FOUNDATIONONE®LIQUID CDx

PATIENT
Lin, Chia-Mao

TUMOR TYPE
Prostate acinar adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
22 Jun 2022
ORDERED TEST #
ORD-1388893-01

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

PATIENT
DISEASE Prostate acinar adenocarcinoma
NAME Lin, Chia-Mao
DATE OF BIRTH 22 April 1949
SEX Male
MEDICAL RECORD # 18448925

PHYSICIAN
ORDERING PHYSICIAN Yeh, Yi-Chen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN ID C.M.L. 04/22/1949
SPECIMEN TYPE Blood
DATE OF COLLECTION 09 June 2022
SPECIMEN RECEIVED 13 June 2022

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.

ATM L2535fs*1
DNMT3A Q842*
NOTCH3 A1927T
PTPN11 V428M

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 8)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***ATM* L2535fs*1** (p. 5)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***ATM* L2535fs*1** (p. 5), ***DNMT3A* Q842*** (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).**

GENOMIC FINDINGS		VAF %	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
ATM -	L2535fs*1	0.81%	Olaparib [1]	Niraparib
			Rucaparib	Talazoparib

10 Trials see p. 10

[ ] *NCCN category*

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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.

ATM **-** L2535fs*1 ..... p. 5
DNMT3A **-** Q842* ..... p. 6

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.

DNMT3A **-** Q842* ..... p. 6
NOTCH3 **-** A1927T ..... p. 6
PTPN11 **-** V428M ..... p. 7

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the therapies listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and/or exhaustive. Neither the therapies nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies. Therapies contained in this report may have been approved by the US FDA or other national authorities; however, they might not have been approved in your respective country. In the appropriate clinical context, germline testing of *APC*, *ATM*, *BAP1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FH*, *FLCN*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF1*, *NF2*, *PALB2*, *PMS2*, *POLE*, *PTEN*, *RAD51C*, *RAD51D*, *RB1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TGFBR2*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1* is recommended.

Variant Allele Frequency is not applicable for copy number alterations.

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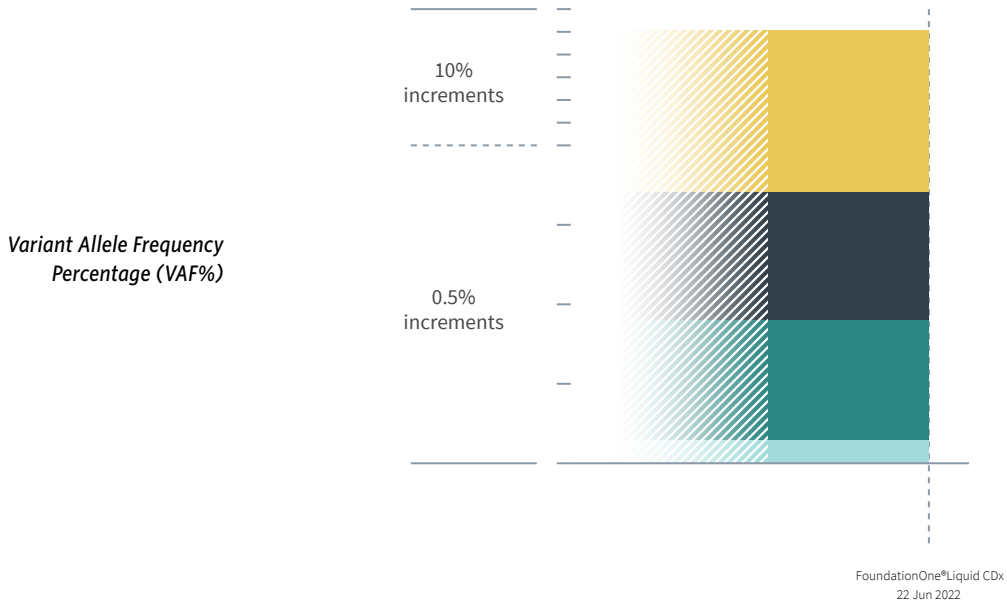

HISTORIC PATIENT FINDINGS		ORD-1388893-01 VAF%
Blood Tumor Mutational Burden		6 Muts/Mb
Microsatellite status		MSI-High Not Detected
Tumor Fraction		Elevated Tumor Fraction Not Detected
ATM	● L2535fs*1	0.81%
DNMT3A	● Q842*	0.75%
NOTCH3	● A1927T	51.0%
PTPN11	● V428M	0.15%

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.

