mOS) of 14.4 months; homologous recombination deficiency was not detected in any patients<sup>177-178</sup>.

## Rucaparib

Assay findings association

**BRCA2**  
loss

### AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer 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 strong clinical evidence in ovarian

cancer<sup>52-53,142</sup>, as well as clinical data in other cancer types<sup>53,179-180</sup>, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

### SUPPORTING DATA

The Phase 2 TRITON2 study of rucaparib for patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious DNA repair gene alterations reported an ORR of 30.5%, including an ORR of 43.9% (25/57, 3 CRs) for patients with BRCA1/2 mutation<sup>181</sup>. Objective responses were reported for patients with ATM, BRIP1, CHEK2, FANCA, PALB2, and RAD51B alterations<sup>181-182</sup>.

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ORDERED TEST #

THERAPIES WITH CLINICAL BENEFIT

IN OTHER TUMOR TYPE

## Niraparib

Assay findings association

**BRCA2**  
loss

### 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 and breast cancers<sup>50-51,183</sup>, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

### SUPPORTING DATA

The Phase 2 study of niraparib for patients with

metastatic castration-resistant prostate cancer (mCRPC) who had progressed on at least 1 line of AR-targeted therapy in addition to at least 1 line of taxane chemotherapy reported a median radiographic PFS (rPFS) of 8.2 months and median OS of 12.6 months for patients with biallelic BRCA alterations, with a 63% (29/46) composite response rate<sup>184</sup>. Patients in this trial with biallelic alterations in non-BRCA1/2 DNA repair genes experienced a 17% (6/35) CRR with a median rPFS of 5.3 months and median OS of 14.0 months<sup>184</sup>. In a Phase 1 study of niraparib for patients with solid tumors, 57% (12/21) of patients with locally advanced or mCRPC achieved SD, and 8 patients exhibited a 30% or greater decrease in circulating tumor cells<sup>51</sup>.

## Talazoparib

Assay findings association

**BRCA2**  
loss

### 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 strong clinical data in breast cancer<sup>185-187</sup> and additional clinical evidence in ovarian, pancreatic, and prostate cancer<sup>188-190</sup>, loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

### SUPPORTING DATA

A study of talazoparib monotherapy reported 2 PRs in patients with BRCA-mutant prostate cancer patients<sup>188</sup>. A case series in metastatic castration-resistant prostate cancer reported a decrease in the prostate-specific antigen (PSA) levels in one patient with a BRCA2 mutation after

talazoparib treatment<sup>190</sup>. 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>186-187</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>191</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>188-190,192</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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ORDERED TEST #

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

**GENE**  
**BRCA2**

**RATIONALE**  
BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors or to ATR

inhibitors.

**ALTERATION**  
loss

**NCT03395197**

**PHASE 3**

Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC (TALAPRO-2)

**TARGETS**  
PARP

**LOCATIONS:** Pennsylvania, Ohio

**NCT03748641**

**PHASE 3**

A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Participants With Metastatic Prostate Cancer

**TARGETS**  
CYP17, PARP

**LOCATIONS:** Pennsylvania, Ohio, Virginia, Michigan, Maryland, Hamilton (Canada), Toronto (Canada), Indiana

**NCT03834519**

**PHASE 3**

Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Metastatic Castration-resistant Prostate Cancer (mCRPC) (MK-7339-010/KEYLYNK-010)

**TARGETS**  
PD-1, CYP17, PARP, AR

**LOCATIONS:** Ohio, Michigan, Virginia, Hamilton (Canada), Maryland, Toronto (Canada), North Carolina

**NCT03517969**

**PHASE 2**

ATR Kinase Inhibitor VX-970 and Carboplatin With or Without Docetaxel in Treating Participants With Metastatic Castration-Resistant Prostate Cancer

**TARGETS**  
ATR

**LOCATIONS:** Pennsylvania, Ohio, Virginia, New Jersey, Connecticut

**NCT03317392**

**PHASE 1/2**

Olaparib and Radium Ra 223 Dichloride in Treating Men With Metastatic Castration-Resistant Prostate Cancer That Has Spread to the Bone

**TARGETS**  
PARP

**LOCATIONS:** Pennsylvania, Ohio, Michigan, New Jersey, Connecticut, Kansas, California

**NCT01827384**

**PHASE 2**

Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors

**TARGETS**  
PARP, mTOR, MEK, WEE1

**LOCATIONS:** Pennsylvania, Maryland, Kentucky, New Jersey, Texas, Colorado

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ORDERED TEST #

CLINICAL TRIALS

**NCT02975934**

PHASE 3

A Study of Rucaparib Verses Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency

