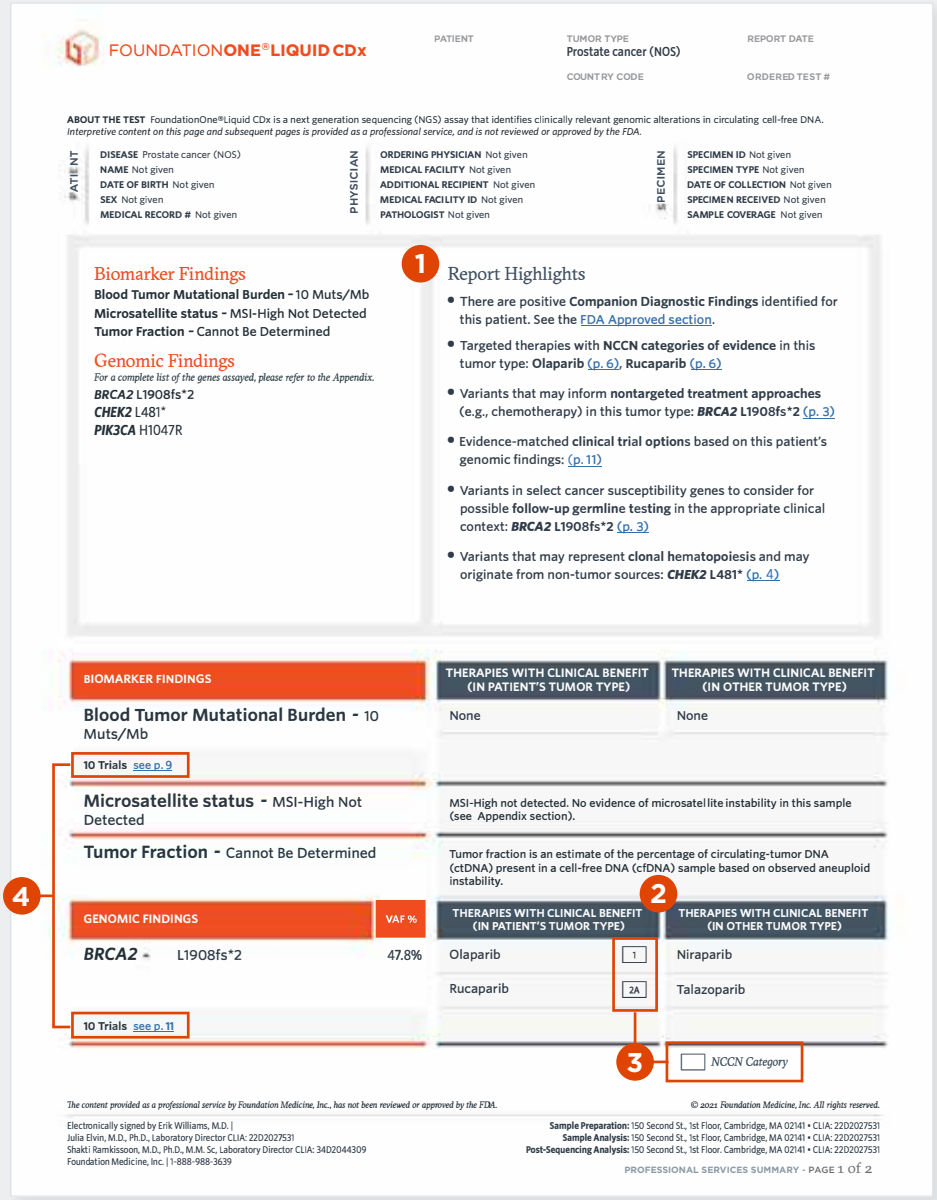
FOUNDATIONONE®CDx FOUNDATIONONE®LIQUID CDx

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) | REPORT DATE | COUNTRY CODE | 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

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	None	None
10 Trials see p. 9		
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	1	Niraparib
		Rucaparib	2A	Talazoparib
10 Trials see p. 11				

3 NCCN Category

4

2

The content provided as a professional service by Foundation Medicine, Inc., has not been reviewed or approved by the FDA.

