FoundationOne®Liquid CDx Report Interpretation

April 2022

M-ES-00006841

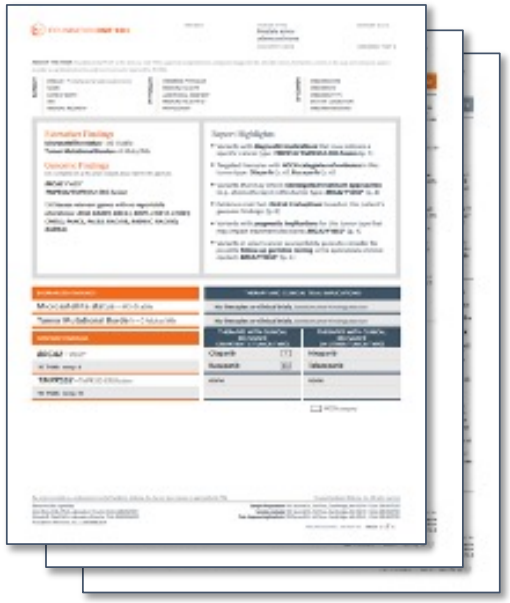
FOUNDATION MEDICINE

Components of the current FMI report | Claims and PS

US and Japan F1CDx or F1LCDx reports

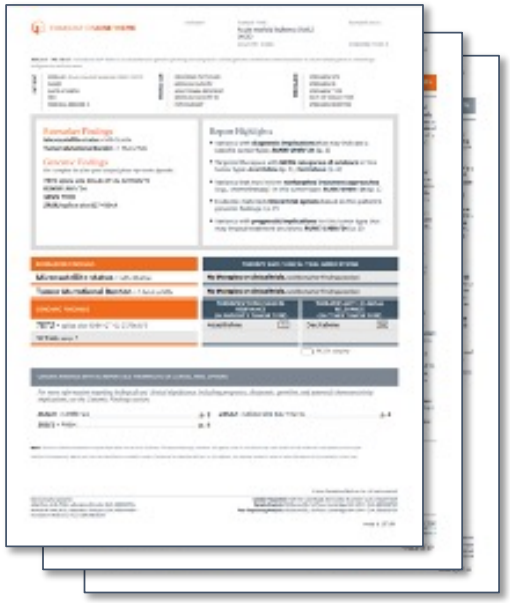
Claims page

Professional Services



EU, RoW, USZ F1CDx or F1LCDx; F1Heme (all regions)

Professional Services



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Claims vs. Professional Services

Claims page

- An approved set of disease-alteration-therapy associations and/or reportable alterations
- Different versions due to FDA and PMDA
- Generated automatically

Professional Services

- Evolving disease-alteration-therapy associations based on drug approval and evidence
- All reportable and VUS alterations
- Content updated by TOCR; report generation largely automated

Common mismatches between Claims and PS

- **Therapy associations**
- **Resistance**
- **Alteration renaming**

FOUNDATION MEDICINE

Professional Services Summary Page Supports Guideline-Based Decision Making

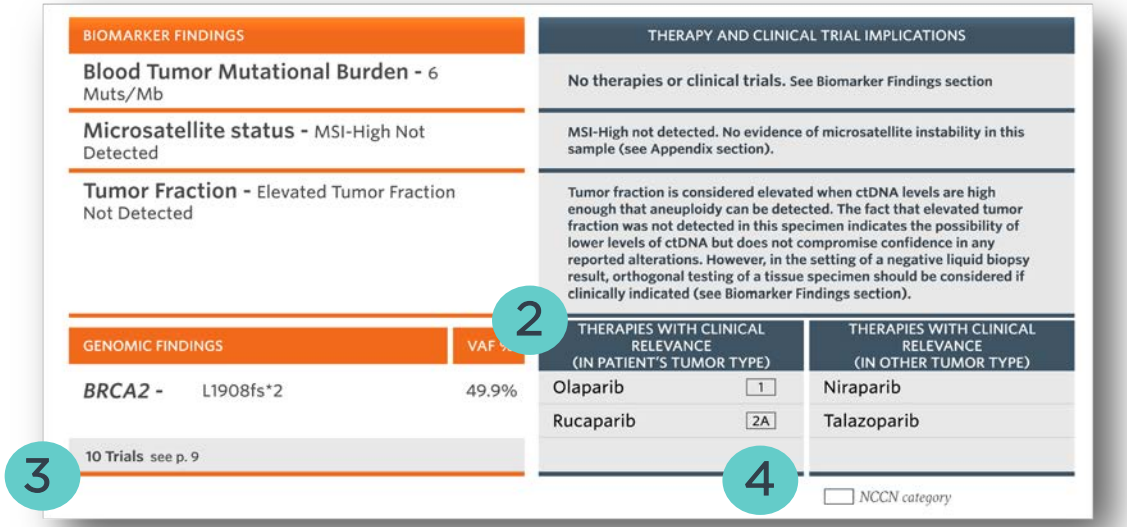
Interpretive content provided in professional services section

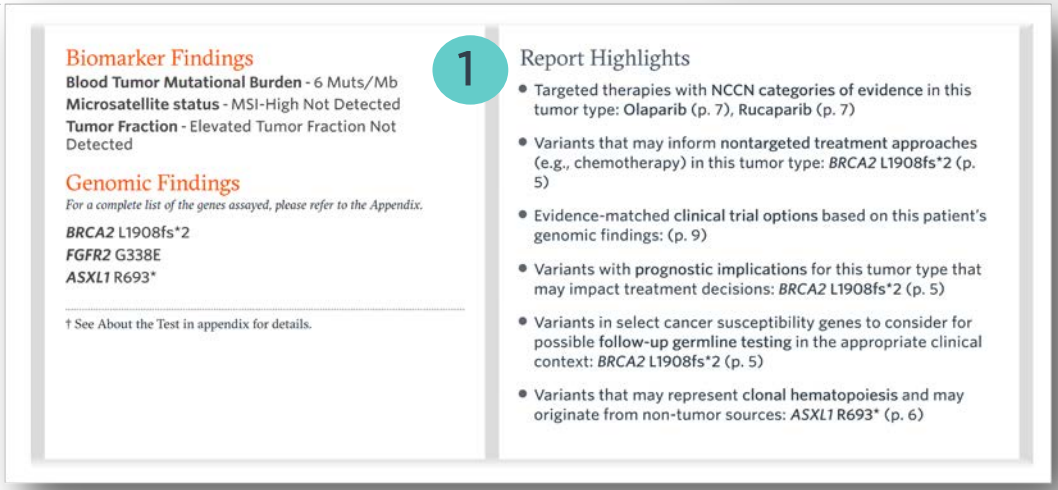
1 Report Highlights
Highlights key actionable findings

2 Therapies with Clinical Benefit
Therapies for each associated genomic finding are listed in alphabetical order within your patient's tumor type and other tumor types

3 Clinical Trials
Identifies trials based on your patient's unique genomic profile with page number for quick reference

4 NCCN Categories of Evidence and Consensus
Associated NCCN Category that has been assigned to the therapy listed within your patient's tumor type





Current as of April 2022.

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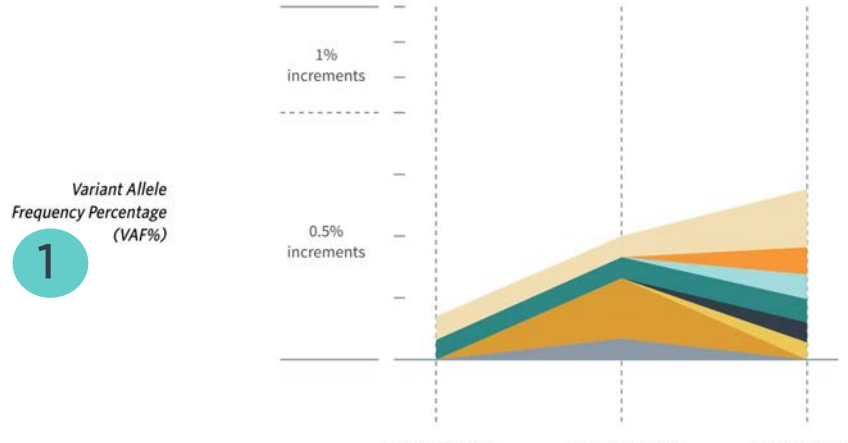
FoundationOne®Liquid CDx Reporting of Patient Historic Findings

1 **Variant Allele Frequency (VAF) Percentage**
Represents the fraction of sequencing reads in which the variant is observed



HISTORIC PATIENT FINDINGS		FoundationOne®Liquid CDx Fall 2020 VAF% 1	FoundationOne®Liquid CDx Summer 2021 VAF%	FoundationOne®Liquid CDx Spring 2022 VAF%	CHANGE FROM PREV
Blood Tumor Mutational Burden		4 Muts/Mb	4 Muts/Mb	5 Muts/Mb	-
Microsatellite status		MSI-High Not Detected	MSI-High Not Detected	MSI-High Not Detected	-
Tumor Fraction		Elevated Tumor Fraction Not Detected	Elevated Tumor Fraction Not Detected	Elevated Tumor Fraction Not Detected	-
KRAS	G12C	Not Detected	Not Detected	0.16%	+0.16%
ATM	G2891D	0.16%	0.17%	0.19%	+0.02%
APC	S1421fs*52	Not Detected	Not Detected	0.14%	+0.14%
CHEK2	Y445fs*1	Not Detected	Not Detected	0.20%	+0.20%
	R137*	Not Detected	0.17%	Not Detected	-0.17%
TP53	R213*	Not Detected	Not Detected	0.22%	+0.22%
	Y220C	0.19%	0.17%	0.47%	+0.30%
DNMT3A	P871fs*7	Not Detected	0.49%	Not Detected	-0.49%

Current as of April 2022.

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FoundationOne®Liquid CDx Examples of DO-Specific Report Slides

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Non-Small Cell Lung Cancer With *EGFR* Mutation

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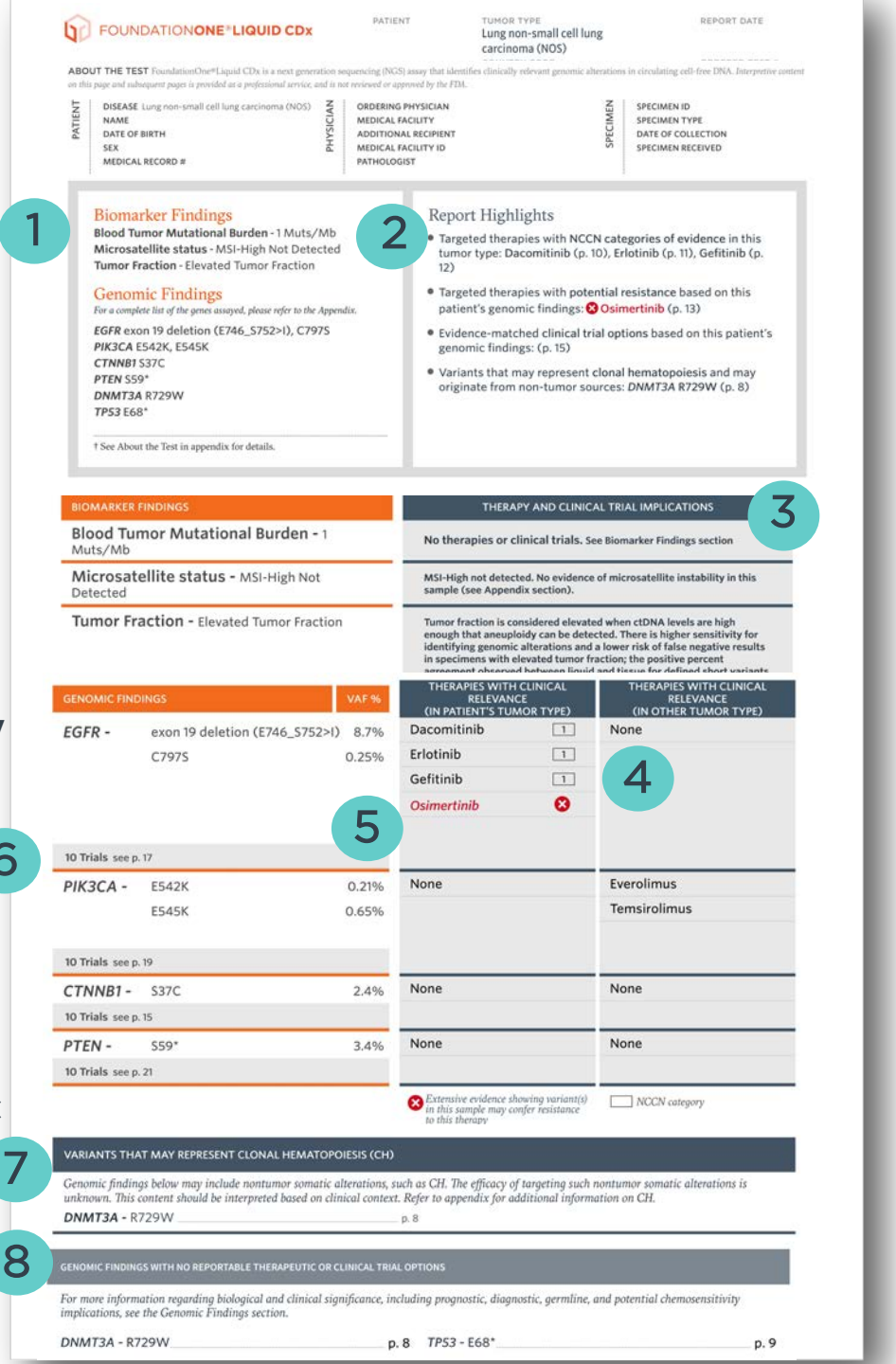
FoundationOne®Liquid CDx Professional Services Summary Page

Lung Cancer

1. **Biomarker and Genomic Findings**
2. **Report Highlights**
3. **Findings and Actionability**
4. **NCCN Category of Evidence**
5. **Potential Resistance to Indicated Therapy Warning**
6. **Clinical Trials**
7. **Variants That May Represent Clonal Hematopoiesis**
8. **Findings Without Reportable Therapeutic or Clinical Trial Options**



Current as of February 2, 2022.