For some genes in FoundationOne Liquid CDx, only select exons are assayed. Therefore, an alteration found by a previous test may not have been confirmed despite overlapping gene lists. Please refer to the Appendix for the complete list of genes and exons assayed. The gene and biomarker list will be updated periodically to reflect new knowledge about cancer biology.

As new scientific information becomes available, alterations that had previously been listed as Variants of Unknown Significance (VUS) may become reportable.

Tissue Tumor Mutational Burden (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%.

Not Tested = not baited, not reported on test, or test preceded addition of biomarker or gene

Not Detected = baited but not detected on test

Detected = present (VAF% is not applicable)

VAF% = variant allele frequency percentage

Cannot Be Determined = Sample is not of sufficient data quality to confidently determine biomarker status

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BIOMARKER

Blood Tumor Mutational Burden

RESULT

6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in NSCLC and HSNCC, increased bTMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[1-2] and anti-PD-1[3] therapies. In NSCLC, multiple clinical trials have shown patients with higher bTMB derive clinical benefit from immune checkpoint inhibitors following single agent or combination treatments with 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 combination with a CTLA-4 inhibitor[4].

FREQUENCY & PROGNOSIS

Average bTMB levels in solid tumors other than NSCLC have not been evaluated (cBioPortal, COSMIC, PubMed, Mar 2022)[5-7]. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2022).

FINDING SUMMARY

Blood tumor mutational burden (bTMB, also 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 cancer[10-11], treatment with temozolomide-based chemotherapy in glioma[12-13], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[14-18], and microsatellite instability (MSI)[14,17-18]. High bTMB levels were not detected in this sample. It is unclear whether the bTMB levels in this sample would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[1-3]. Depending on the clinical context, TMB testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Fraction

RESULT

Elevated Tumor Fraction Not Detected

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Specimens with elevated tumor fraction values have high circulating-tumor DNA (ctDNA) content, and thus high sensitivity for identifying genomic alterations. Such specimens are at low risk of false negative results. However, if elevated tumor fraction is not detected, it does not exclude the presence of disease burden or compromise the confidence of reported alterations. Tumor fraction levels currently have limited implications for diagnosis, surveillance, or therapy and should not 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].

FREQUENCY & PROGNOSIS

Detectible ctDNA levels have been reported in a variety of tumor types, with higher tumor fraction levels reported for patients with metastatic (Stage 4) tumors compared with patients with localized disease (Stages 1 to 3)[25]. Elevated tumor fraction levels have been reported to be associated with worse prognosis in a variety of cancer types, including pancreatic cancer[26], Ewing sarcoma and osteosarcoma[27], prostate cancer[22], breast cancer[28], leiomyosarcoma[29], esophageal cancer[30], colorectal 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 allele frequencies of approximately 1,000 single-nucleotide polymorphism (SNP) sites across the genome. Unlike the maximum somatic allele frequency (MSAF) method of estimating ctDNA content[33], the tumor fraction metric does not take into account the allele frequency of individual variants but rather produces a more holistic estimate of ctDNA content using data from across the genome. The amount of ctDNA detected may correlate with disease burden and response to therapy[34-35].

