FOUNDATIONONE®CDx

PATIENT

TUMOR TYPE
Prostate acinar adenocarcinoma

REPORT DATE

ORDERED TEST #

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	FDA-APPROVED THERAPEUTIC OPTIONS
BRCA1 Q563*	Lynparza® (Olaparib)

OTHER ALTERATIONS & BIOMARKERS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for additional information.

Microsatellite status MS-Stable §

Tumor Mutational Burden 4 Muts/Mb §

TMPRSS2 TMPRSS2(NM_005656)-ERG(NM_004449) fusion (T1; E5) §

§ 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).

FoundationOne®CDx (F1CDx) is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

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

The F1CDx assay is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

TABLE 1: COMPANION DIAGNOSTIC INDICATIONS

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), Alunbrig® (Brigatinib), Xalkori® (Crizotinib), or Zykadia® (Ceritinib)
	BRAF V600E	Tafinlar® (Dabrafenib) in combination with Mekinist® (Trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	Tabrecta® (Capmatinib)
Melanoma	*BRAF* V600E	Tafinlar® (Dabrafenib) or Zelboraf® (Vemurafenib)
	BRAF V600E and V600K	Mekinist® (Trametinib) or Cotellic® (Cobimetinib) in combination with Zelboraf® (Vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	Herceptin® (Trastuzumab), Kadcyla® (Ado-trastuzumab emtansine), or Perjeta® (Pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	Piqray® (Alpelisib)
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	Erbitux® (Cetuximab)
	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)
Ovarian cancer	*BRCA1/2* alterations	Lynparza® (Olaparib) or Rubraca® (Rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre® (Pemigatinib) or Truseltiq™ (Infigratinib)
Prostate cancer	Homologous Recombination Repair (*HRR*) gene (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*) alterations	Lynparza® (Olaparib)
Solid Tumors	*TMB* ≥ 10 mutations per megabase	Keytruda® (Pembrolizumab)
	NTRK1/2/3 fusions	Vitrakvi® (Larotrectinib)

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

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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	PHYSICIAN	SPECIMEN
DISEASE Prostate acinar adenocarcinoma	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH	ADDITIONAL RECIPIENT	SPECIMEN TYPE
SEX	MEDICAL FACILITY ID	DATE OF COLLECTION
MEDICAL RECORD #	PATHOLOGIST	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*
TMPRSS2 TMPRSS2-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: ***TMPRSS2*** **TMPRSS2-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	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 4 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA1 **-** Q563*	Olaparib [1]	Niraparib
10 Trials *see p. 9*	Rucaparib [2A]	Talazoparib
TMPRSS2 **-** TMPRSS2-ERG fusion	none	none
10 Trials *see p. 11*		

[ ] *NCCN category*

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

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

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.

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NOTE Genomic alterations detected may be associated with activity of certain FDA-approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type.

Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI has been reported in 3.1-14.6% of prostate cancer samples[6-10]. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases[11-13]. 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)[14].

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[15]. 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[15-17]. 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[18-20]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15,17,19-20].

BIOMARKER

Tumor Mutational Burden

RESULT
4 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[21-23], anti-PD-1 therapies[21-24], and combination nivolumab and ipilimumab[25-30]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[21-24,31]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[21]. 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[32] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[24,31]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. The Phase 2 CheckMate 650 trial of nivolumab and ipilimumab treatment for patients with metastatic castration-resistant prostate cancer reported that patients harboring above the median study TMB experienced increased ORR and PSA responses[30].

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)[33]. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors[34-35], with approximately 0.5-1.5 (muts/Mb) in localized tumor samples[36-38], and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples[39-41]. 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[41]. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2021).

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[42-43] and cigarette smoke in lung cancer[44-45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[48-52], and microsatellite instability (MSI)[48,51-52]. 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[22-23,31].

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GENE
BRCA1

ALTERATION
Q563*

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
1687C>T

VARIANT ALLELE FREQUENCY (% VAF)
47.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[53-70] or ATR inhibitors[71-73]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[54,59,62,69-70] and for patients with platinum-resistant or -refractory disease[53,58,65,68]. 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 SD[71]. 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 topotecan[72]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[75]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[76]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[77], ovarian carcinoma[78], and TNBC[79] 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 BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[80]. 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 progression[81].

— Nontargeted Approaches —

Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[82-91]. 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 v2.2021)[92-95].

FREQUENCY & PROGNOSIS

BRCA1 mutation has been reported in 1.1% of prostate adenocarcinomas (cBioPortal, Jan 2021)[96-97]. Although germline BRCA2 mutations have been identified as an independent marker of poor prognosis, the link between germline BRCA1 mutation status and prognosis in prostate cancer is not as definitive (NCCN Prostate Cancer Guidelines v2.2021)[98-104]. In some studies, germline BRCA1 mutations were associated with poor prognosis and reduced survival times[99,101], whereas other studies did not find a statistically significant association[98,105-107].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[108]. Alterations such as seen here may disrupt BRCA1 function or expression[109-111].

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)[112]. 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 cancer[113-114], 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%, respectively[115]. 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%[116]. 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[115,117-122]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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