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FoundationOne®Liquid CDx Patient Historic Findings

Lung Cancer

1 Variant Allele Frequency Percentage

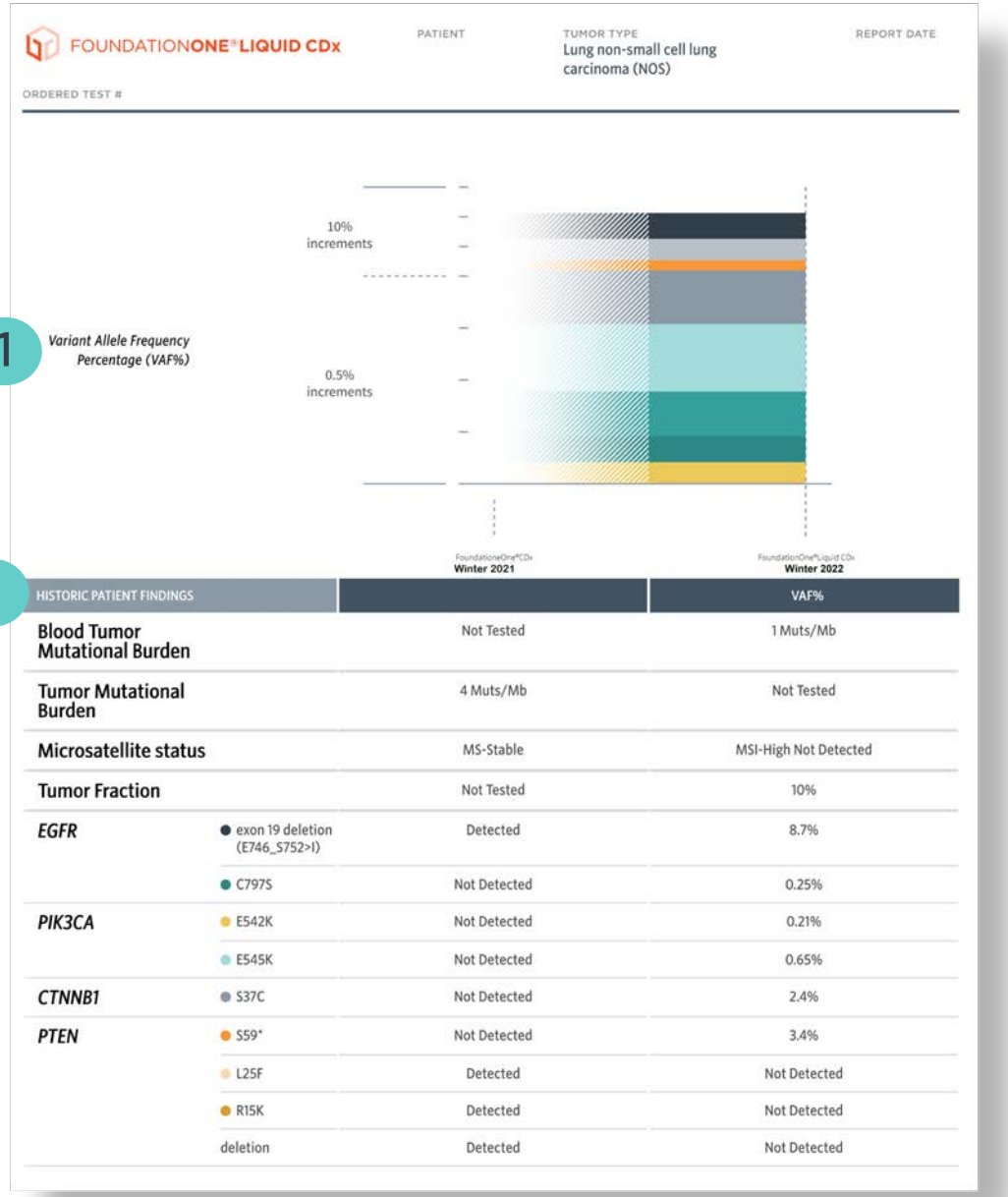
VAF% for short variants in all liquid test types are plotted on a stacked bar graph in chronological order

- Rearrangement VAFs and VAFs from tissue testing are not included in graph

2 Patient Historic Findings Table

In addition to genomic alterations, the patient historic findings table shows tumor mutational burden, blood tumor mutational burden, microsatellite status, and tumor fraction

VAFs from liquid biopsy are also shown in the patient historic findings table



Current as of February 2, 2022.

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FoundationOne®Liquid CDx: Biomarker and Genomic Findings

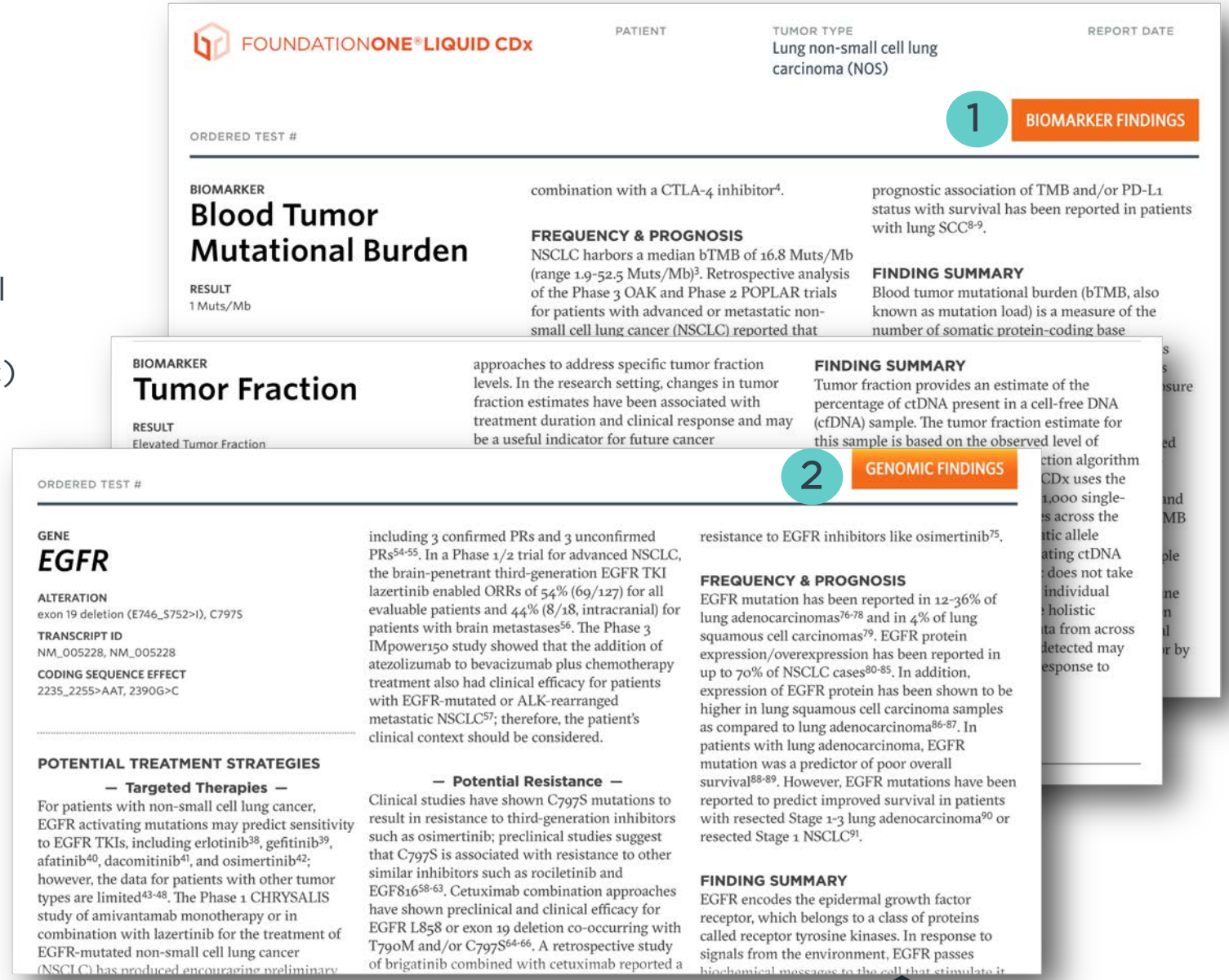
Lung Cancer

1 Biomarker Findings

- Result
- Potential Treatment Strategies (pre-clinical and clinical evidence)
- Frequency and Prognosis (disease-specific)
- Finding Summary (result, relevance)

2 Genomic Findings

- Gene Variant Information
- Potential Treatment Strategies: Clinical relevance
- Frequency and Prognosis: In the specimen tumor type and/or other tumor types
- Finding Summary: Gene, function, biological implication of the alteration



Current as of February 2, 2022.

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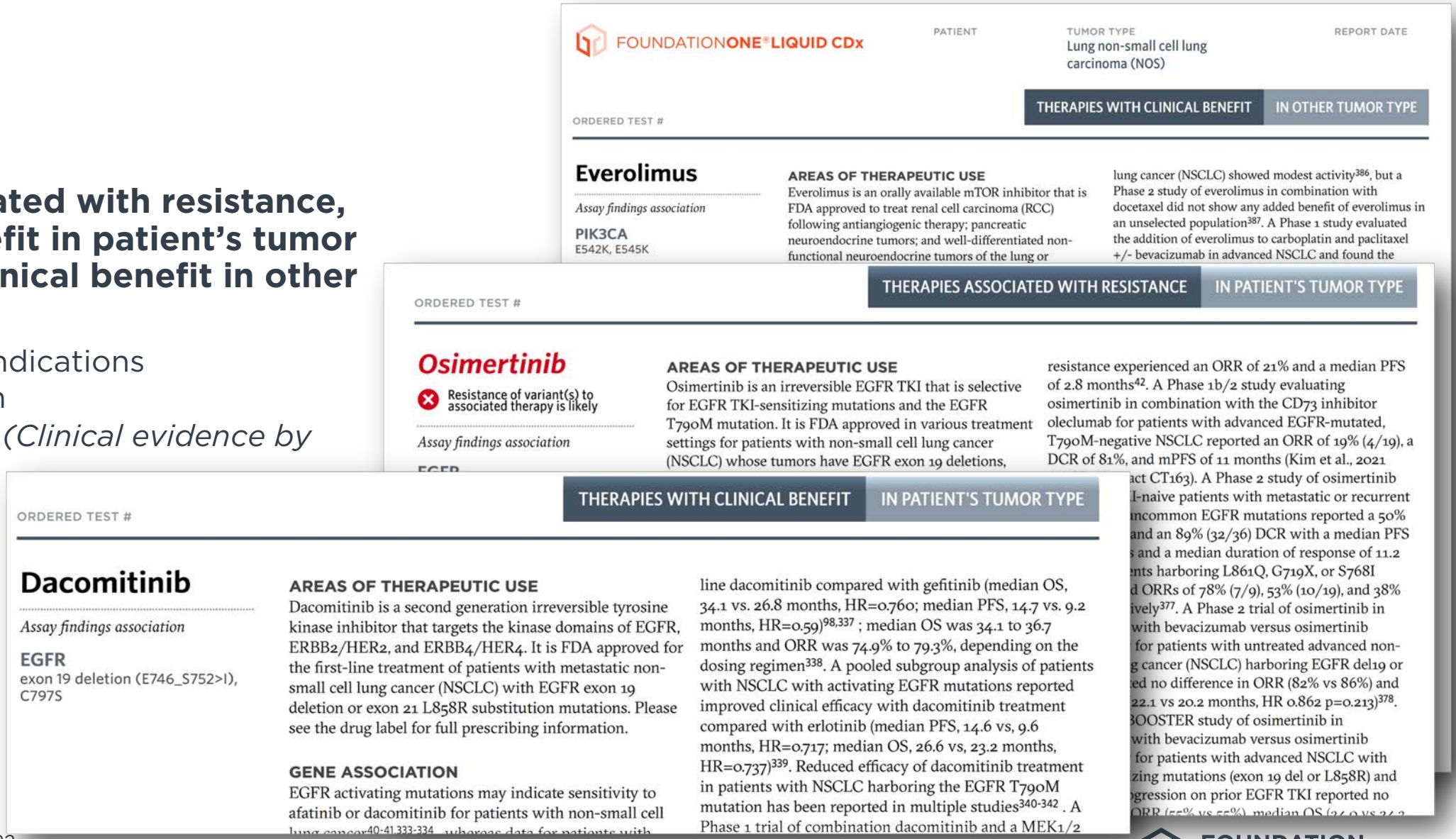
FoundationOne®Liquid CDx: Therapeutic Options Section