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GENE
ATM

ALTERATION
L2535fs*1

TRANSCRIPT ID
NM_000051

CODING SEQUENCE EFFECT
7603delC

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Loss of functional ATM results in a defective DNA damage response and homologous recombination-mediated DNA repair and may predict sensitivity to PARP inhibitors[36-37]. Clinical responses have been reported for patients with ATM-mutated prostate cancer treated with PARP inhibitors[38-40] and PARP inhibitors have shown limited clinical benefit for patients with other ATM-mutated solid tumors including pancreatic cancer[41-42] , colorectal cancer[43], papillary renal cell carcinoma[44], ovarian cancer[45], small cell bowel cancer,[42], and biliary tract cancer[46]. 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)[47]. In Phase 1 trials of ATR inhibitors, a heavily pretreated patient with colorectal cancer who achieved a CR to berzosertib[48] and 4 out of 4 patients with diverse solid tumors who achieved PRs to BAY1895344[49] harbored ATM inactivation or protein loss; studies showing reduced cell viability and increased DNA damage in preclinical models of solid tumors[50-52] and hematologic malignancies[50,53] also support the increased sensitivity of ATM-deficient cells to ATR inhibitors. Preclinical experiments also indicate that loss of ATM causes dependency on DNA-PKcs in cancer cells; DNA-PKcs inhibitors promoted apoptosis in ATM-deficient cells and were active in a lymphoma mouse model lacking ATM activity[54].

— 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, v3.2022)[55-58]. Clinical data from small retrospective studies[59] and case reports[60-64] are conflicting as to whether alterations in DNA repair genes such as BRCA1, BRCA2, and ATM are associated with outcomes for patients with CRPC treated with PSMA-targeted radionuclide-based therapies such as lutetium Lu 177 vipivotide tetraxetan (177Lu-PSMA-617).

FREQUENCY & PROGNOSIS

ATM mutations have been reported in 2-6% of prostate tumors, including in 2% of localized prostate cancers and in 6% of metastatic castration-resistant prostate cancers[65-67]. In advanced prostate cancer tissue samples, ATM deep deletion has been observed in 0-2% of cases[66-68]. ATM mutations have been detected in liquid biopsies for 3-9% of patients with metastatic prostate cancer and circulating tumor DNA[69] and may be more frequent in liquid compared to tissue biopsies[70]. An exome sequencing study of aggressive and non-aggressive prostate cancer cases reported that patients with pathogenic, likely pathogenic, or deleterious ATM mutations had statistically higher odds of aggressive disease (2.2-fold), death due to prostate cancer (2.2-fold), and metastatic disease (3.0-fold)[71]; however, ATM mutations in liquid or tissue biopsies of metastatic prostate cancer had no prognostic impact in two large retrospective studies[67,69]. ATM mutations also did not correlate with time on treatment with first-line abiraterone or enzalutamide for patients with metastatic castration-resistant prostate cancer[67].

FINDING SUMMARY

ATM encodes the protein ataxia telangiectasia mutated, which is a serine/threonine protein kinase that plays a key role in the DNA damage response[72]. Loss of functional ATM promotes tumorigenesis[73]. Alterations such as seen here may disrupt ATM function or expression[74-76].

POTENTIAL GERMLINE IMPLICATIONS

ATM mutation carriers have increased cancer risk, with female carriers displaying a 38% lifetime risk of breast cancer[77]. Biallelic mutations in ATM underlie the rare autosomal-recessive inherited disorder ataxia-telangiectasia (A-T), also referred to as genome instability or DNA damage response syndrome[78]. This disease is characterized by genomic instability, sensitivity to DNA-damaging agents, and increased risk of developing cancer[72,78]. The prevalence of A-T is estimated at 1:40,000 to 1:100,000 worldwide[78]. In the appropriate clinical context, germline testing of ATM is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[79-84]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[83,85-86]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
DNMT3A

ALTERATION
Q842*

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2524C>T

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in DNMT3A in solid tumors.

FREQUENCY & PROGNOSIS

DNMT3A alterations have been reported at relatively low frequencies in solid tumors and are more prevalent in hematological malignancies (cBioPortal, Feb 2022)[5-6]. Published data investigating the prognostic implications of DNMT3A alterations in solid tumors are limited (PubMed, Feb 2022).

FINDING SUMMARY

The DNMT3A gene encodes the protein DNA methyltransferase 3A, an enzyme that is involved in the methylation of newly synthesized DNA, a function critical for gene regulation[87-88]. The role of DNMT3A in cancer is uncertain, as some reports describe increased expression and contribution to tumor growth, whereas others propose a role for DNMT3A as a tumor suppressor[89-94]. Alterations such as seen here may disrupt DNMT3A function or expression[95-98].

