

Guide to FoundationOne® CDx and FoundationOne® Liquid CDx Reports

Professional Services Summary Page

As the first page of the report (page 1), the Professional Services summary page provides information for all of the reported biomarker and genomic findings upfront. It serves as the overview for clinicians to help ensure no findings are missed. This section is not reviewed or approved by the FDA.

 FOUNDATIONONE® LIQUID CDx

PATIENT
 TUMOR TYPE
 PROSTATE CANCER (NOS)
 COUNTRY CODE
 REPORT DATE
 ORDERED TEST #

ABOUT THE TEST FoundationOne® Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA. 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 cancer (NOS) NAME Not given DATE OF BIRTH Not given SEX Not given MEDICAL RECORD # Not given	PHYSICIAN ORDERING PHYSICIAN Not given MEDICAL FACILITY Not given ADDITIONAL RECIPIENT Not given MEDICAL FACILITY ID Not given PATHOLOGIST Not given	SPECIMEN SPECIMEN ID Not given SPECIMEN TYPE Not given DATE OF COLLECTION Not given SPECIMEN RECEIVED Not given SAMPLE COVERAGE Not given
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Biomarker Findings

Blood Tumor Mutational Burden - 10 Muts/Mb

Microsatellite status - MSI-High Not Detected

Tumor Fraction - Cannot Be Determined

Genomic Findings

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

BRCA2 L1908fs*2

CHEK2 L481*

PIK3CA H1047R

1 Report Highlights

- There are positive **Companion Diagnostic Findings** identified for this patient. See the [FDA Approved section](#).
- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 6), **Rucaparib** (p. 6)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: **BRCA2** L1908fs*2 (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: **BRCA2** L1908fs*2 (p. 3)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: **CHEK2** L481* (p. 4)

BIOMARKER FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)	
Blood Tumor Mutational Burden - 10 Muts/Mb 10 Trials see p. 9	None	None	
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).		
Tumor Fraction - Cannot Be Determined	Tumor fraction is an estimate of the percentage of circulating-tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample based on observed aneuploid instability.		
GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
BRCA2 = L1908fs*2	47.8%	Olaparib Rucaparib	Niraparib Talazoparib
10 Trials see p. 11			1 2A 3 NCCN Category

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.
Electronically signed by Erik Williams, M.D. | Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 2202027531 | Shakil Ramkissoon, M.D., Ph.D., M.M. Sc., Laboratory Director CLIA: 34D2044309 | Foundation Medicine, Inc. | 1-888-988-3639
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Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 2202027531 | Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 2202027531 | Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 2202027531
PROFESSIONAL SERVICES SUMMARY - PAGE 1 OF 2

1 Report Highlights

This feature distills important genomic insights in one easy-to-find place, helping you focus on the key actionable results to inform your patient's treatment plan.

Such key findings may include targeted therapies with **potential resistance, germline implications, non-targeted therapy implications and more** depending on each patient case.

2 Therapies with Clinical Benefit

Therapies for each associated genomic finding are listed in the therapy table. On the left are therapies within your patient's tumor type, and on the right are those with proven clinical benefit in other tumor types. Therapy resistance based on your patient's genomic profile will also be indicated.

3 National Comprehensive Cancer Network® (NCCN®) Categories of Evidence and Consensus¹

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

4 Clinical Trials

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

+ Pertinent Negatives

Identifies important negative results on FoundationOne CDx that can be used for patient management when applicable.

Pertinent negatives do not appear for FoundationOne Liquid CDx.

FDA-Approved Claims Page

Any FDA-approved claims for companion diagnostic (CDx) findings will appear on the FDA-approved claims page, which comes directly after the Professional Services Summary page(s).

1 Companion Diagnostic (CDx) Associated Findings

GENOMIC FINDINGS DETECTED	FDA-APPROVED THERAPEUTIC OPTIONS
BRCA2 L1908fs*2	LYNPARZA® (olaparib) RUBRACA® (rucaparib)

OTHER SHORT VARIANTS AND SELECT REARRANGEMENTS AND COPY NUMBER ALTERATIONS IDENTIFIED

Results reported in this section are not prescriptive or conclusive for labeled use of any specific therapeutic product. See *professional services* section for information on the alterations listed in this section as well as any additional detected copy number alterations, gene rearrangements, or biomarkers.

BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE IN TISSUE SUPPORTED BY ANALYTICAL VALIDATION USING cfDNA

CHEK2 L481*[#]

OTHER BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

PIK3CA H1047R

Variants in this gene may be derived from a nontumor source such as clonal hematopoiesis (CH). The efficacy of targeting such nontumor somatic alterations (e.g., CH) is unknown. Refer to the appendix for additional details.