Lung Cancer

Therapies associated with resistance, with clinical benefit in patient's tumor type, and with clinical benefit in other tumor type

- FDA Approved Indications
- Gene Association
- Supporting Data *(Clinical evidence by phase)*



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Everolimus

Assay findings association

PIK3CA
E542K, E545K

AREAS OF THERAPEUTIC USE
Everolimus is an orally available mTOR inhibitor that is FDA approved to treat renal cell carcinoma (RCC) following antiangiogenic therapy; pancreatic neuroendocrine tumors; and well-differentiated non-functional neuroendocrine tumors of the lung or lung cancer (NSCLC) showed modest activity[386], but a Phase 2 study of everolimus in combination with docetaxel did not show any added benefit of everolimus in an unselected population[387]. A Phase 1 study evaluated the addition of everolimus to carboplatin and paclitaxel +/- bevacizumab in advanced NSCLC and found the

ORDERED TEST #

THERAPIES ASSOCIATED WITH RESISTANCE | IN PATIENT'S TUMOR TYPE

Osimertinib

Resistance of variant(s) to associated therapy is likely

Assay findings association

AREAS OF THERAPEUTIC USE
Osimertinib is an irreversible EGFR TKI that is selective for EGFR TKI-sensitizing mutations and the EGFR T790M mutation. It is FDA approved in various treatment settings for patients with non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions, resistance experienced an ORR of 21% and a median PFS of 2.8 months[42]. A Phase 1b/2 study evaluating osimertinib in combination with the CD73 inhibitor oleclumab for patients with advanced EGFR-mutated, T790M-negative NSCLC reported an ORR of 19% (4/19), a DCR of 81%, and mPFS of 11 months (Kim et al., 2021 ...act CT163). A Phase 2 study of osimertinib ...I-naive patients with metastatic or recurrent ...ncommon EGFR mutations reported a 50% ...and an 89% (32/36) DCR with a median PFS ...s and a median duration of response of 11.2 ...nts harboring L861Q, G719X, or S768I ...d ORRs of 78% (7/9), 53% (10/19), and 38% ...ively[377]. A Phase 2 trial of osimertinib in ...with bevacizumab versus osimertinib ... for patients with untreated advanced non- ...g cancer (NSCLC) harboring EGFR del19 or ...ed no difference in ORR (82% vs 86%) and ...22.1 vs 20.2 months, HR 0.862 p=0.213)[378]. ...OOSTER study of osimertinib in ...with bevacizumab versus osimertinib ... for patients with advanced NSCLC with ...zing mutations (exon 19 del or L858R) and ...gression on prior EGFR TKI reported no ...ORR (55% vs 55%), median OS (24.0 vs 24.2

ORDERED TEST #

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Dacomitinib

Assay findings association

EGFR
exon 19 deletion (E746_S752>I), C797S

AREAS OF THERAPEUTIC USE
Dacomitinib is a second generation irreversible tyrosine kinase inhibitor that targets the kinase domains of EGFR, ERBB2/HER2, and ERBB4/HER4. It is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 19 deletion or exon 21 L858R substitution mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION
EGFR activating mutations may indicate sensitivity to afatinib or dacomitinib for patients with non-small cell lung cancer[40-41,333-334], whereas data for patients with line dacomitinib compared with gefitinib (median OS, 34.1 vs. 26.8 months, HR=0.760; median PFS, 14.7 vs. 9.2 months, HR=0.59)[98,337] ; median OS was 34.1 to 36.7 months and ORR was 74.9% to 79.3%, depending on the dosing regimen[338]. A pooled subgroup analysis of patients with NSCLC with activating EGFR mutations reported improved clinical efficacy with dacomitinib treatment compared with erlotinib (median PFS, 14.6 vs, 9.6 months, HR=0.717; median OS, 26.6 vs, 23.2 months, HR=0.737)[339]. Reduced efficacy of dacomitinib treatment in patients with NSCLC harboring the EGFR T790M mutation has been reported in multiple studies[340-342] . A Phase 1 trial of combination dacomitinib and a MEK1/2

Current as of February 2, 2022.

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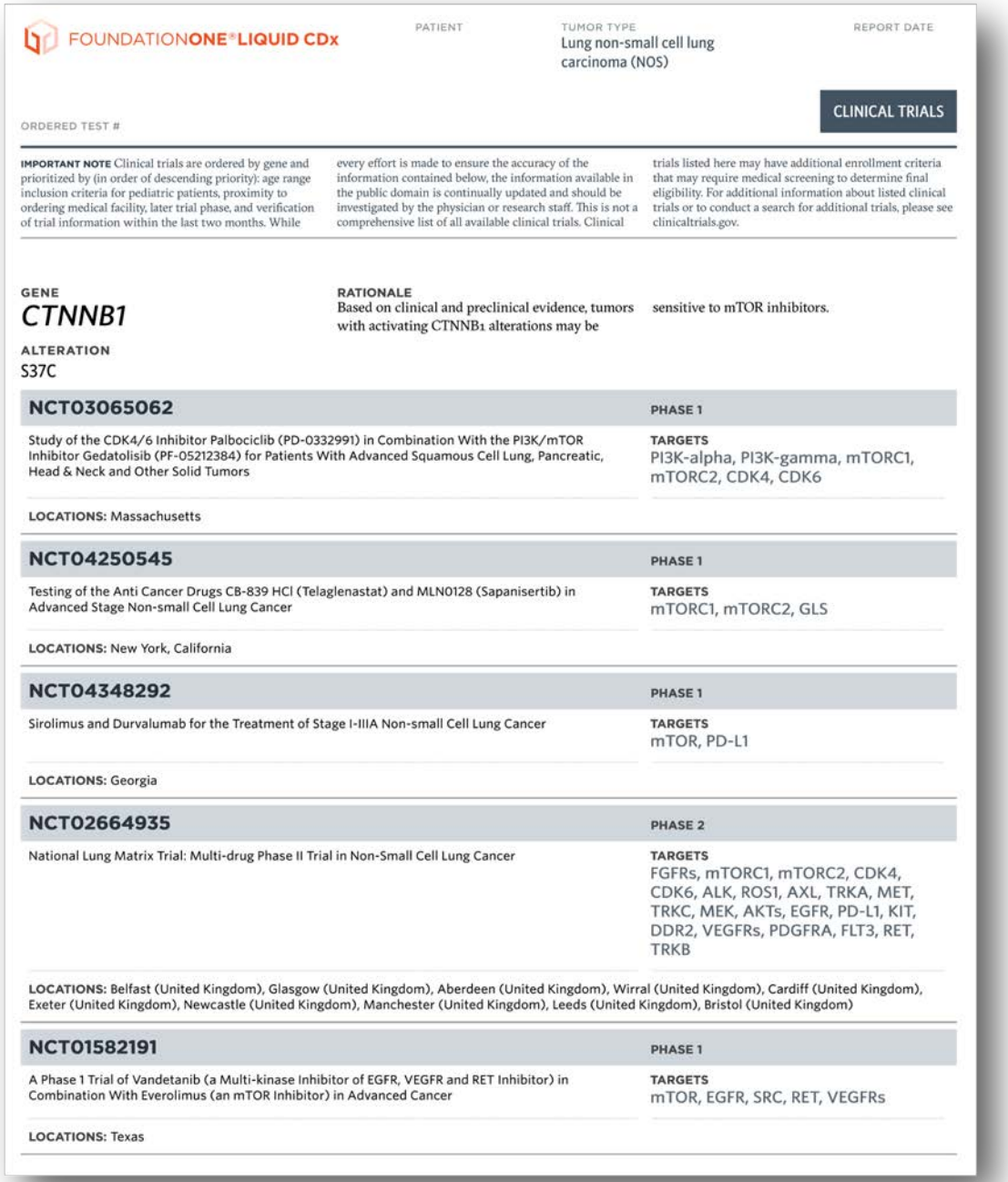
FoundationOne®Liquid CDx: Clinical Trials Section

Lung Cancer

Clinical Trials

- **Gene, alteration**
- **Rationale**
- **Trial Options:** Ordered by gene and prioritized based on age range, proximity to ordering medical facility, trial phase (favoring later phases), and whether trial information has been verified within the last 2 months

Select subset of currently available clinical trials for which the patient may be eligible. Includes: Trial ID, Title, Phase, Relevant Targets, and 10 closest locations to the ordering medical facility



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

CLINICAL TRIALS

IMPORTANT NOTE Clinical trials are ordered by gene and prioritized by (in order of descending priority): 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. 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.

GENE
CTNNB1

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors.

ALTERATION
S37C

NCT03065062 — PHASE 1

Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination With the PI3K/mTOR Inhibitor Gedatolisib (PF-05212384) for Patients With Advanced Squamous Cell Lung, Pancreatic, Head & Neck and Other Solid Tumors

TARGETS: PI3K-alpha, PI3K-gamma, mTORC1, mTORC2, CDK4, CDK6

LOCATIONS: Massachusetts

NCT04250545 — PHASE 1

Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer

TARGETS: mTORC1, mTORC2, GLS

LOCATIONS: New York, California

NCT04348292 — PHASE 1

Sirolimus and Durvalumab for the Treatment of Stage I-IIIA Non-small Cell Lung Cancer

TARGETS: mTOR, PD-L1

LOCATIONS: Georgia

NCT02664935 — PHASE 2

National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

TARGETS: FGFRs, mTORC1, mTORC2, CDK4, CDK6, ALK, ROS1, AXL, TRKA, MET, TRKC, MEK, AKTs, EGFR, PD-L1, KIT, DDR2, VEGFRs, PDGFRA, FLT3, RET, TRKB

LOCATIONS: Belfast (United Kingdom), Glasgow (United Kingdom), Aberdeen (United Kingdom), Wirral (United Kingdom), Cardiff (United Kingdom), Exeter (United Kingdom), Newcastle (United Kingdom), Manchester (United Kingdom), Leeds (United Kingdom), Bristol (United Kingdom)

NCT01582191 — PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS: mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: Texas

Current as of February 2, 2022.

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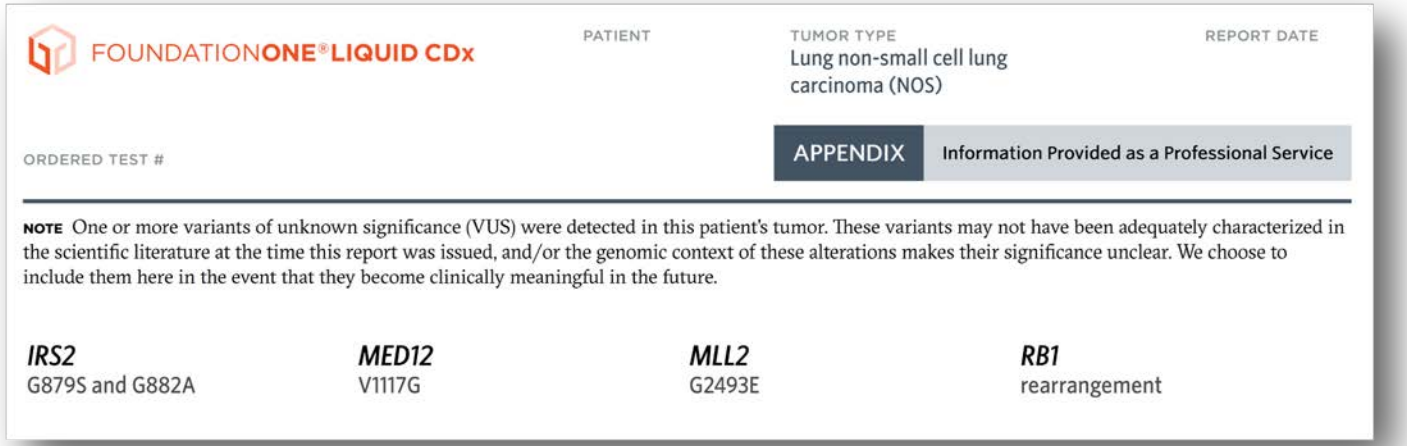
FoundationOne®Liquid CDx: Appendices

Lung Cancer



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX Information Provided as a Professional Service

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.