**TARGETS**  
CYP17, PARP, AR

**LOCATIONS:** Ohio, London (Canada), Michigan, Maryland, Toronto (Canada), New York

**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:** Ohio, Virginia, Kentucky, New York, Georgia, Montreal (Canada), Florida, Texas, Utah

**NCT02854436**

PHASE 2

An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies

**TARGETS**  
PARP

**LOCATIONS:** Virginia, Michigan, Pennsylvania, Toronto (Canada), Kentucky, North Carolina, New York, Illinois

**NCT03810105**

PHASE 2

A Study of Olaparib and Durvalumab in Prostate Cancer

**TARGETS**  
PARP, PD-L1

**LOCATIONS:** Michigan, New Jersey, Illinois, New York, California

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**APPENDIX**

Information Provided as a Professional Service

ORDERED TEST #

**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.

**CASP8**  
M108V

**KEAP1**  
N49S

**MET**  
V136I

**NBN**  
amplification

**PARK2**  
P437L

**RAC1**  
amplification

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Electronically signed by Daniel Duncan, M.D. | 10 June 2020  
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ORDERED TEST # ORD-0820091-01

**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) 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 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**

INDICATION	BIOMARKER	THERAPY
Non-small cell lung cancer (NSCLC)	<i>EGFR</i> exon 19 deletions and <i>EGFR</i> exon 21 L858R alterations	Gilotrif® (Afatinib), Iressa® (Gefitinib), Tagrisso® (Osimertinib), or Tarceva® (Erlotinib)
	<i>EGFR</i> exon 20 T790M alterations	Tagrisso® (Osimertinib)
	<i>ALK</i> rearrangements	Alecensa® (Alectinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	<i>BRAF</i> V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
Melanoma	<i>MET</i> single nucleotide variants (SNVs) and indels that lead to <i>MET</i> exon 14 skipping	Tabrecta™ (Capmatinib)
	<i>BRAF</i> V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
Breast cancer	<i>BRAF</i> V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib), in combination with Zelboraf® (Vemurafenib)
	<i>ERBB2</i> (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
Colorectal cancer	<i>PIK3CA</i> C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
	<i>KRAS</i> wild-type (absence of mutations in codons 12 and 13)	Erbix® (Cetuximab)
Ovarian cancer	<i>KRAS</i> wild-type (absence of mutations in exons 2, 3, and 4) and <i>NRAS</i> wild type (absence of mutations in exons 2, 3, and 4)	Vectibix® (Panitumumab)
	<i>BRCA1/2</i> alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	<i>FGFR2</i> fusions and select rearrangements	Pemazyre™ (Pemigatinib)
Prostate Cancer	<i>HRR</i> alterations	Lynparza® (Olaparib)

The median exon coverage for this sample is 729x

ORDERED TEST # ORD-0820091-01

## TEST PRINCIPLE

FoundationOne®CDx (F1CDx) is performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The assay employs 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 (refer to Table 2 and Table 3 for complete list of genes included in F1CDx). In total, the assay detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid capture-selected libraries are sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data is then processed using a customized analysis pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous gene deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) are reported.

## PERFORMANCE CHARACTERISTICS

Please refer to product label:  
[foundationmedicine.com/f1cdx](http://foundationmedicine.com/f1cdx)

## LIMITATIONS

- For *in vitro* diagnostic use.
- For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
- A negative result does not rule out the presence of a mutation below the limits of detection of the assay.
- Samples with <25% tumor may have decreased sensitivity for the detection of CNAs including *ERBB2*.
- Clinical performance of Tagrisso® (osimertinib) in patients with an *EGFR* exon 20 T790M mutation detected with an allele fraction <5% is ongoing and has not been established.
- Concordance with other validated methods for CNA (with the exception of *ERBB2*) and gene rearrangement (with the exception of *ALK*) detection has not been demonstrated and will be provided in the post-market setting. Confirmatory testing using a clinically validated assay should be performed for all CNAs and rearrangements not associated with CDx claims noted in Table 1 of the Intended Use, but used for clinical decision making.
- The MSI-H/MSS designation by FMI FoundationOne®CDx (F1CDx) test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. Refer [https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/P170019B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf) for additional details on methodology. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. Patients with microsatellite status of "Cannot Be Determined" should be retested with an orthogonal (alternative) method. The clinical validity of the qualitative MSI designation has not been established.
- TMB by F1CDx is defined based by counting the total number of all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and reported as mutations per megabase (mut/Mb) unit. TMB is a function of the characteristics of a patient's specimen and testing parameters; therefore, TMB may differ among specimens (e.g., primary vs. metastatic, tumor content) and targeted panels. 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 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 not been established.
- 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.
- The test is intended to be performed on specific serial number-controlled instruments by Foundation Medicine, Inc.
- Alterations in polyT homopolymer runs may not be reliably detected in *BRCA1/2*.
- Certain large rearrangements in *BRCA1/2* including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements

