FoundationOne®CDx 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 mutation 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, FoundationOne®CDx 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. See professional services section for additional information.

Microsatellite status  MS-Stable
Tumor Mutational Burden  4 Muts/Mb

$ Refer to appendix for limitation statements related to detection of any copy number alterations, gene rearrangements, 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).

### 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>ALK rearrangements</td>
<td>Alectinib (Alectinib), Alunbrig® (Brigatinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)</td>
</tr>
<tr>
<td></td>
<td>BRAF V600E</td>
<td>Tabrecta® (Larotrectinib)</td>
</tr>
<tr>
<td></td>
<td>MET single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping</td>
<td>Tagrisso® (Gefitinib), Vemurafenib (Vemurafenib), Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)</td>
</tr>
<tr>
<td>Maligina</td>
<td>BRAF V600E and V600K</td>
<td>Tabrecta® (Larotrectinib)</td>
</tr>
<tr>
<td></td>
<td>BRAF V600E and V600K</td>
<td>Mekinist® (Trametinib) or Cobimetinib (Cetuximab) in combination with Zelboraf® (Vemurafenib)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>EBER (HER2) amplification</td>
<td>Herceptin® (Trastuzumab), Radasvyl® (Ado-trastuzumab emtansine), or Perjeta® (Perifosine)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>KRAS wild-type (absence of mutations in codons 12 and 13)</td>
<td>Panitumumab (Panitumumab)</td>
</tr>
<tr>
<td></td>
<td>KRAS wild-type (absence of mutations in exons 2, 3, and 4)</td>
<td>Erbitux® (Cetuximab), Vectibix® (Panitumumab)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>BRCA1/2 alterations</td>
<td>Lynparza® (Olaparib) or Rucaparib® (Rucaparib)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>FGFR2 fusions and select rearrangements</td>
<td>Piparib® (Pemigatinib) or Truxafib® (Infigratinib)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Humoral Recombination Repair (HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDX2, CHEK1, CHEK2, FANCD2, PALB2, RAD51B, RAD51D, RAD51C, RAD51D and RAD51C) alterations</td>
<td>Lynparza® (Olaparib)</td>
</tr>
<tr>
<td>Solid Tumors</td>
<td>TMB &lt; 5 mutations per megabase</td>
<td>Keytruda® (Pembrolizumab)</td>
</tr>
<tr>
<td></td>
<td>NTRK1/2/3 fusions</td>
<td>Lactotrabectedin (Larotrectinib)</td>
</tr>
</tbody>
</table>

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**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/1cdx](http://www.foundationmedicine.com/1cdx)
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.

PATIENT

DISEASE: Prostate acinar adenocarcinoma

ORDERING PHYSICIAN

NAME

DATE OF BIRTH

SEX

MEDICAL RECORD #

PHYSICIAN

ADDITIONAL RECIPIENT

MEDICAL FACILITY ID

PATHOLOGIST

SPECIMEN

SPECIMEN SITE

SPECIMEN ID

SPECIMEN TYPE

DATE OF COLLECTION

SPECIMEN RECEIVED

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.

BRCA1 Q563*

TMEM128A TPM2A-ERG fusion

13 Disease relevant genes with no reportable alterations: ATM, BARD1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L

† See About the Test in appendix for details.

Report Highlights

- Variants with diagnostic implications that may indicate a specific cancer type: TMEM128A TPM2A-ERG fusion (p. 5)

- Targeted therapies with NCCN categories of evidence in this tumor type: Olaparib (p. 6), Rucaparib (p. 7)

- Variants that may inform nontargeted treatment approaches (e.g., chemotherapy) in this tumor type: BRCA1 Q563* (p. 4)

- Evidence-matched clinical trial options based on this patient’s genomic findings: (p. 9)

- Variants in select cancer susceptibility genes to consider for possible follow-up germline testing in the appropriate clinical context: BRCA1 Q563* (p. 4)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 4 Muts/Mb

GENOMIC FINDINGS

BRCA1 - Q563*

10 Trials see p. 9

TMEM128A TPM2A-ERG fusion

10 Trials see p. 11

No therapies or clinical trials. see Biomarker Findings section

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.

BRCA1 - Q563* .......................................................... p. 4

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.