IRS2	***MED12***	***MLL2***	***RB1***
G879S and G882A	V1117G	G2493E	rearrangement

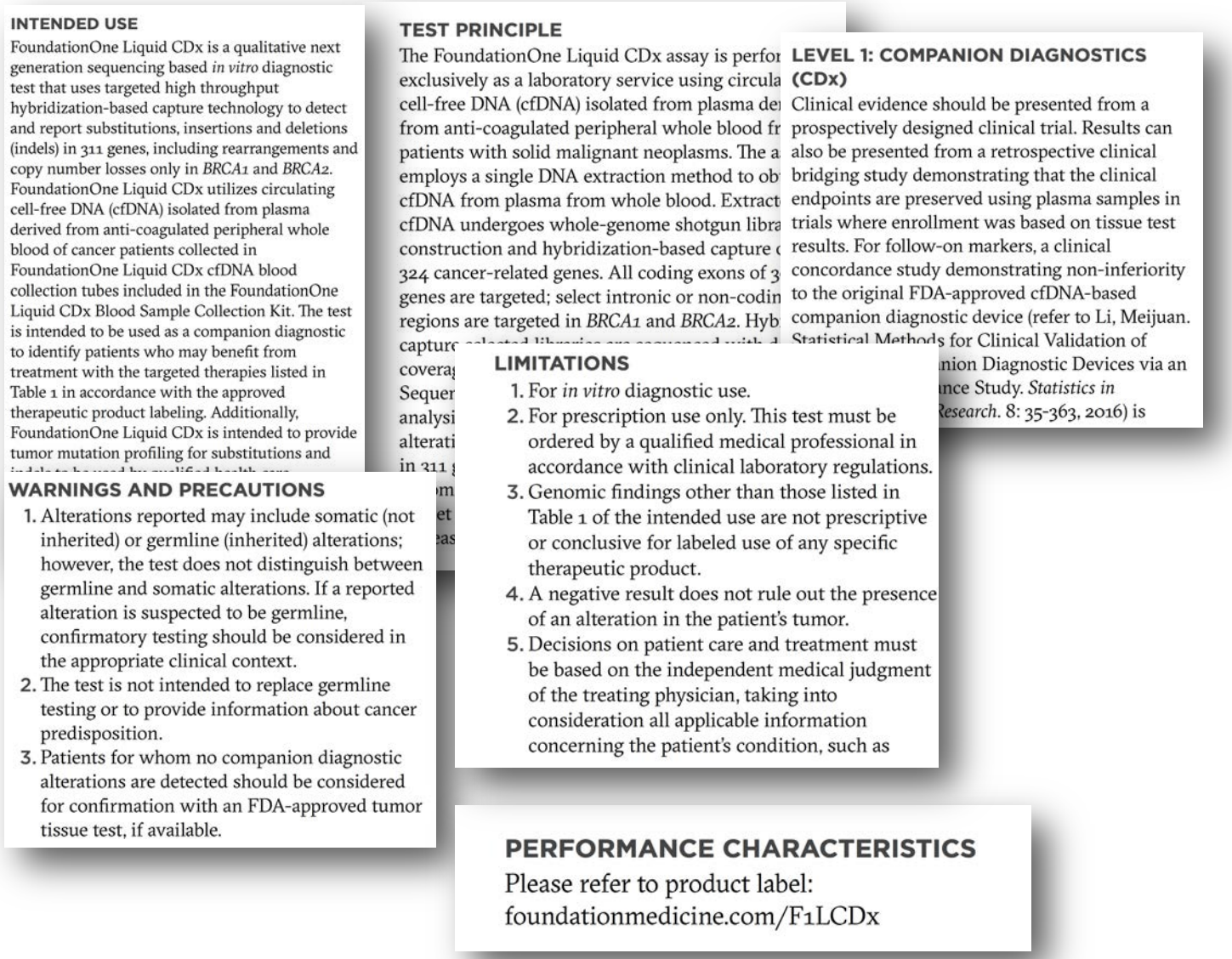
Variants of Unknown Significance (VUS)
Alterations not adequately characterized in the scientific literature and/or have unclear significance based on genomic context

**VUS are included for completeness should the alterations become clinically meaningful in the future.*

Current as of February 2, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)



INTENDED USE

FoundationOne Liquid CDx is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements and copy number losses only in *BRCA1* and *BRCA2*. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit. The test is intended to be used 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 Liquid CDx is intended to provide tumor mutation profiling for substitutions and

TEST PRINCIPLE

The FoundationOne Liquid CDx assay is perfor
exclusively as a laboratory service using circula
cell-free DNA (cfDNA) isolated from plasma de
from anti-coagulated peripheral whole blood fr
patients with solid malignant neoplasms. The a
employs a single DNA extraction method to ob
cfDNA from plasma from whole blood. Extract
cfDNA undergoes whole-genome shotgun libra
construction and hybridization-based capture
324 cancer-related genes. All coding exons of 3
genes are targeted; select intronic or non-codin
regions are targeted in *BRCA1* and *BRCA2*. Hyb
capture
coverag
Sequer
analysi
alterati
in 311

LEVEL 1: COMPANION DIAGNOSTICS (CDx)

Clinical evidence should be presented from a prospectively designed clinical trial. Results can also be presented from a retrospective clinical bridging study demonstrating that the clinical endpoints are preserved using plasma samples in trials where enrollment was based on tissue test results. For follow-on markers, a clinical concordance study demonstrating non-inferiority to the original FDA-approved cfDNA-based companion diagnostic device (refer to Li, Meijuan. Statistical Methods for Clinical Validation of
nion Diagnostic Devices via an
nce Study. *Statistics in*
Research. 8: 35-363, 2016) is

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of an alteration in the patient's tumor.
5. 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

WARNINGS AND PRECAUTIONS

1. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
2. The test is not intended to replace germline testing or to provide information about cancer predisposition.
3. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an FDA-approved tumor tissue test, if available.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/F1LCDx

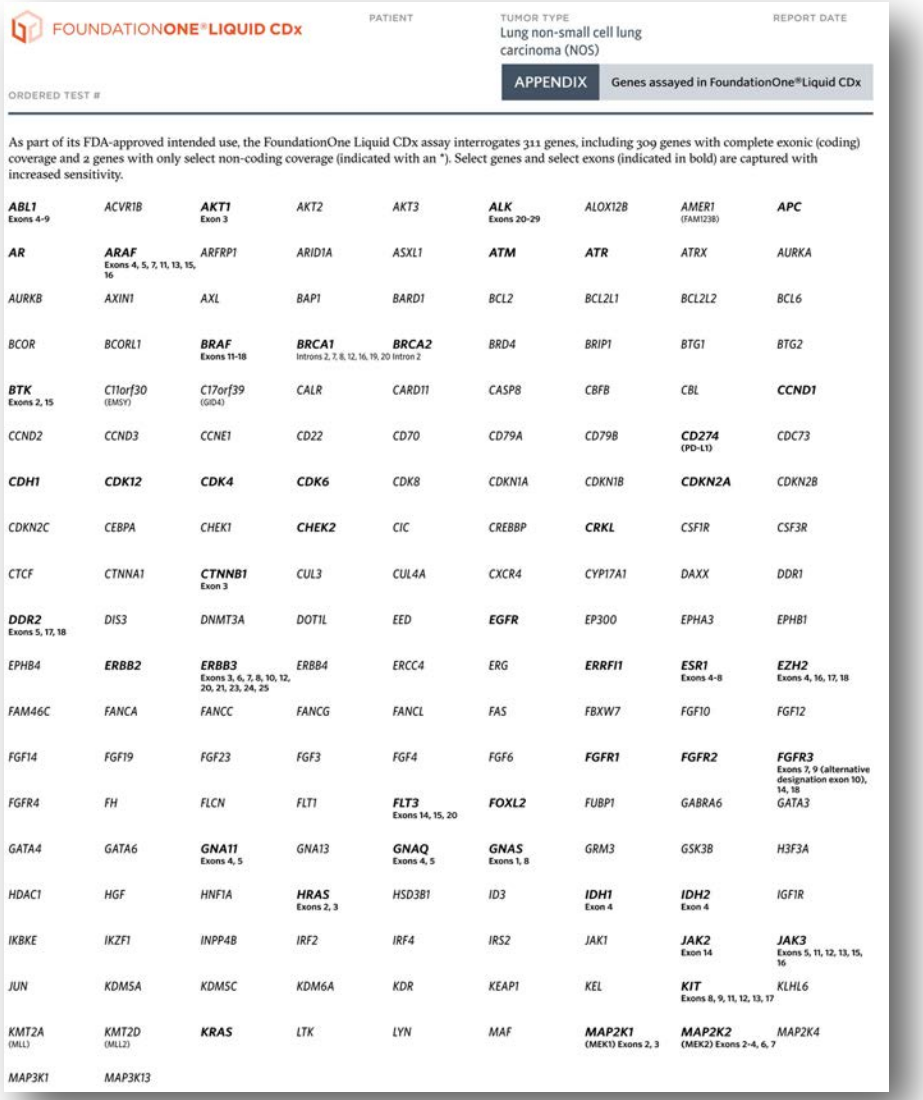
About FoundationOne®Liquid CDx

- Intended Use (FDA approved indications)
- Test Principle, Performance Characteristics, Limitations, Levels of Evidence

Current as of February 2, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX Genes assayed in FoundationOne®Liquid CDx

As part of its FDA-approved intended use, the FoundationOne Liquid CDx assay interrogates 311 genes, including 309 genes with complete exonic (coding) coverage and 2 genes with only select non-coding coverage (indicated with an *). Select genes and select exons (indicated in bold) are captured with increased sensitivity.

ABL1 Exons 4-9	ACVR1B	**AKT1** Exon 3	AKT2	AKT3	**ALK** Exons 20-29	ALOX12B	AMER1 (FAM123B)	**APC**
AR	**ARAF** Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	**ATM**	**ATR**	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	**BRAF** Exons 11-18	**BRCA1** Introns 2, 7, 8, 12, 16, 19, 20 Intron 2	**BRCA2**	BRD4	BRIP1	BTG1	BTG2
BTK Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL	**CCND1**
CCND2	CCND3	CCNE1	CD22	CD70	CD79A	CD79B	**CD274** (PD-L1)	CDC73
CDH1	**CDK12**	**CDK4**	**CDK6**	CDK8	CDKN1A	CDKN1B	**CDKN2A**	CDKN2B
CDKN2C	CEBPA	CHEK1	**CHEK2**	CIC	CREBBP	**CRKL**	CSF1R	CSF3R
CTCF	CTNNA1	**CTNNB1** Exon 3	CUL3	CUL4A	CXCR4	CYP17A1	DAXX	DDR1
DDR2 Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	**EGFR**	EP300	EPHA3	EPHB1
EPHB4	**ERBB2**	**ERBB3** Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	**ERRFI1**	**ESR1** Exons 4-8	**EZH2** Exons 4, 16, 17, 18
FAM46C	FANCA	FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12
FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	**FGFR1**	**FGFR2**	**FGFR3** Exons 7, 9 (alternative designation exon 10), 14, 18
FGFR4	FH	FLCN	FLT1	**FLT3** Exons 14, 15, 20	**FOXL2**	FUBP1	GABRA6	GATA3
GATA4	GATA6	**GNA11** Exons 4, 5	GNA13	**GNAQ** Exons 4, 5	**GNAS** Exons 1, 8	GRM3	GSK3B	H3F3A
HDAC1	HGF	HNF1A	**HRAS** Exons 2, 3	HSD3B1	ID3	**IDH1** Exon 4	**IDH2** Exon 4	IGF1R
IKBKE	IKZF1	INPP4B	IRF2	IRF4	IRS2	JAK1	**JAK2** Exon 14	**JAK3** Exons 5, 11, 12, 13, 15, 16
JUN	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KEL	**KIT** Exons 8, 9, 11, 12, 13, 17	KLHL6
KMT2A (MLL)	KMT2D (MLL2)	**KRAS**	LTK	LYN	MAF	**MAP2K1** (MEK1) Exons 2, 3	**MAP2K2** (MEK2) Exons 2-4, 6, 7	MAP2K4
MAP3K1	MAP3K13							

Genes Assayed in FoundationOne®Liquid CDx
FDA-approved intended use list interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage; select genes and exons are captured with increased sensitivity

Current as of February 2, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX Information Provided as a Professional Service

QUALIFIED ALTERATION CALLS (EQUIVOCAL)
All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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 THERAPIES AND CLINICAL TRIALS
Ranking of Therapies in Summary Table
Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of 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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, 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
This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in 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 Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF THE PHYSICIAN
Drugs referenced in this report 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 entirely within the discretion of the treating 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.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

REPORT HIGHLIGHTS
The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatmer hematopoiesis implic in the Report Highlig advances in scientific Findings included in be considered in the information in this r patient information. treatment are the res physician.