POTENTIAL CLONAL HEMATOPOIESIS

IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[79-84]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[79-80]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[99]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[83,85-86]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
NOTCH3

ALTERATION
A1927T

TRANSCRIPT ID
NM_000435

CODING SEQUENCE EFFECT
5779G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Several approaches for inhibiting NOTCH3 signaling are being developed, including neutralizing NOTCH antibodies such as tarextumab (OMP-59R5)[100], which targets NOTCH2 and NOTCH3, and pan-NOTCH inhibitors, such as gamma-secretase inhibitors (GSI)[101-103]. In a Phase 2 study, the GSI AL101 (BMS-906024) elicited PR in 15% (6/39) and SD in 54% (21/39) of patients with metastatic adenoid cystic carcinoma harboring NOTCH activating alterations[104]. Phase 2 studies have evaluated the efficacy of tarextumab in combination with chemotherapy in metastatic pancreatic cancer or extensive-stage small cell lung cancer, though NOTCH3 expression was not found to be a predictor of OS or PFS in either study[105]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

NOTCH3 mutations have been reported in up to 2% of metastatic prostate cancers[66,106] but not in two other studies of prostate adenocarcinoma[107-108]. NOTCH3 amplification or overexpression has been associated with poor clinicopathological features in prostate carcinoma, although the role of NOTCH signaling in this disease is complex[109-110].

FINDING SUMMARY

NOTCH3 encodes a member of the NOTCH family of receptors, which are involved in cell fate determination and various developmental processes. Upon binding of membrane-bound ligands, NOTCH signaling involves cleavage of the NOTCH intracellular domain (NICD), which subsequently forms part of a transcription factor complex that regulates downstream target genes[111-112]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

GENE

PTPN11

ALTERATION
V428M

TRANSCRIPT ID
NM_002834

CODING SEQUENCE EFFECT
1282G>A

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

SHP-2 has been reported to activate the RAS-MEK-ERK, PI3K-AKT-mTOR, and SRC kinase pathways[113-116]. Based on a case study of a patient with histiocytic sarcoma harboring an activating PTPN11 mutation who experienced a PR to trametinib[117], as well as preclinical data[118-120], PTPN11 activation may predict sensitivity to MEK inhibitors in histiocytic neoplasms. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

PTPN11 mutations have been reported in <2% of prostate carcinoma cases[67,121]. A lower ratio of positive SHP-2 expression, measured by IHC, in tissue samples from patients with prostate cancer was associated with shorter time to biochemical recurrence (BCR)[122].

FINDING SUMMARY

PTPN11 encodes the protein tyrosine-protein phosphatase non-receptor type 11, also known as SHP-2. PTPN11 plays a critical role in both embryonic development and cancer[123]. PTPN11 is also known to be somatically mutated in a variety of cancers, where both oncogenic and tumor suppressor roles for PTPN11 have been described[124-126]. Although alterations such as seen here have not been fully characterized and are of unknown functional significance, similar alterations have been previously reported in the context of cancer, which may indicate biological relevance.

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in PTPN11 have been found in the developmental disorder Noonan syndrome, which predisposes individuals to various cancers, including embryonal rhabdomyosarcoma, neuroblastoma, and juvenile myelomonocytic leukemia[127-132].

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Olaparib

Assay findings association

ATM
L2535fs*1

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

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in prostate cancer[38-40,133] .