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

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

Olaparib 1

Rucaparib 2A

Niraparib

Talazoparib

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

BRCA1 - Q563* .......................................................... p. 4

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.
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.
Microsatellite status

RESULT
MS-Stable

FREQUENCY & PROGNOSIS
MSI has been reported in 3.1-14.6% of prostate cancer samples. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases. For patients with advanced prostate cancer, dMMR/MSI status was associated with shorter median OS compared with patients with proficient MMR (3.8 vs. 70 years) by univariate and multivariate analysis (adjusted HR=4.09; P=0.005). 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, including approved therapies nivolumab and pembrolizumab. 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).

Potential treatment strategies

— Targeted Therapies —

On the basis of current clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors, including approved therapies nivolumab and pembrolizumab. 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). 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, including approved therapies nivolumab and pembrolizumab. 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).

Tumor Mutational Burden

RESULT
4 Muts/Mb

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). Prostate cancer has been reported to harbor a relatively low TMB among solid tumors, with approximately 0.5-1.5 Muts/Mb in localized tumor samples, and a higher but still low TMB of 2-5 Muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples. One study reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 Muts/Mb), which is less than the number of cases.

Potential treatment strategies

— Targeted Therapies —

On the basis of current clinical evidence, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1 and ipilimumab. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors. The Phase 2 CheckMate 650 trial of nivolumab and ipilimumab treatment for patients with metastatic castration-resistant prostate cancer (mCRPC) samples reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 Muts/Mb), which is less than the number of cases.

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins. Findings summary

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins.

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). 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.
SAMPLE ORDERED TEST #
berzosertib plus carboplatin
germline BRCA1 mutation experienced a PR from berzosertib combined with topotecan
experienced prolonged SD from the ATR inhibitor
other Phase 1 trials of combination approaches, a carcinoma experienced a PR or prolonged SD
alterations and platinum-refractory ovarian
BA Y1895344, 2 patients with deleterious BRCA1/2
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Electronically signed by J. Keith Killian, M.D. |
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G E N E  B R C A 1
A L T E R A T I O N  Q563*
T R A N S C R I P T I D  NM_007294
C O D I N G S E Q U E N C E E F F E C T  1687C>T
V A R I A N T A L E N E F R E Q U E N C Y ( % V A F )  47.9%

P O T E N T I A L T R E A T M E N T S T R A T E G I E S —  T a r g e t e d  T h e r a p i e s —
Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors55-70 or ATR inhibitors71,72. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations54,59,62,68-70, and for patients with platinum-resistant or -refractory disease63,65,68. 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)74. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD73. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan72, another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin75, and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib76. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)77, ovarian carcinoma78, and TNBC79 showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA1-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments80. In a Phase 1 monotherapy trial of adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression81.

P O T E N T I A L G E R M L I N E  I M P L I C A T I O N S —  N o n t a r g e t e d  A p p r o a c h e s —
Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinitedina82-91. Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, RAD51D, CHEK2, and CDK12 have been reported to be predictive for sensitivity to platinum agents in castration resistant prostate cancer (CRPC) (NCCN Prostate Cancer Guidelines v.2.2021)92-95.

F R E Q U E N C Y  &  P R O G N O S I S
BRCA1 mutation has been reported in 1.1% of patients with BRCA1-mutated triple-negative breast cancer (TNBC), 1 of 1,057 patients with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib76. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)77, ovarian carcinoma78, and TNBC79 showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA1-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments80. In a Phase 1 monotherapy trial of adavosertib that included 9 patients with BRCA1/2-mutated solid tumors, 2 patients with BRCA1-mutated cancers (1 with ovarian serous carcinoma and 1 with oral squamous cell carcinoma) achieved PRs, and a third patient with ovarian serous carcinoma harboring mutations in BRCA1 and TP53 experienced 14% tumor shrinkage prior to disease progression81.

Additional relevant data include:
- Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinitedina82-91. Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, RAD51D, CHEK2, and CDK12 have been reported to be predictive for sensitivity to platinum agents in castration resistant prostate cancer (CRPC) (NCCN Prostate Cancer Guidelines v.2.2021)92-95.

FINDING SUMMARY
The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation90,98. Alterations such as seen here may disrupt BRCA1 function or expression90-91.

POTENTIAL GERMLINE IMPLICATIONS
One or more of the BRCA1 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2021)72. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer93,94, and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively95. 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%96. 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 population95,97-99. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 - CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 - CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 - CLIA: 22D2027531