TUMOR MUTATIO
Tissue TMB and bloc from the number of s synonymous single-r insertions and deleti genome sampled, aft likely oncogenic driv Tissue TMB is calcul allele frequency of ≥ based on variants wi ≥20.5%.

TUMOR FRACTIO
Tumor fraction is the tumor DNA (ctDNA) (cfDNA) sample. The computationally deri aneuploidy in the sar considered elevated enough that aneuploi significantly distinct non-tumor samples.

MICROSATELLITE
Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines for solid tissue testing.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING
The variants indicated for consideration of follow-

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

Information Provided as a Professional Service
Several categories of information:

- Qualified Alteration Calls, Rankings, Qualifiers
- Responsibility of Physician for Treatment Decisions
- Variants to Consider for Follow-up Germline Testing
- Select Abbreviations

Current as of February 2, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Lung non-small cell lung carcinoma (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX References Associated with Professional Services Content

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References used in curation of the report content

Current as of February 2, 2022.

FOUNDATION MEDICINE

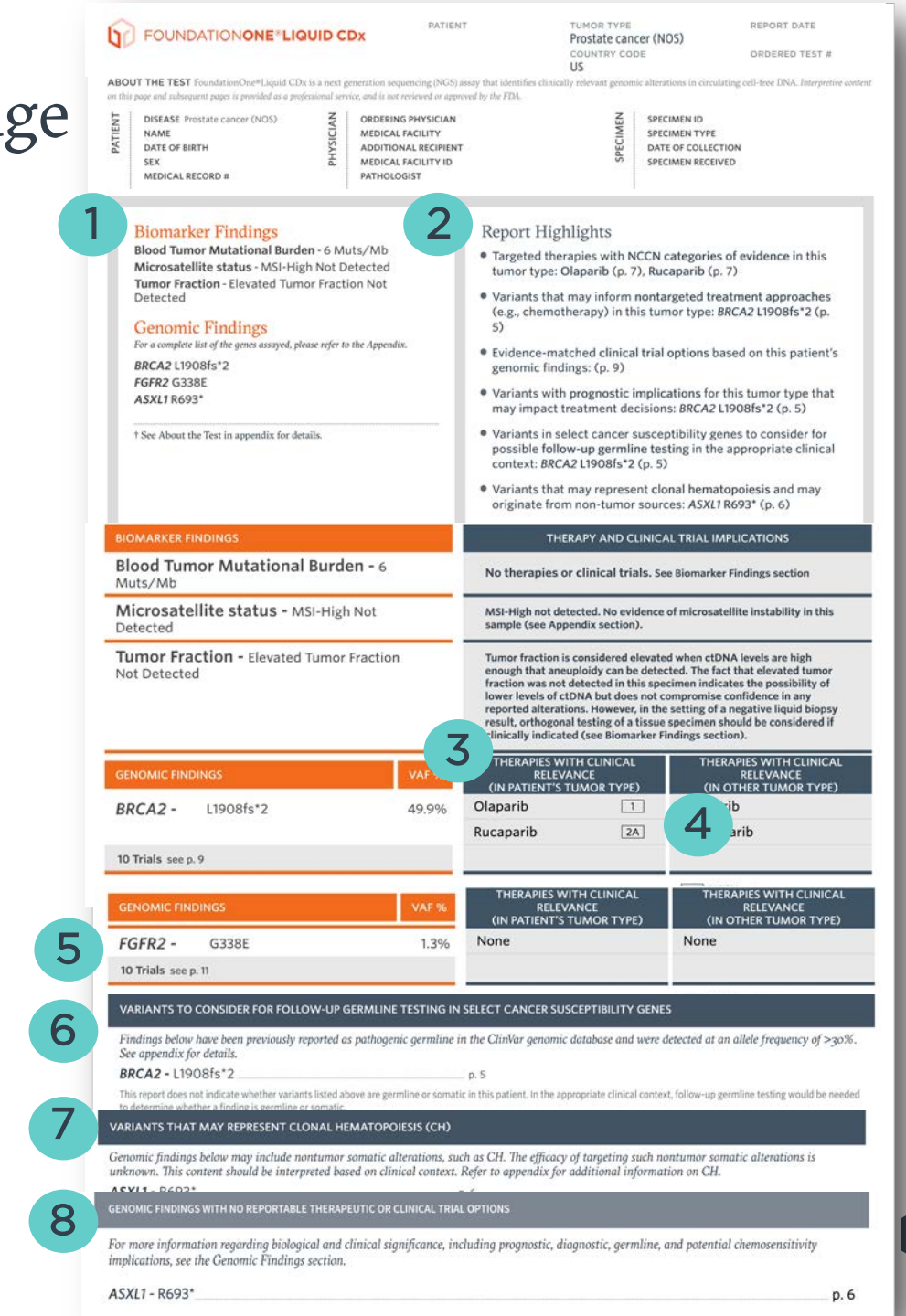
Prostate Cancer with *BRCA2* Mutation

FOUNDATION MEDICINE

FoundationOne®Liquid CDx Professional Services Summary Page

Prostate Cancer

1. **Biomarker and Genomic Findings**
2. **Report Highlights**
3. **Findings and Actionability**
4. **NCCN Category of Evidence**
5. **Clinical Trials**
6. **Variants to Consider for Follow-up Germline Testing**
7. **Variants That May Represent Clonal Hematopoiesis**
8. **Findings Without Reportable Therapeutic or Clinical Trial Options**


FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)
COUNTRY CODE
US

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; 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 Biomarker Findings

Blood Tumor Mutational Burden - 6 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - Elevated Tumor Fraction Not Detected

Genomic Findings

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

BRCA2 L1908fs*2
FGFR2 G338E
ASXL1 R693*

† See About the Test in appendix for details.

2 Report Highlights

- Targeted therapies with NCCN categories of evidence in this tumor type: Olaparib (p. 7), Rucaparib (p. 7)
- Variants that may inform nontargeted treatment approaches (e.g., chemotherapy) in this tumor type: *BRCA2* L1908fs*2 (p. 5)
- Evidence-matched clinical trial options based on this patient's genomic findings: (p. 9)
- Variants with prognostic implications for this tumor type that may impact treatment decisions: *BRCA2* L1908fs*2 (p. 5)
- Variants in select cancer susceptibility genes to consider for possible follow-up germline testing in the appropriate clinical context: *BRCA2* L1908fs*2 (p. 5)
- Variants that may represent clonal hematopoiesis and may originate from non-tumor sources: *ASXL1* R693* (p. 6)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Blood Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section
Microsatellite status - MSI-High Not Detected	MSI-High not detected. No evidence of microsatellite instability in this sample (see Appendix section).
Tumor Fraction - Elevated Tumor Fraction Not Detected	Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected. The fact that elevated tumor fraction was not detected in this specimen indicates the possibility of lower levels of ctDNA but does not compromise confidence in any reported alterations. However, in the setting of a negative liquid biopsy result, orthogonal testing of a tissue specimen should be considered if clinically indicated (see Biomarker Findings section).

3

GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRCA2 - L1908fs*2	49.9%	Olaparib 1	4
10 Trials see p. 9		Rucaparib 2A	

GENOMIC FINDINGS	VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
5 *FGFR2* - G338E	1.3%	None	None
10 Trials see p. 11			

6 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 >30%. See appendix for details.

BRCA2 - L1908fs*2 p. 5

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.

7 VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

ASXL1 - R693*

8 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.

ASXL1 - R693* p. 6

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx Patient Historic Findings

Prostate Cancer

1 Variant Allele Frequency Percentage

VAF% for short variants in all liquid test types are plotted on a stacked bar graph in chronological order

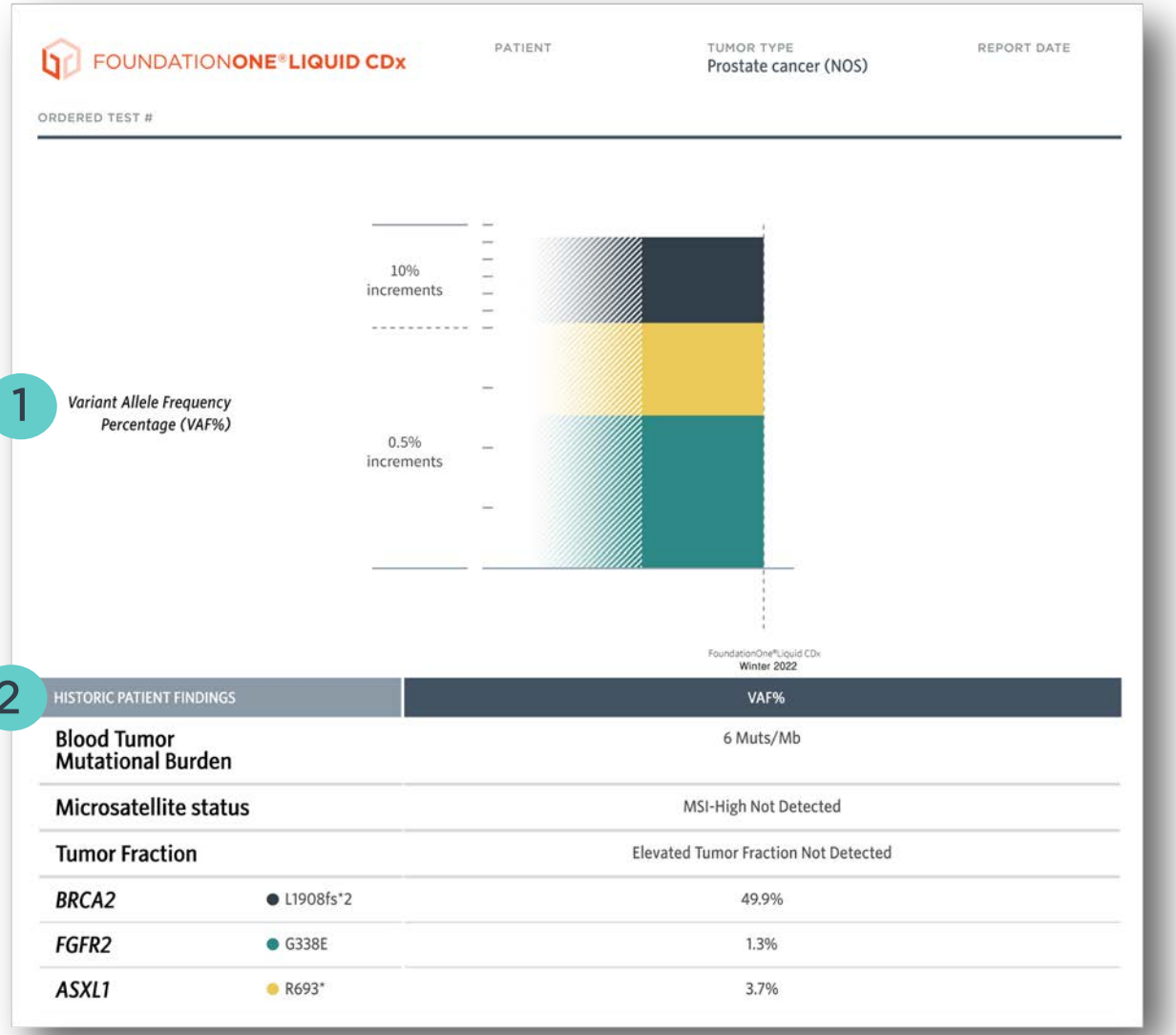
- Rearrangement VAFs and VAFs from tissue testing are not included in graph

2 Patient Historic Findings Table

In addition to genomic alterations, the patient historic findings table shows tumor mutational burden, blood tumor mutational burden, microsatellite status, and tumor fraction

VAFs from liquid biopsy are also shown in the patient historic findings table

Up to five previous tests may be shown



Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Biomarker and Genomic Findings