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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

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 Consensus[1]

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

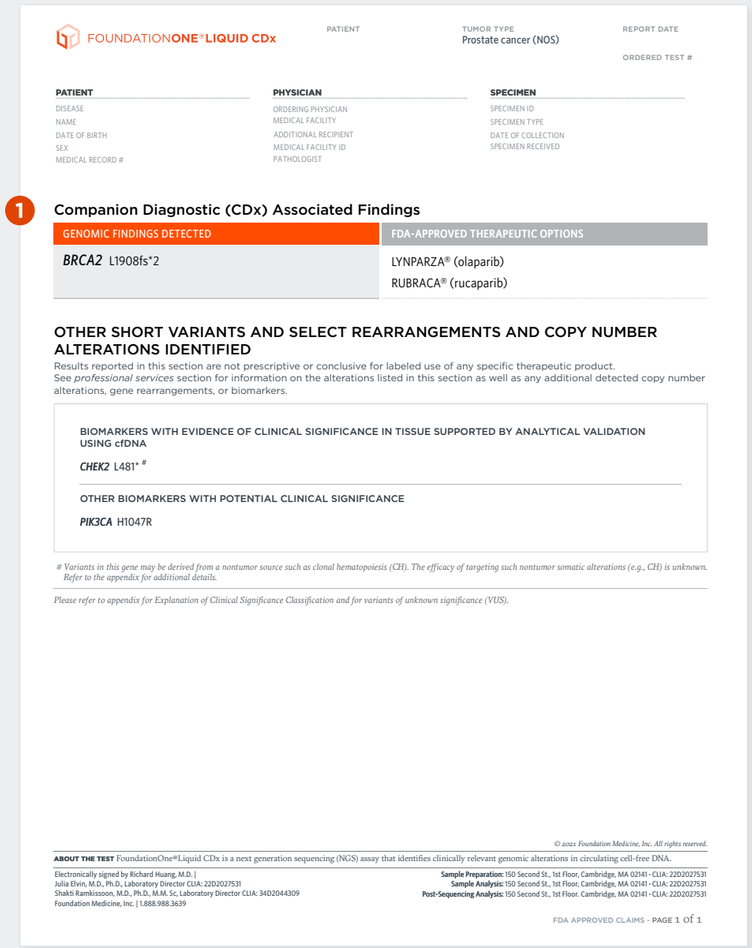
Identifies important negative results on FoundationOne CDx that can be used for patient management when applicable.

Pertinent negatives do not appear for FoundationOne Liquid CDx.

Continued →

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).



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

PATIENT
DISEASE
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD #

PHYSICIAN
ORDERING PHYSICIAN
MEDICAL FACILITY
ADDITIONAL RECIPIENT
MEDICAL FACILITY ID
PATHOLOGIST

SPECIMEN
SPECIMEN ID
SPECIMEN TYPE
DATE OF COLLECTION
SPECIMEN RECEIVED

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.

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FDA APPROVED CLAIMS - PAGE 1 OF 1

1 **FDA-Approved CDx Claims**

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

A companion diagnostic provides essential information for the safe and effective use of a corresponding drug or biological product.

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.

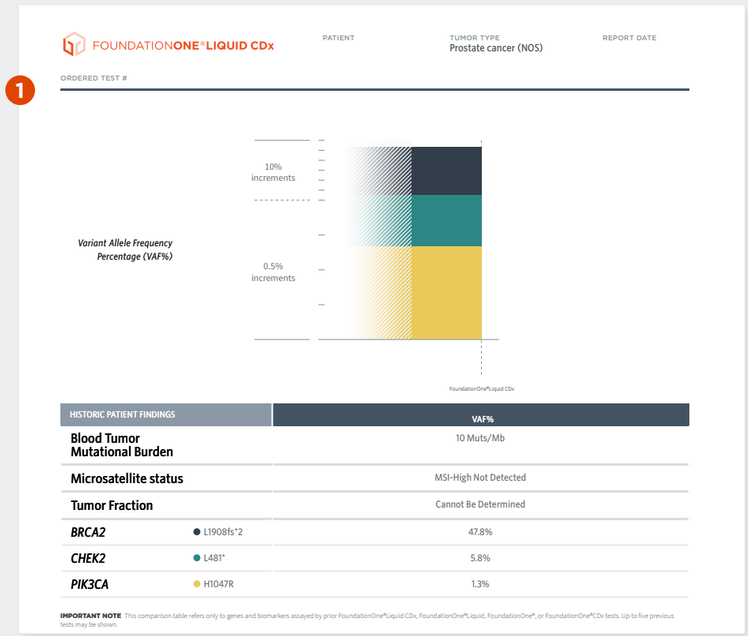
Sample report images last updated December 2021.

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.