SUPPORTING DATA

The Phase 3 PROfound study for patients with metastatic castration-resistant prostate cancer (mCRPC) reported improved radiographic PFS (rPFS; 7.4 vs. 3.6 months, HR=0.34) and median OS (mOS; 19.1 vs. 14.7 months, HR=0.69) with olaparib compared with physician's choice of abiraterone plus prednisone or enzalutamide for patients with BRCA1/2 or ATM alterations[134-135] . For patients with other homologous recombination repair (HRR) gene alterations, PFS (4.8 vs. 3.3 months, HR=0.88) and mOS (14.1 vs. 11.5 months, HR=0.96) were numerically increased with olaparib[135]. Other studies, including the Phase 2 TOPARP-A and TOPARP-B studies, reported similar results[38-39,136] . In a real-world study of olaparib and/or rucaparib for heavily pretreated prostate cancer, patients with pathogenic BRCA2 mutations experienced greater benefit than patients with other HRR mutations (median PFS 7.2 vs. 2.8 months, p=0.291; PSA30 69.2% vs. 4.0%, p<0.001)[137]. In the Phase 3 PROpel study for patients with mCRPC, treatment with first-line olaparib plus abiraterone and prednisone led to significantly improved rPFS (25 vs. 17 months, HR=0.66) and prolonged time to first subsequent treatment (HR=0.74) and time to second PFS or death (HR=0.69) compared with placebo; patients benefited from the combination regardless of their HRR mutation status[138]. Benefits were also seen in Phase 1 or 2 studies of olaparib in combination with durvalumab[139], pembrolizumab[140-141] , or the ATP inhibitor ceralasertib[142] for patients with prostate cancer. PROfound patients with BRCA1/2 or ATM alterations also had improved ORR (33.3% [28/84] vs. 2.3% [1/43], p<0.001) with olaparib compared with physician's choice of enzalutamide or abiraterone/prednisone[134]. The Phase 2 TOPARP-A and -B olaparib trials reported PSA50 responses for 60% (3/5) and 5.2% (1/19) of patients with ATM-altered metastatic castration-resistant prostate cancer (mCRPC), respectively, as well as 1 PR and 1 SD >16 weeks[38-39] .

Rucaparib

Assay findings association

ATM
L2535fs*1

AREAS OF THERAPEUTIC USE

The PARP inhibitor rucaparib is FDA approved to treat patients with metastatic castration-resistant prostate cancer (mCRPC) or epithelial ovarian, Fallopian tube, or primary peritoneal cancer and deleterious somatic or germline BRCA mutations. Rucaparib is also approved as a maintenance treatment of patients with recurrent epithelial ovarian, Fallopian tube, or primary peritoneal cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in prostate cancer[38-40,133] .

SUPPORTING DATA

The Phase 2 TRITON2 study of rucaparib for patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious DNA-repair gene alterations reported an ORR of 44% (27/62, 7 CRs) and radiographic PFS of 9.0 months[143]. Objective responses were reported for patients with ATM, BRIP1, CHEK2, FANCA, PALB2, and RAD51B alterations[40]. In a real-world study of olaparib and/or rucaparib for heavily pretreated prostate cancer, patients with pathogenic BRCA2 mutations experienced greater benefit than patients with other HRR mutations (median PFS 7.2 vs. 2.8 months, p=0.291; PSA30 69.2% vs. 4.0%, p<0.001)[137]. The Phase 1b/2 BrUOG360 study of rucaparib combined with copanlisib to treat patients with mCRPC achieved a confirmed prostate-specific antigen (PSA) ≥50% decline for 2 patients (22%, 2/9), 1 of whom had a BRCA2 loss and 1 of whom had a PALB2 alteration[144]. A Phase 1b study of rucaparib combined with ipatasertib for patients with mCRPC reported a PSA ≥50% decline rate of 35% (9/26) and median OS of 13.3 months[145].

Niraparib

Assay findings association

ATM
L2535fs*1

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

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in prostate cancer[38-40,133] .

SUPPORTING DATA

The Phase 2 GALAHAD study of niraparib for patients with 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 an ORR of 34% (26/76) and a median radiographic PFS (rPFS) of 5.5 months for patients with biallelic BRCA1 or BRCA2 alterations[146]. Patients in this trial with biallelic alterations in non-BRCA1/2 DNA repair genes experienced an 11% (5/47) ORR[146]. In a Phase 1 study of niraparib for patients with solid tumors, 57% (12/21) of patients with locally advanced castration-resistant prostate cancer or mCRPC achieved SD, and 8 patients exhibited a decrease in circulating tumor cells ≥30%[147]. In the Phase 3 MAGNITUDE study for patients with homologous recombination repair (HRR) gene-altered mCRPC, treatment with first-line niraparib plus abiraterone and prednisone led to significantly improved rPFS (16.5 vs. 13.7 months, HR=0.73) and prolonged time to PSA progression (18.5 vs. 9.3 months, HR=0.57) compared with placebo; similar rPFS (16.6 vs. 10.9 months, HR=0.53) and time to PSA progression (not evaluable vs. 9.2 months, HR=0.46) were observed for patients harboring BRCA1/2 alterations, while no benefit was observed for patients without HRR gene alterations[148].