ORDERED TEST # ORD-0820091-01

APPENDIX

About FoundationOne®CDx

including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with BRCA1/2 mutations by F1CDx.

13. Certain potentially deleterious missense or small in-frame deletions in BRCA1/2 may not be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.
14. Alterations at allele frequencies below the established limit of detection may not be detected consistently.
15. Detection of LOH has been verified only for ovarian cancer patients.
16. Performance of the LOH classification has not been established for samples below 35% tumor content and with LOH scores near the cutoff of 16.
17. 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.

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APPENDIX

Genes assayed in FoundationOne®CDx

ORDERED TEST # ORD-0820091-01

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)	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	C11orf30 (EMSY)	C17orf39 (GID4)	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	EP300	EPHA3	EPHB1
EPHB4	ERBB2	ERBB3	ERBB4	ERCC4	ERG	ERRF1	ESR1	EZH2
FAM46C	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	GNA11	GNA13	GNAQ	GNAS	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	HRAS	HSD3B1	ID3	IDH1	IDH2	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	JAK2	JAK3
JUN	KDMSA	KDMS5C	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	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	NSD3 (WHSC1L1)	NT5C2	NTRK1	NTRK2	NTRK3	P2RY8	PALB2
PARK2	PARP1	PARP2	PARP3	PAX5	PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA
PDGFRB	PDK1	PIK3C2B	PIK3C2G	PIK3CA	PIK3CB	PIK3R1	PIM1	PMS2
POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKARIA	PRKCI	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	SOCS1
SOX2	SOX9	SPEEN	SPOP	SRC	STAG2	STAT3	STK11	SUFU
SYK	TBX3	TEK	TET2	TGFBR2	TIPARP	TNFAIP3	TNFRSF14	TP53
TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	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	RSPO2	SDC4	SLC34A2	TERC*	TERT**	TMPPSS2

\*TERC is an NCRNA

\*\*Promoter region of TERT is interrogated

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

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

**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.

**PROFESSIONAL SERVICES FINDINGS**

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. 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.

**RANKING OF ALTERATIONS AND THERAPIES**

*Biomarker and Genomic Findings*

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

*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). 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. 2020. All rights reserved. To view the most recent and complete version of the guideline, go online to 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.

**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**

Foundation Medicine makes no promises or guarantees that a particular drug will be effective in the treatment of disease of 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 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 with the 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.

**LOSS OF HETEROZYGOSITY SCORE**

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. 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.

**MICROSATELLITE STATUS**

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

**TUMOR MUTATIONAL BURDEN**

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne CDx test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne CDx samples and is reported in Professional Services as the number of mutations per megabase (Muts/Mb) rounded to the nearest integer. Tumor Mutational Burden is reported as “Cannot Be Determined” if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

*Genomic Findings with Evidence of Clinical Significance*

Genomic findings listed at Level 2 are associated with clinical significance. Clinical significance may be indicated by evidence of therapeutic sensitivity or resistance and/or diagnostic, prognostic or other clinically relevant implications. Included in this category will be findings associated with clinical validity as supported by professional guidelines and/or peer-reviewed publications.

*Genomic Findings with Potential Clinical Significance*

Genomic findings listed at Level 3 are cancer-related mutations and biomarkers with potential clinical significance. These include findings in genes known to be associated with cancer and are supported by evidence from publicly available databases, and/or peer-reviewed publications.

*A Fluid Approach to Reporting Levels*

As additional information becomes available, as recognized by the clinical community (professional guidelines and/or peer-reviewed publications), findings may move between Levels 2 and 3 in accordance with the above descriptions.

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**SELECT ABBREVIATIONS**

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

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**APPENDIX**
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