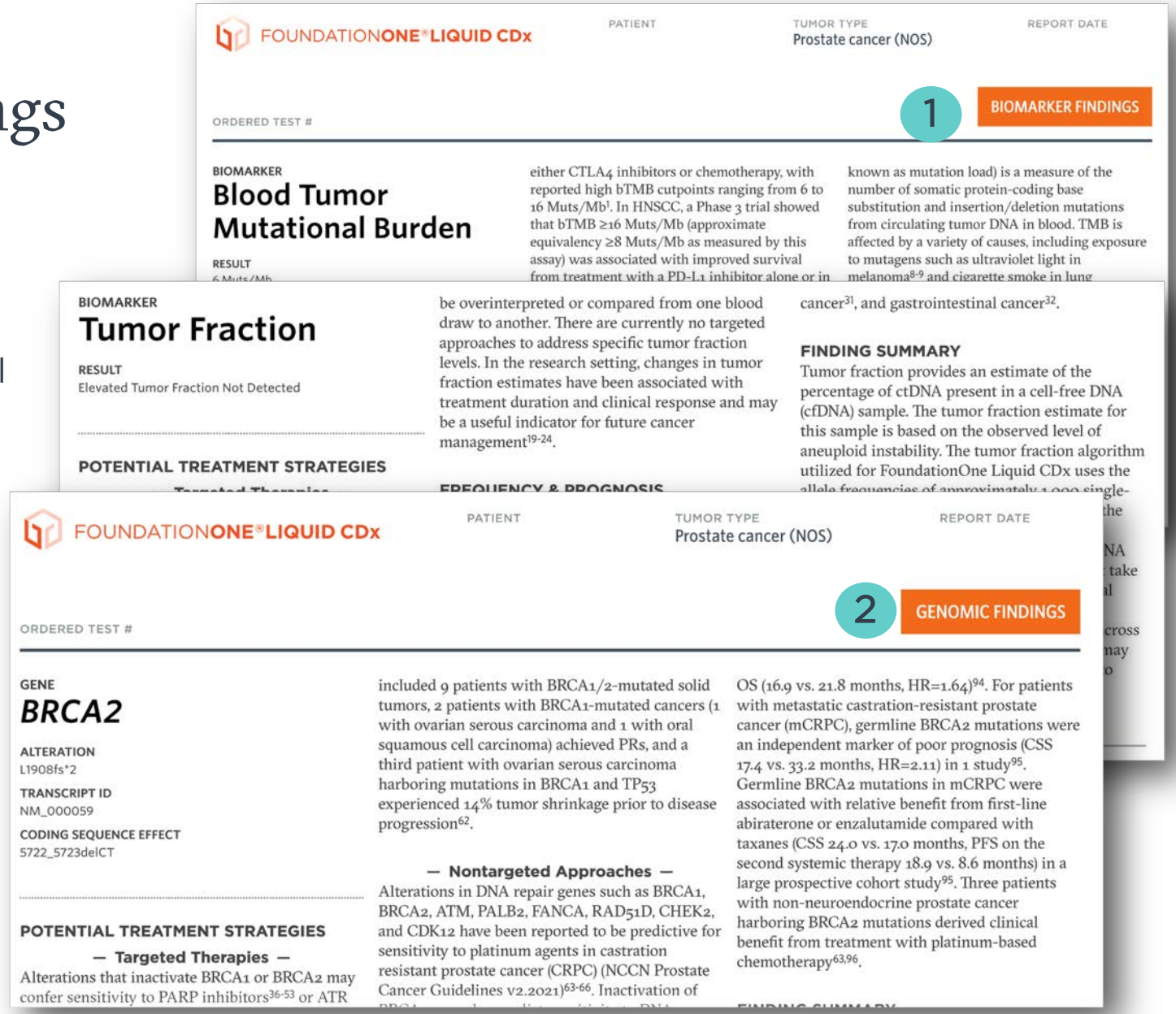
Prostate Cancer

1 Biomarker Findings

- Result
- Potential Treatment Strategies (pre-clinical and clinical evidence)
- Frequency and Prognosis (disease-specific)
- Finding Summary (result, relevance)

2 Genomic Findings

- Gene Variant Information
- Potential Treatment Strategies: Clinical relevance
- Frequency and Prognosis: In the specimen tumor type and/or other tumor types
- Finding Summary: Gene, function, biological implication of the alteration


FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

1 BIOMARKER FINDINGS

BIOMARKER
Blood Tumor Mutational Burden

RESULT

either CTLA4 inhibitors or chemotherapy, with reported high bTMB cutpoints ranging from 6 to 16 Muts/Mb[1]. In HNSCC, a Phase 3 trial showed that bTMB ≥16 Muts/Mb (approximate equivalency ≥8 Muts/Mb as measured by this assay) was associated with improved survival from treatment with a PD-L1 inhibitor alone or in

known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations from circulating tumor DNA in blood. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[8-9] and cigarette smoke in lung

BIOMARKER
Tumor Fraction

RESULT
Elevated Tumor Fraction Not Detected

be overinterpreted or compared from one blood draw to another. There are currently no targeted approaches to address specific tumor fraction levels. In the research setting, changes in tumor fraction estimates have been associated with treatment duration and clinical response and may be a useful indicator for future cancer management[19-24].

cancer[31], and gastrointestinal cancer[32].

FINDING SUMMARY
Tumor fraction provides an estimate of the percentage of ctDNA present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate for this sample is based on the observed level of aneuploid instability. The tumor fraction algorithm utilized for FoundationOne Liquid CDx uses the

POTENTIAL TREATMENT STRATEGIES

FREQUENCY & PROGNOSIS

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

2 GENOMIC FINDINGS

GENE
BRCA2

ALTERATION
L1908fs*2

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
5722_5723delCT

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[62].

OS (16.9 vs. 21.8 months, HR=1.64)[94]. 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[95]. 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[95]. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy[63,96].

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[36-53] or ATR

— Nontargeted Approaches —

Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, FANCA, 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)[63-66]. Inactivation of

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Potential Germline Implications

Prostate Cancer

1 Potential Germline Implications

Reported for genes identified by the American College of Medical Genetics and Genomics for reporting of incidental findings in clinical exome and genomic sequencing[1]

Recommendation for follow-up germline testing in the appropriate clinical context included

FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

GENOMIC FINDINGS

GENE
BRCA2

ALTERATION
L1908fs*2

TRANSCRIPT ID
NM_000059

CODING SEQUENCE EFFECT
5722_5723delCT

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[36-53] or ATR inhibitors[54-56]. 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[56]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[57], ovarian carcinoma[58], and triple-negative breast cancer (TNBC)[59] 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)[60]. 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[61]. 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[62].

— Nontargeted Approaches —

Alterations in DNA repair genes such as BRCA1, BRCA2, ATM, PALB2, FANCA, 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)[63-66]. Inactivation of BRCA2 may also predict sensitivity to DNA-damaging drugs such as trabectedin, lurbinectedin, and the platinum chemotherapies cisplatin and carboplatin[67-77].

FREQUENCY & PROGNOSIS

BRCA2 mutations have been identified in 3–6% of primary and 6–7% of metastatic prostate cancer specimens[78-80], with deleterious germline mutations present in 5% of men with metastatic prostate cancer[81]. BRCA2 homozygous deletion has been reported in 3–6% of prostate adenocarcinoma cases[82-84]. 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[85]. BRCA2 germline mutations predict poor prognosis for patients with prostate cancer (NCCN Prostate Cancer Guidelines v2.2021)[86-92] and have been associated with attributes of aggressive prostate cancer at diagnosis, including high Gleason score, nodal involvement, advanced tumor stage, and metastatic spread[86]. Germline BRCA2 mutation carriers had a significantly shorter cause-specific survival (CSS, 8.6 vs. 15.7 years) than noncarriers[86]. 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[93]. Patients with germline or somatic BRCA2 mutations have been reported to experience significantly shorter time to castration resistant disease progression on first-line abiraterone or enzalutamide treatment (9.4 vs. 18.4 months, HR=1.58) and significantly shorter OS (16.9 vs. 21.8 months, HR=1.64)[94]. 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[95]. 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[95]. Three patients with non-neuroendocrine prostate cancer harboring BRCA2 mutations derived clinical benefit from treatment with platinum-based chemotherapy[63,96].

FINDING SUMMARY

The BRCA2 tumor suppressor gene encodes a protein that regulates the response to DNA damage[97]. Inactivating mutations in BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis[98]. Alterations such as seen here may disrupt BRCA2 function or expression[97,99-114].

1

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) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2021)[115]. 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[116-117], 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[118]. 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%[119]. 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[118,120-125]. In the appropriate clinical context, germline testing of BRCA2 is recommended.

Current as of January 18, 2022.

1. National Center for Biotechnology Information. Clinvar. Accessed December 2020. https://www.ncbi.nlm.nih.gov/clinvar/.

FOUNDATION MEDICINE

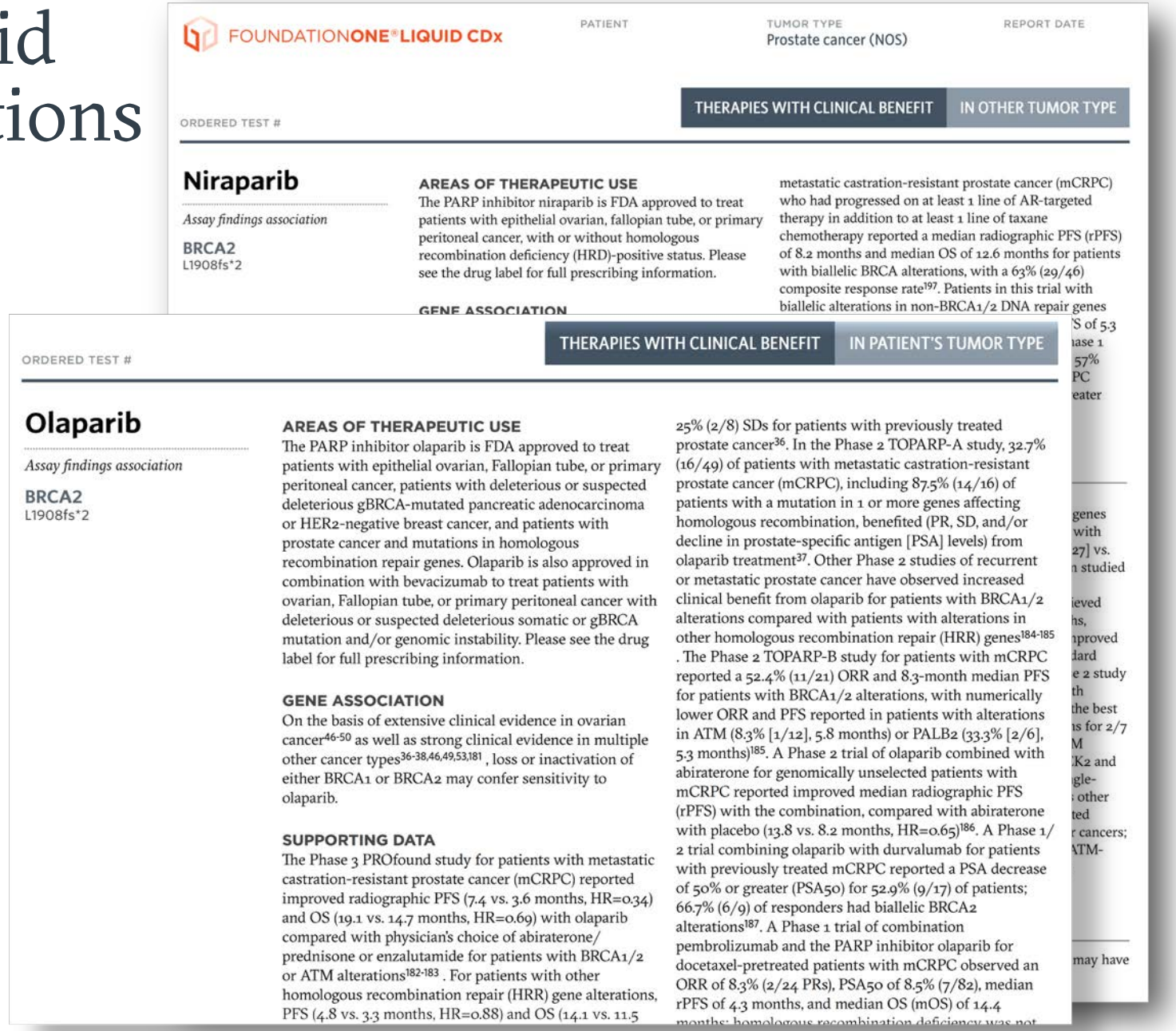
FoundationOne®Liquid CDx: Therapeutic Options Section

Prostate Cancer

Therapies With Clinical Benefit in Patient's Tumor Type and in Other Tumor Type

- FDA Approved Indications
- Gene Association
- Supporting Data *(Clinical evidence by phase)*

Includes details on therapies to which the patient's cancer may be sensitive based on the genomic profile



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

THERAPIES WITH CLINICAL BENEFIT | IN OTHER TUMOR TYPE

Niraparib

Assay findings association

BRCA2
L1908fs*2

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

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[197]. Patients in this trial with biallelic alterations in non-BRCA1/2 DNA repair genes

ORDERED TEST #

THERAPIES WITH CLINICAL BENEFIT | IN PATIENT'S TUMOR TYPE

Olaparib

Assay findings association

BRCA2
L1908fs*2

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[46-50] as well as strong clinical evidence in multiple other cancer types[36-38,46,49,53,181] , 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 (7.4 vs. 3.6 months, HR=0.34) and OS (19.1 vs. 14.7 months, HR=0.69) with olaparib compared with physician's choice of abiraterone/prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations[182-183] . For patients with other homologous recombination repair (HRR) gene alterations, PFS (4.8 vs. 3.3 months, HR=0.88) and OS (14.1 vs. 11.5

25% (2/8) SDs for patients with previously treated prostate cancer[36]. 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[37]. 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[184-185] . 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)[185]. 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)[186]. 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[187]. 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

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Clinical Trials Section

Prostate Cancer

Clinical Trials

- **Gene, alteration**
- **Rationale**
- **Trial Options:** Ordered by gene and prioritized based on age range, proximity to ordering medical facility, trial phase (favoring later phases), and whether trial information has been verified within the last 2 months

Select subset of currently available clinical trials for which the patient may be eligible. Includes: Trial ID, Title, Phase, Relevant Targets, and 10 closest locations to the ordering medical facility

FOUNDATIONONE®LIQUID CDx

PATIENT | TUMOR TYPE: Prostate cancer (NOS) | REPORT DATE

ORDERED TEST #

CLINICAL TRIALS

IMPORTANT NOTE Clinical trials are ordered by gene and prioritized by (in order of descending priority): 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. 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.