Talazoparib

Assay findings association

ATM
L2535fs*1

AREAS OF THERAPEUTIC USE

The PARP inhibitor talazoparib is FDA approved to treat HER2-negative locally advanced or metastatic breast cancer with deleterious or suspected deleterious germline BRCA mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

ATM inactivation may predict sensitivity to PARP inhibitors. ATM alterations have been associated with clinical benefit from PARP inhibitors in prostate cancer[38-40,133] .

SUPPORTING DATA

The Phase 2 TALAPRO-1 trial of talazoparib monotherapy for patients with docetaxel-treated metastatic castration-resistant prostate cancer (mCRPC) harboring alterations in DNA repair genes reported a study-wide ORR of 30% with median radiographic PFS (rPFS) of 5.6 months, with an ORR of 46% (28/61) and rPFS of 11.2 months for patients with BRCA1/2 mutations[149]. A retrospective subgroup analysis found no association between antitumor activity and germline homologous recombination repair alterations (gHRRm) (ORR: 31% [5/16] vs. 26% [14/54] in men with vs. without gHRRm, respectively); ORRs were also similar for patients with gHRRm or with only somatic HRRm (25% [10/40] vs. 19% [4/21], respectively, [p = 0.7528])[150].

NOTE Genomic alterations detected may be associated with activity of certain US FDA or other specific country approved therapies; however, the therapies listed in this report may have varied evidence in the patient's tumor type. The listed therapies are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. The therapies listed in this report may not be complete and/or exhaustive. Furthermore, the listed therapies are limited to US FDA approved pharmaceutical drug products that are linked to a specific genomic alteration. There may also be US FDA approved pharmaceutical drug products that are not linked to a genomic alteration. Further there may also exist pharmaceutical drug products that are not approved by the US FDA or other national authorities. There may also be other treatment modalities available than pharmaceutical drug products.

Electronically signed by Vamsi Parimi, M.D., M.P.H. | 22 June 2022
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IMPORTANT Clinical trials are ordered by gene and prioritized by: 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. There may also be compassionate use or early access programs available, which are not listed in this report. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type. 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. However, clinicaltrials.gov does not list all clinical trials that might be available.

GENE
ATM

ALTERATION
L2535fs*1

RATIONALE
Loss or inactivation of ATM may increase sensitivity to PARP inhibitors, ATR inhibitors, or DNA-PKcs inhibitors.

NCT04821622

PHASE 3

Study of Talazoparib With Enzalutamide in Men With DDR Gene Mutated mCSPC

TARGETS
PARP, AR

LOCATIONS: Taipei (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Ningbo (China), Hangzhou (China), Shanghai (China), Suzhou (China), Nantong (China), Nanjing (China)

NCT04691804

PHASE 3

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study of Fuzuloparib Combined With Abiraterone Acetate and Prednisone (AA-P) Versus Placebo Combined With AA-P as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer

TARGETS
CYP17, PARP

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Changhua (Taiwan), Fuzhou (China), Tainan (Taiwan), Kaohsiung (Taiwan), Hangzhou (China), Jiaxing (China), Shanghai (China)

NCT02861573

PHASE 1/2

Study of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (MK-3475-365/KEYNOTE-365)

TARGETS
AR, PD-1, PARP, CYP17

LOCATIONS: Taipei (Taiwan), Stockholm (Sweden), Istanbul (Turkey), Warsaw (Poland), Glostrup (Denmark), Auckland (New Zealand), Vienna (Austria), Haar (Germany), Haarlem (Netherlands), Rome (Italy)