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

1 ORDERED TEST #

HISTORIC PATIENT FINDINGS	VAF%	
Blood Tumor Mutational Burden	10 Muts/Mb	
Microsatellite status	MSI-High Not Detected	
Tumor Fraction	Cannot Be Determined	
BRCA2	● L1908fs*2	47.8%
CHEK2	● L481*	5.8%
PIK3CA	● H1047R	1.3%

IMPORTANT NOTE This comparison table refers only to genes and biomarkers assayed by prior FoundationOne®Liquid CDx, FoundationOne®Liquid, FoundationOne®, or FoundationOne®CDx tests. Up to five previous tests may be shown.

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.

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

2 ORDERED TEST #

GENOMIC FINDINGS

GENE
BRCA2

ALTERATION
L1908fs*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[36-53] or to ATR inhibitors[54-55]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[37,42,45,52-53] and for patients with platinum-resistant or -refractory disease[36,41,48,51]. 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[55]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[56], ovarian carcinoma[57], and triple-negative breast cancer (TNBC)[58] 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)[59]. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[60-70].

FREQUENCY & PROGNOSIS

BRCA2 mutations have been identified in 3–6% of primary and 6–7% of metastatic prostate cancer specimens[71-73], 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[75]. 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[76]. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers[76]. 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[77]. 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 18.9 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[81,83-98].

POTENTIAL GERMLINE IMPLICATIONS

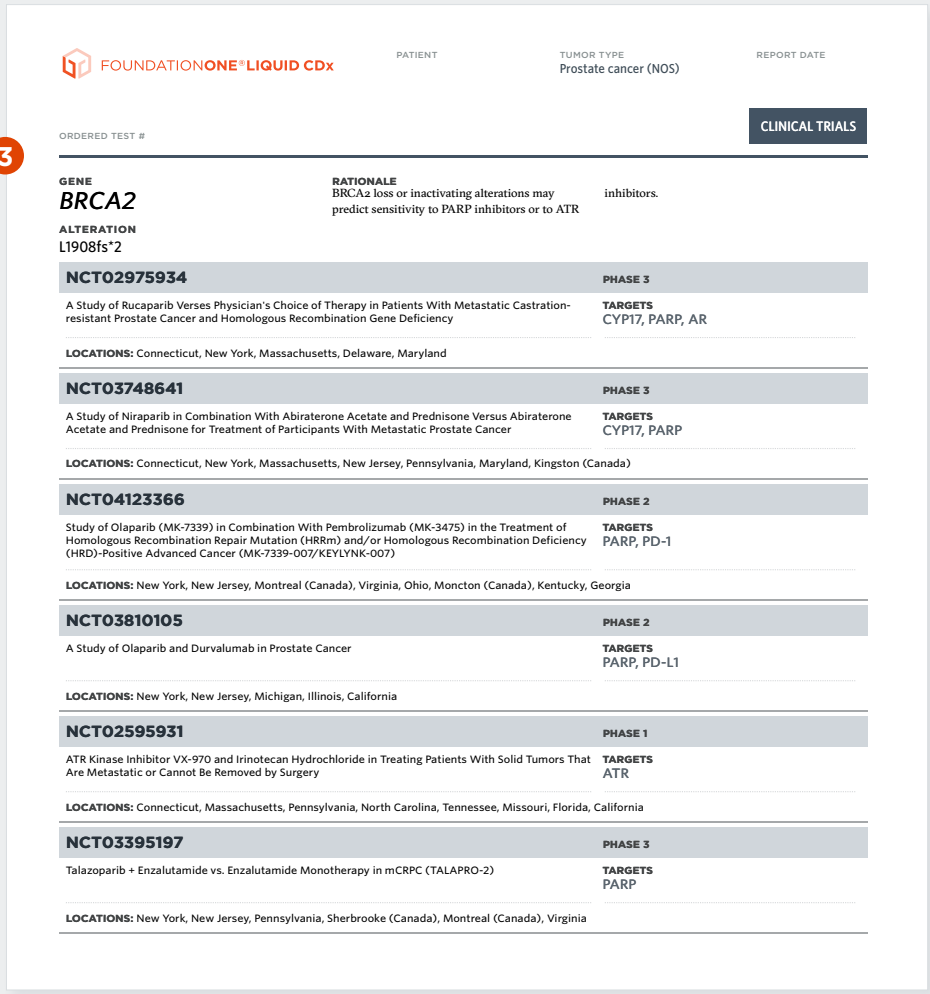
One or more of the BRCA2 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters with no conflicts) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2020)[99]. Follow-up 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[100-101], 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[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[102,104-109]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

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 →

Professional Services Continued



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

CLINICAL TRIALS

3

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 testingand 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:

1. Referenced with permission from the National Comprehensive Cancer Network, Inc. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the recommendations, 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.

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