GENE
BRCA2

ALTERATION
L1908fs*2

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

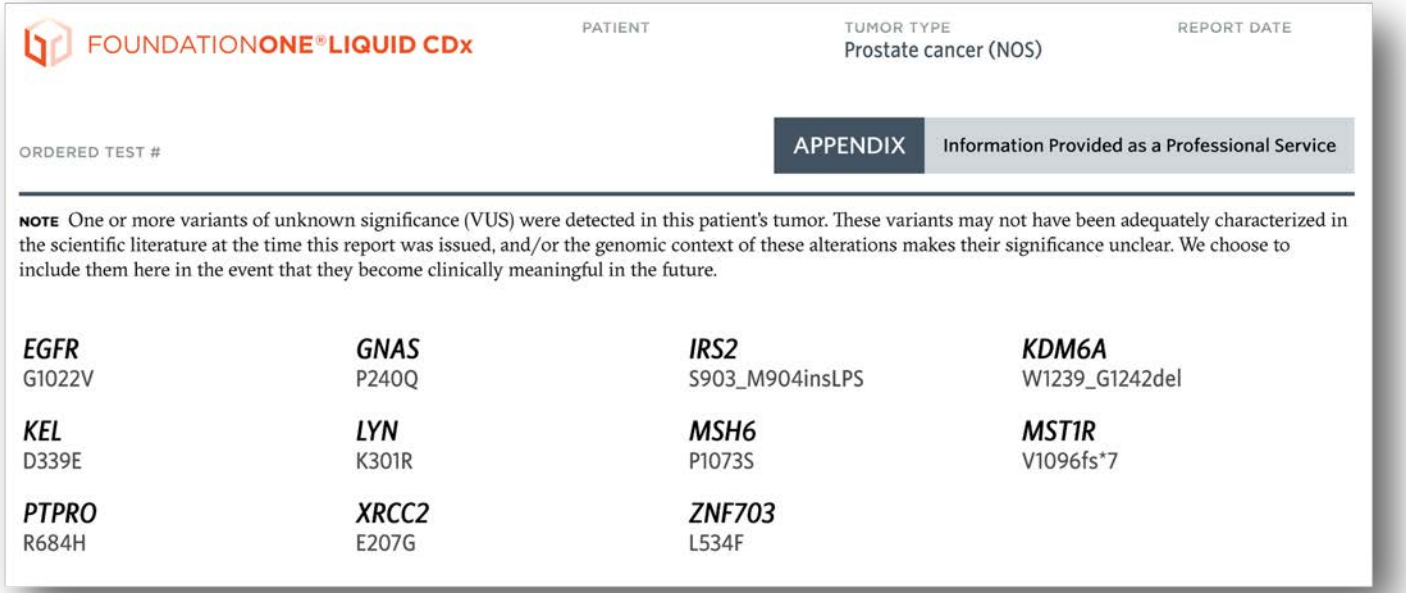
NCT03395197		**PHASE 3**
Talazoparib + Enzalutamide vs. Enzalutamide Monotherapy in mCRPC (TALAPRO-2)		**TARGETS** PARP
LOCATIONS: Pennsylvania, Virginia, New Jersey, New York		
NCT02975934		**PHASE 3**
A Study of Rucaparib Verses Physician's Choice of Therapy in Patients With Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency		**TARGETS** CYP17, PARP, AR
LOCATIONS: Delaware, Maryland, New York, Connecticut, Virginia, Toronto (Canada), Oshawa (Canada)		
NCT04288687		**PHASE 2**
A Trial of Niraparib in Platinum-Sensitive Castration-Resistant Prostate Cancer With DNA Repair Defects		**TARGETS** PARP
LOCATIONS: Pennsylvania		
NCT03221400		**PHASE 1/2**
PEN-866 in Patients With Advanced Solid Malignancies		**TARGETS** PARP, HSP90
LOCATIONS: Pennsylvania, Maryland, Virginia, Michigan, South Carolina, Tennessee, Florida		
NCT03047135		**PHASE 2**
Olaparib in Men With High-Risk Biochemically-Recurrent Prostate Cancer Following Radical Prostatectomy, With Integrated Biomarker Analysis		**TARGETS** PARP
LOCATIONS: Pennsylvania, Maryland, Nebraska		
NCT04038502		**PHASE 2**
Carboplatin or Olaparib for BRcA Deficient Prostate Cancer		**TARGETS** PARP
LOCATIONS: Pennsylvania, District of Columbia, New York, North Carolina, Michigan, Illinois, Florida, Washington, California		

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices

Prostate Cancer



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX | Information Provided as a Professional Service

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.

EGFR G1022V	***GNAS*** P240Q	***IRS2*** S903_M904insLPS	***KDM6A*** W1239_G1242del
KEL D339E	***LYN*** K301R	***MSH6*** P1073S	***MST1R*** V1096fs*7
PTPRO R684H	***XRCC2*** E207G	***ZNF703*** L534F	

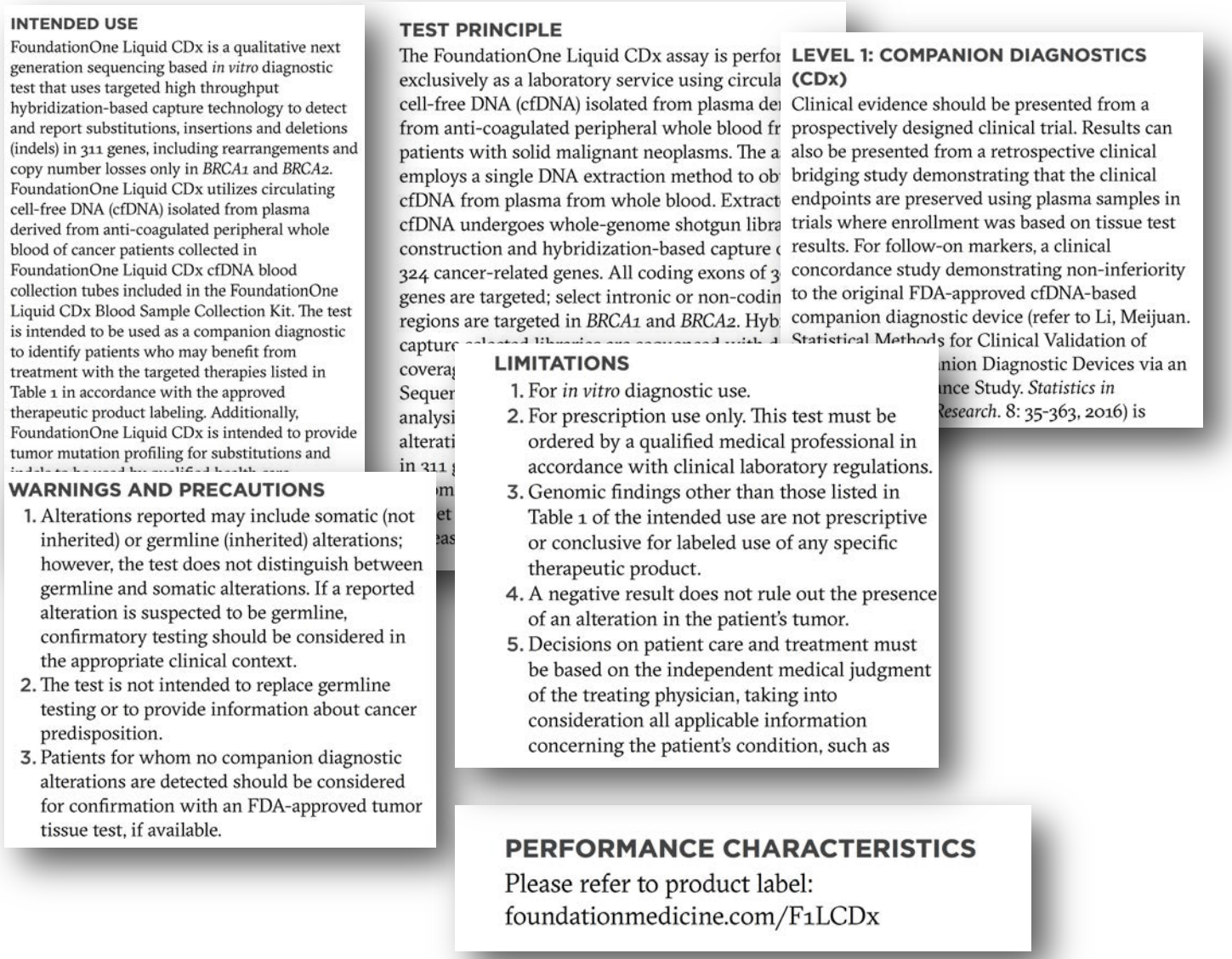
Variants of Unknown Significance (VUS)
Alterations not adequately characterized in the scientific literature and/or have unclear significance based on genomic context

**VUS are included for completeness should the alterations become clinically meaningful in the future.*

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)



INTENDED USE

FoundationOne Liquid CDx is a qualitative next generation sequencing based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements and copy number losses only in *BRCA1* and *BRCA2*. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne Liquid CDx cfDNA blood collection tubes included in the FoundationOne Liquid CDx Blood Sample Collection Kit. The test is intended to be used 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 Liquid CDx is intended to provide tumor mutation profiling for substitutions and

TEST PRINCIPLE

The FoundationOne Liquid CDx assay is perfor
exclusively as a laboratory service using circula
cell-free DNA (cfDNA) isolated from plasma de
from anti-coagulated peripheral whole blood fr
patients with solid malignant neoplasms. The a
employs a single DNA extraction method to ob
cfDNA from plasma from whole blood. Extract
cfDNA undergoes whole-genome shotgun libra
construction and hybridization-based capture
324 cancer-related genes. All coding exons of 3
genes are targeted; select intronic or non-codin
regions are targeted in *BRCA1* and *BRCA2*. Hyb
capture
coverag
Sequer
analysi
alterati
in 311

LEVEL 1: COMPANION DIAGNOSTICS (CDx)

Clinical evidence should be presented from a prospectively designed clinical trial. Results can also be presented from a retrospective clinical bridging study demonstrating that the clinical endpoints are preserved using plasma samples in trials where enrollment was based on tissue test results. For follow-on markers, a clinical concordance study demonstrating non-inferiority to the original FDA-approved cfDNA-based companion diagnostic device (refer to Li, Meijuan. Statistical Methods for Clinical Validation of
nion Diagnostic Devices via an
nce Study. *Statistics in*
Research. 8: 35-363, 2016) is

LIMITATIONS

1. For *in vitro* diagnostic use.
2. For prescription use only. This test must be ordered by a qualified medical professional in accordance with clinical laboratory regulations.
3. Genomic findings other than those listed in Table 1 of the intended use are not prescriptive or conclusive for labeled use of any specific therapeutic product.
4. A negative result does not rule out the presence of an alteration in the patient's tumor.
5. 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

WARNINGS AND PRECAUTIONS

1. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
2. The test is not intended to replace germline testing or to provide information about cancer predisposition.
3. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an FDA-approved tumor tissue test, if available.