NCT05171816

PHASE 3

Study on Olaparib Plus Abiraterone as First-line Therapy in Men With Metastatic Castration-resistant Prostate Cancer (China Cohort)

TARGETS
CYP17, PARP

LOCATIONS: Ningbo (China), Zhejiang (China), Shanghai (China), Nanchang (China), Nanjing (China), Guangzhou (China), Beijing (China), Hunan (China), Hubei (China), Henan (China)

NCT04768296

PHASE 2

Berzosertib + Topotecan in Relapsed Platinum-Resistant Small-Cell Lung Cancer (DDRiver SCLC 250)

TARGETS
TOP1, ATR

LOCATIONS: Zhejiang (China), Hangzhou (China), Nanjing (China), Wuhan (China), Xi'an (China), Osaka (Japan), Beijing (China), Hirakata-shi (Japan), Takatsuki-shi (Japan), Sichuan (China)

NCT05223582

PHASE 2

Fluzoparib and Abiraterone in the preSurgery Treatment of Prostate Cancer: FAST Trial

TARGETS
CYP17, PARP

LOCATIONS: Shanghai (China)

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: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Nedlands (Australia), Port Macquarie (Australia), Darlinghurst (Australia), Adana (Turkey), Ankara (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom), Villejuif (France)

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Seoul (Korea, Republic of), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Warszawa (Poland), Gdynia (Poland), Grzepnica (Poland), Budapest (Hungary), Brno (Czechia), Padova (Italy)

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.

CDKN2A/B
N141K

CSF1R
P927L

DNMT3A
C514W and L653V

FGF23
P110L

HNF1A
H302R

MUTYH
R412C

PDK1
R238C

RET
R540S

TNFAIP3
A595V

VHL
P2H

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APPENDIX Genes assayed in FoundationOne®Liquid CDx

FoundationOne Liquid CDx interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *) ; 75 genes (indicated in bold) are captured with increased sensitivity and have 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 or WTX)	***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**	*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**	*EMSY* (C11orf30)	*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	*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*	*GID4* (C17orf39)	***GNA11*** **Exons 4, 5**
GNA13	***GNAQ*** **Exons 4, 5**	***GNAS*** **Exons 1, 8**	*GRM3*	*GSK3B*	*H3-3A* (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,** Intron 16	*KLHL6*	*KMT2A* (MLL) Introns 6, 8-11, Intron 7	*KMT2D* (MLL2)	

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KRAS	*LTK*	*LYN*	*MAF*	***MAP2K1*** **(MEK1) Exons 2, 3**	***MAP2K2*** **(MEK2) Exons 2-4, 6, 7**	*MAP2K4*	*MAP3K1*	*MAP3K13*
MAPK1	*MCL1*	***MDM2***	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MERTK*	***MET***
MITF	*MKNK1*	*MLH1*	***MPL*** **Exon 10**	*MRE11* (MRE11A)	*MSH2* Intron 5	*MSH3*	*MSH6*	*MST1R*
MTAP	***MTOR*** **Exons 19, 30, 39, 40, 43-45, 47, 48, 53, 56**	*MUTYH*	*MYB** Intron 14	***MYC*** **Intron 1**	*MYCL* (MYCL1)	***MYCN***	***MYD88*** **Exon 4**	*NBN*
NF1	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2* Intron 26	*NOTCH3*	***NPM1*** **Exons 4-6, 8, 10**
NRAS **Exons 2, 3**	*NSD2* (WHSC1 or MMSET)	*NSD3* (WHSC1L1)	*NT5C2*	***NTRK1*** **Exons 14, 15, Introns 8-11**	*NTRK2* Intron 12	***NTRK3*** **Exons 16, 17**	*NUTM1** Intron 1	*P2RY8*
PALB2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1* (PD-1)	***PDCD1LG2*** **(PD-L2)**	***PDGFRA*** **Exons 12, 18, Introns 7, 9, 11**
PDGFRB **Exons 12-21, 23**	*PDK1*	*PIK3C2B*	*PIK3C2G*	***PIK3CA*** **Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)**	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PRKN* (PARK2)
PTCH1	***PTEN***	***PTPN11***	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*
RAD51C	*RAD51D*	*RAD52*	*RAD54L*	***RAF1*** **Exons 3, 4, 6, 7, 10, 14, 15, 17,** Introns 4-8	*RARA* Intron 2	***RB1***	*RBM10*	*REL*
RET Introns 7, 8, **Exons 11, 13-16, Introns 9-11**	*RICTOR*	*RNF43*	***ROS1*** **Exons 31, 36-38, 40, Introns 31-35**	*RPTOR*	*RSPO2** Intron 1	*SDC4** Intron 2	*SDHA*	*SDHB*
SDHC	*SDHD*	*SETD2*	*SF3B1*	*SGK1*	*SLC34A2** Intron 4	*SMAD2*	*SMAD4*	*SMARCA4*
SMARCB1	***SMO***	*SNCAIP*	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*
STAG2	*STAT3*	***STK11***	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C* (FAM46C)	*TERC** ncRNA
TERT* **Promoter**	*TET2*	*TGFBR2*	*TIPARP*	*TMPRSS2** Introns 1-3	*TNFAIP3*	*TNFRSF14*	***TP53***	*TSC1*
TSC2	*TYRO3*	*U2AF1*	***VEGFA***	*VHL*	*WT1*	*XPO1*	*XRCC2*	*ZNF217*
ZNF703								