Please refer to appendix for Explanation of Clinical Significance Classification and for variants of unknown significance (VUS)

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ABOUT THE TEST FoundationOne®Liquid CDx is a next generation sequencing (NGS) assay that identifies clinically relevant genomic alterations in circulating cell-free DNA.

Electronically signed by Richard Huang, M.D. |

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 - CLIA: 22D202753
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 - CLIA: 22D202753

Shakti Ramkissoon, M.D., Ph.D., M.M.Sc. Laboratory Director CIIA: 34D2044306

Post-Sequencing Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 • CLIA: 22D202753

FDA APPROVED CLAIMS - PAGE 1 Of 1

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

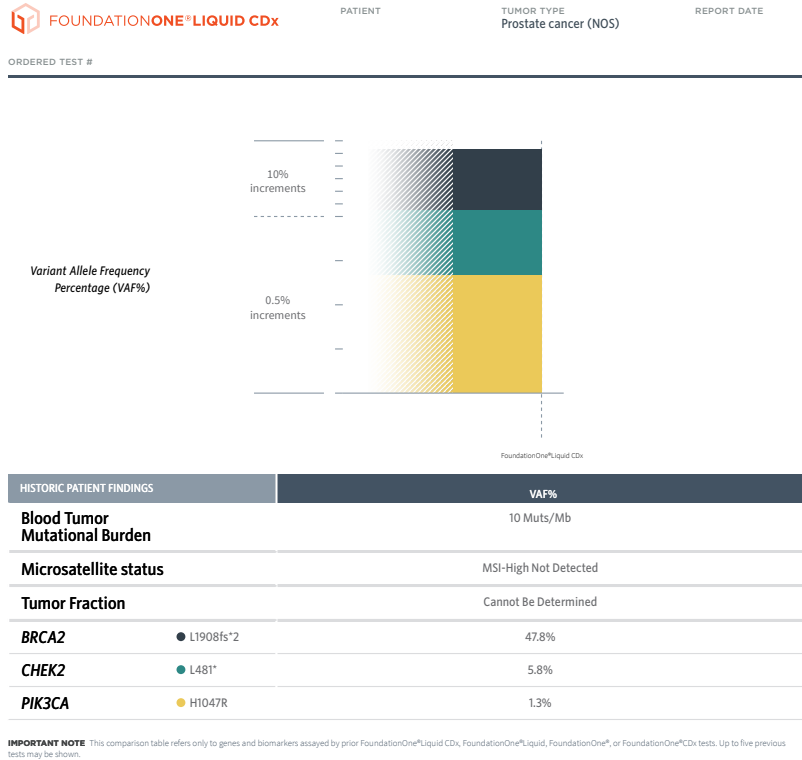
Sample report images last updated December 2021.

Professional Services Continued

Medical Case Consulting

You can find the remaining of the professional services section after the FDA-approved claims page.

1



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FOUNDATION ONE LIQUID CDX	PATIENT TUMOR TYPE Prostate Cancer (NOS)	REPORT DATE
ORDERED TEST #		
GENOMIC FINDINGS		
GENE BRCA2		
ALTERATION L19085*2		
TRANSCRIPT ID NM_000059		
CODING SEQUENCE EFFECT 5722_5723delCT		
POTENTIAL TREATMENT STRATEGIES		
Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors ⁸⁶⁻⁹³ or to ATR inhibitors ⁹⁴⁻⁹⁵ . Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations ^{92,94,95,99} and for patients with platinum-resistant or -refractory disease ^{86,91,98,99} . 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 ⁹⁵ . Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL), ovarian carcinoma ⁹⁷ , and triple-negative breast cancer (TNBC) ⁹⁸ 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) ⁹⁹ . Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lirinectatin, and the platinum chemotherapies cisplatin and carboplatin ¹⁰⁰⁻¹⁰² .		
FREQUENCY & PROGNOSIS		
BRCA2 mutations have been identified in 3-6% of primary and 6-7% of metastatic prostate cancer specimens ⁷⁶⁻⁷⁷ , with deleterious germline BRCA2 mutations present in 5% of men with metastatic prostate cancer ⁷⁴ . 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 ⁷⁷ . 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 ⁷⁸ . Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers ⁷⁵ . 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=2.47) than noncarriers ⁷⁵ . 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 1 study ⁷⁸). 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 38.9 vs. 8.6 months) in a large prospective cohort study ⁷⁸ . Three patients with non-neuroendocrine prostate cancer harboring BRCA2		
mutations derived clinical benefit from treatment with platinum-based chemotherapy ⁷⁹⁻⁸⁰ .		
FINDING SUMMARY		
The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage ⁸¹ . Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis ⁸² . Alterations such as seen here may disrupt BRCA2 function or expression ^{81,83-88} .		
POTENTIAL GERMLINE IMPLICATIONS		
One or more of the BRCA2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation ⁸⁹ (by an expert panel or multiple submitters with no conflicts) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2020) ⁸⁹ . 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 ⁹⁰⁻¹⁰¹ , and the lifetime risk of breast and ovarian cancer in BRCA2 mutation carriers has been estimated to be as high as >86% and 23%, respectively ¹⁰² . 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% ¹⁰³ . 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 ^{103,104-106} . In the appropriate clinical context, germline testing of BRCA2 is recommended.		