PERFORMANCE CHARACTERISTICS

Please refer to product label:
foundationmedicine.com/F1LCDx

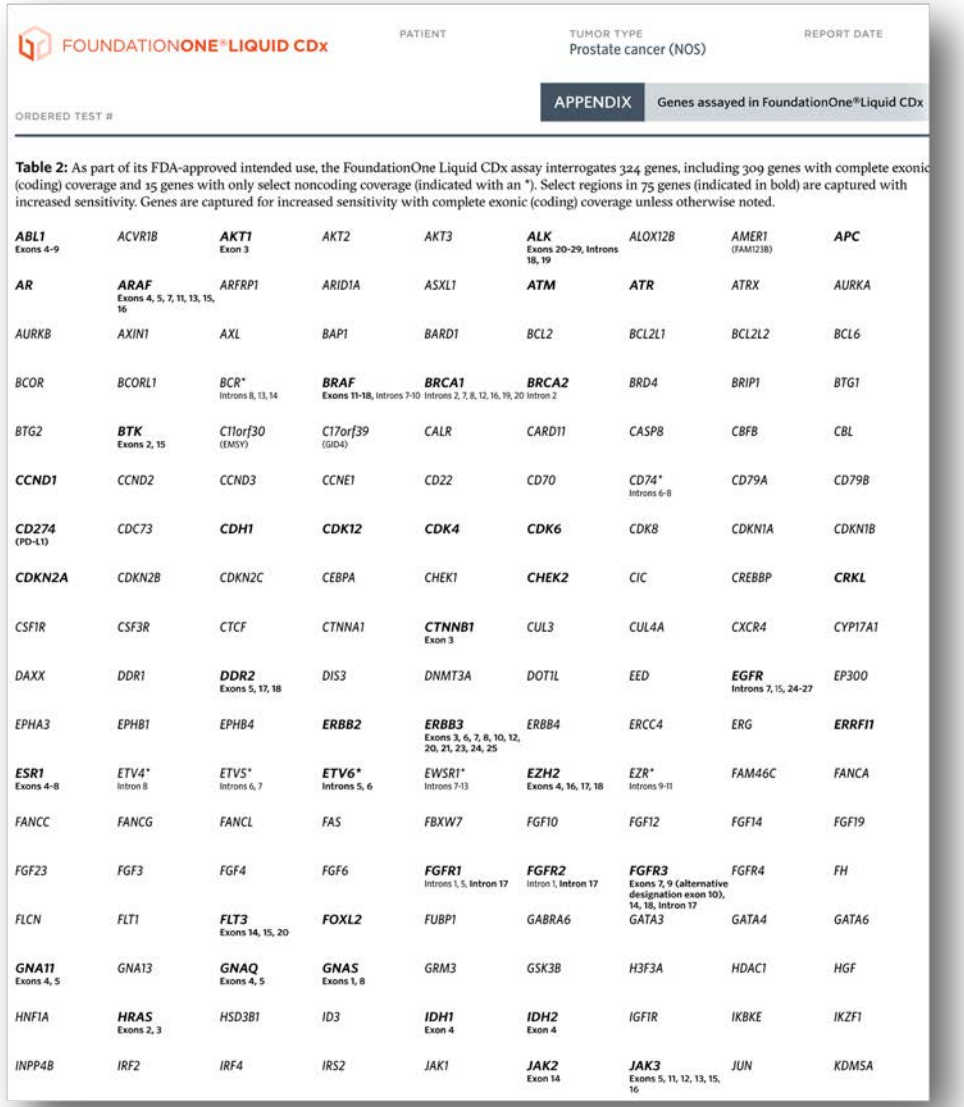
About FoundationOne®Liquid CDx

- Intended Use (FDA approved indications)
- Test Principle, Performance Characteristics, Limitations, Levels of Evidence

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)



FOUNDATIONONE®LIQUID CDx

PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

APPENDIX Genes assayed in FoundationOne®Liquid CDx

Table 2: As part of its FDA-approved intended use, the FoundationOne Liquid CDx assay interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select noncoding coverage (indicated with an *). Select regions in 75 genes (indicated in bold) are captured with increased sensitivity. Genes are captured for increased sensitivity with complete exonic (coding) coverage unless otherwise noted.

ABL1 Exons 4-9	ACVR1B	**AKT1** Exon 3	AKT2	AKT3	**ALK** Exons 20-29, Introns 18, 19	ALOX12B	AMER1 (FAM123B)	**APC**
AR	**ARAF** Exons 4, 5, 7, 11, 13, 15, 16	ARFRP1	ARID1A	ASXL1	**ATM**	**ATR**	ATRX	AURKA
AURKB	AXIN1	AXL	BAP1	BARD1	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BCR* Introns 8, 13, 14	**BRAF** Exons 11-18, Introns 7-10	**BRCA1** Introns 2, 7, 8, 12, 16, 19, 20	**BRCA2** Intron 2	BRD4	BRIP1	BTG1
BTG2	**BTK** Exons 2, 15	C11orf30 (EMSY)	C17orf39 (GID4)	CALR	CARD11	CASP8	CBFB	CBL
CCND1	CCND2	CCND3	CCNE1	CD22	CD70	CD74* Introns 6-8	CD79A	CD79B
CD274 (PD-L1)	CDC73	**CDH1**	**CDK12**	**CDK4**	**CDK6**	CDK8	CDKN1A	CDKN1B
CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	**CHEK2**	CIC	CREBBP	**CRKL**
CSF1R	CSF3R	CTCF	CTNNA1	**CTNNB1** Exon 3	CUL3	CUL4A	CXCR4	CYP17A1
DAXX	DDR1	**DDR2** Exons 5, 17, 18	DIS3	DNMT3A	DOT1L	EED	**EGFR** Introns 7, 15, 24-27	EP300
EPHA3	EPHB1	EPHB4	**ERBB2**	**ERBB3** Exons 3, 6, 7, 8, 10, 12, 20, 21, 23, 24, 25	ERBB4	ERCC4	ERG	**ERRFI1**
ESR1 Exons 4-8	ETV4* Intron 8	ETV5* Introns 6, 7	**ETV6*** Introns 5, 6	EWSR1* Introns 7-13	**EZH2** Exons 4, 16, 17, 18	EZR* Introns 9-11	FAM46C	FANCA
FANCC	FANCG	FANCL	FAS	FBXW7	FGF10	FGF12	FGF14	FGF19
FGF23	FGF3	FGF4	FGF6	**FGFR1** Introns 1, 5, Intron 17	**FGFR2** Intron 1, Intron 17	**FGFR3** Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17	FGFR4	FH
FLCN	FLT1	**FLT3** Exons 14, 15, 20	**FOXL2**	FUBP1	GABRA6	GATA3	GATA4	GATA6
GNA11 Exons 4, 5	GNA13	**GNAQ** Exons 4, 5	**GNAS** Exons 1, 8	GRM3	GSK3B	H3F3A	HDAC1	HGF
HNF1A	**HRAS** Exons 2, 3	HSD3B1	ID3	**IDH1** Exon 4	**IDH2** Exon 4	IGF1R	IKBKE	IKZF1
INPP4B	IRF2	IRF4	IRS2	JAK1	**JAK2** Exon 14	**JAK3** Exons 5, 11, 12, 13, 15, 16	JUN	KDM5A

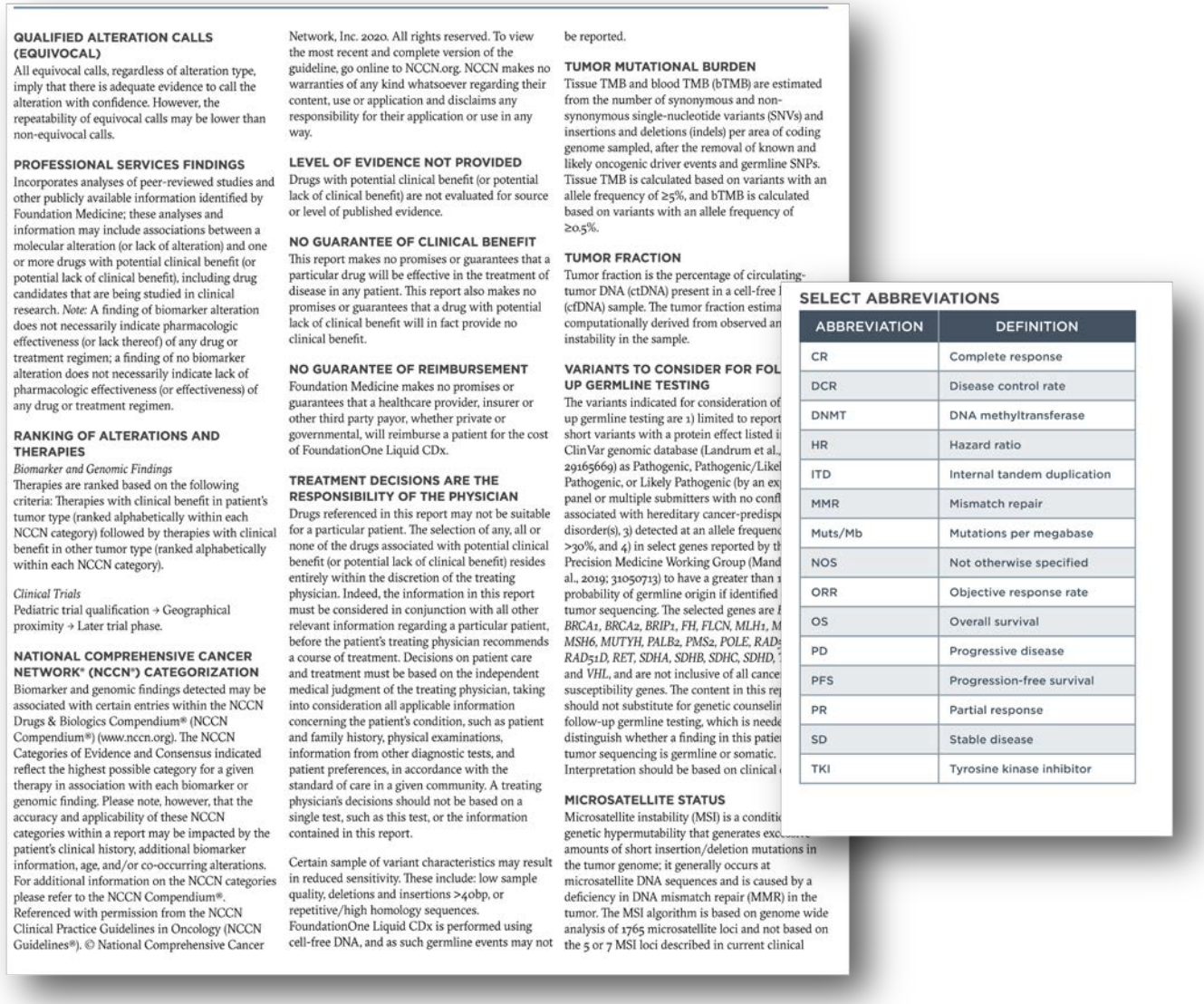
Genes Assayed in FoundationOne®Liquid CDx

FDA-approved intended use list interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage; select genes and exons are captured with increased sensitivity

Current as of January 18, 2022.

FOUNDATION MEDICINE

FoundationOne®Liquid CDx: Appendices (cont.)



QUALIFIED ALTERATION CALLS (EQUIVOCAL)
All equivocal calls, regardless of alteration type, imply that there is adequate evidence to call the alteration with confidence. However, the repeatability of equivocal calls may be lower than non-equivocal calls.

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
This report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in 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 Liquid CDx.

TREATMENT DECISIONS ARE THE RESPONSIBILITY OF THE PHYSICIAN
Drugs referenced in this report 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 entirely within the discretion of the treating 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.

Certain sample of variant characteristics may result in reduced sensitivity. These include: low sample quality, deletions and insertions >40bp, or repetitive/high homology sequences. FoundationOne Liquid CDx is performed using cell-free DNA, and as such germline events may not be reported.

TUMOR MUTATIONAL BURDEN
Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and non-synonymous single-nucleotide variants (SNVs) and insertions and deletions (indels) per area of coding genome sampled, after the removal of known and likely oncogenic driver events and germline SNPs. Tissue TMB is calculated based on variants with an allele frequency of ≥5%, and bTMB is calculated based on variants with an allele frequency of ≥0.5%.

TUMOR FRACTION
Tumor fraction is the percentage of circulating-tumor DNA (ctDNA) present in a cell-free
(cfDNA) sample. The tumor fraction estima
computationally derived from observed an
instability in the sample.

**VARIANTS TO CONSIDER FOR FOL
UP GERMLINE TESTING**
The variants indicated for consideration of
up germline testing are 1) limited to report
short variants with a protein effect listed i
ClinVar genomic database (Landrum et al.,
29165669) as Pathogenic, Pathogenic/Likel
Pathogenic, or Likely Pathogenic (by an ex
panel or multiple submitters with no confl
associated with hereditary cancer-predisp
disorder(s), 3) detected at an allele frequenc
>30%, and 4) in select genes reported by th
Precision Medicine Working Group (Mand
al., 2019; 31050713) to have a greater than
probability of germline origin if identified
tumor sequencing. The selected genes are
*BRCA1, BRCA2, BRIP1, FH, FLCN, MLH1, M
MSH6, MUTYH, PALB2, PMS2, POLE, RAD5
RAD51D, RET, SDHA, SDHB, SDHC, SDHD,
and VHL*, and are not inclusive of all cance
susceptibility genes. The content in this re
should not substitute for genetic counselin
follow-up germline testing, which is neede
distinguish whether a finding in this patie
tumor sequencing is germline or somatic.
Interpretation should be based on clinical

MICROSATELLITE STATUS
Microsatellite instability (MSI) is a conditi
genetic hypermutability that generates exc
amounts of short insertion/deletion mutations in the tumor genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor. The MSI algorithm is based on genome wide analysis of 1765 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical

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

Information Provided as a Professional Service
Several categories of information:

- Qualified Alteration Calls, Rankings, Qualifiers
- Responsibility of Physician for Treatment Decisions
- Variants to Consider for Follow-up Germline Testing
- Select Abbreviations

Current as of January 18, 2022.

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FoundationOne®Liquid CDx: Appendices (cont.)

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PATIENT

TUMOR TYPE
Prostate cancer (NOS)

REPORT DATE

ORDERED TEST #

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