1 FoundationOne Liquid CDx Variant Allele Frequency Percentage (VAF%) Graph and Table

Shows the detected VAF% and where applicable in the patient's biomarkers and/or genomic signatures. Up to 5 previous tests may be shown. For FoundationOne CDx reports, VAF values are displayed in the Genomic Findings section of Professional Services, alongside other variant information.

2 Biomarker and Genomic Findings

Following the initial pages of the report, the professional services section goes into more detail about your patient's findings.

Continued →

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FOUNDATIONONE® LIQUID CDx	PATIENT	TUMOR TYPE	REPORT DATE
		Prostate cancer (NOS)	
ORDERED TEST #			CLINICAL TRIALS
GENE BRCA2 ALTERATION L1908fs*2	RATIONALE BRCA2 loss or inactivating alterations may predict sensitivity to PARP inhibitors or to ATR inhibitors.		
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: Connecticut, New York, Massachusetts, Delaware, Maryland			
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: Connecticut, New York, Massachusetts, New Jersey, Pennsylvania, Maryland, Kingston (Canada)			
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: New York, New Jersey, Montreal (Canada), Virginia, Ohio, Moncton (Canada), Kentucky, Georgia			
NCT03810105	PHASE 2		
A Study of Olaparib and Durvalumab in Prostate Cancer	TARGETS PARP, PD-L1		
LOCATIONS: New York, New Jersey, Michigan, Illinois, California			
NCT02595931	PHASE 1		
ATR Kinase Inhibitor VX-970 and Irinotecan Hydrochloride in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	TARGETS ATR		
LOCATIONS: Connecticut, Massachusetts, Pennsylvania, North Carolina, Tennessee, Missouri, Florida, California			
NCT03395197	PHASE 3		
Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC (TALAPRO-2)	TARGETS PARP		
LOCATIONS: New York, New Jersey, Pennsylvania, Sherbrooke (Canada), Montreal (Canada), Virginia			

3 Clinical Trial Information

Detailed information about the clinical trials your patient has been matched to, ranked for the patient based on location and trial phase.

Medical Case Consulting

For additional help with report interpretation, select the “Ask An Expert” feature on your provider portal or contact client services at (888) 988-3639.

To learn more about our FDA-approved portfolio, go to foundationmedicine.com/portfolio

FoundationOne®CDx and FoundationOne®Liquid CDx are qualitative next-generation sequencing based *in vitro* diagnostic tests for advanced cancer patients with solid tumors and are for prescription use only. FoundationOne CDx utilizes FFPE tissue and analyzes 324 genes as well as genomic signatures. FoundationOne Liquid CDx analyzes 324 genes utilizing circulating cell-free DNA and is FDA-approved to report short variants in 311 genes. The tests are companion diagnostics to identify patients who may benefit from treatment with specific therapies in accordance with the therapeutic product labeling. Additional genomic findings may be reported and are not prescriptive or conclusive for labeled use of any specific therapeutic product. Use of the tests does not guarantee a patient will be matched to a treatment. A negative result does not rule out the presence of an alteration. Some patients may require a biopsy for testing with FoundationOne CDx when archival tissue is not available which may pose a risk. Patients who are tested with FoundationOne Liquid CDx and are negative for companion diagnostic mutations should be reflexed to tumor tissue testing and mutation status confirmed using an FDA-approved tumor tissue test, if feasible.

For the complete label, including companion diagnostic indications and important risk information, please visit www.F1CDxLabel.com and www.F1LCDxLabel.com.

References:

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