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Blood Tumor Mutational Burden (bTMB)
Tumor Fraction

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FoundationOne Liquid CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. The CE-IVD regulatory status of FoundationOne Liquid CDx is applicable in countries that accept and/or recognize the CE mark.

CE IVD

ABOUT FOUNDATIONONE LIQUID CDx

FoundationOne Liquid CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Liquid CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details.

INTENDED USE

FoundationOne Liquid CDx is a next generation sequencing based *in vitro* diagnostic device that analyzes 324 genes. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The test also detects the genomic signatures blood tumor mutational burden (bTMB), microsatellite instability (MSI), and tumor fraction. FoundationOne Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from the anti-coagulated peripheral whole blood of cancer patients. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling. Additionally, FoundationOne Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with malignant neoplasms.

TEST PRINCIPLES

The FoundationOne Liquid CDx assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes including coding exons and select introns of 309 genes, as well as only select intronic regions or non-coding regions of 15 genes. Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq® 6000 platform. Sequence data are processed using a customized analysis pipeline designed to accurately detect genomic alterations, including base substitutions, indels, select copy number variants, and select genomic rearrangements. Substitutions and insertion and deletion alterations (indels) are reported in 311 genes, copy number alterations (CNAs) are reported in 310 genes, and gene rearrangements are reported in 324 genes. The assay also reports tumor fraction, and genomic signatures including MSI and bTMB. A subset of targeted regions in 75 genes is baited for increased sensitivity.

THE REPORT

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.

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.

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.

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. A negative result does not rule out the presence of a mutation below the limits of detection of the assay. Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an appropriately validated tumor tissue test, if available.
4. The FoundationOne Liquid CDx assay does not detect heterozygous deletions.
5. The test is not intended to provide information on cancer predisposition.
6. Performance has not been validated for cfDNA input below the specified minimum input.
7. Tissue TMB and blood TMB (bTMB) are estimated from the number of synonymous and nonsynonymous 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%.
8. Tumor fraction is the percentage of circulating tumor DNA (ctDNA) present in a cell-free DNA (cfDNA) sample. The tumor fraction estimate is computationally derived from the observed level of aneuploidy in the sample. Tumor fraction is considered elevated when ctDNA levels are high enough that aneuploidy can be detected and is significantly distinct from that typically found in non-tumor samples.
9. 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.
10. Genomic findings from circulating cell-free DNA (cfDNA) may originate from circulating tumor DNA fragments, germline alterations, or non-tumor somatic alterations, such as clonal hematopoiesis of indeterminate potential (CHIP). Genes with alterations that may be derived from CHIP include, but are not limited

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to: *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D* (*MLL2*), *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1*.

11. 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.
12. The test is not intended to replace germline testing or to provide information about cancer predisposition.

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 treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >30%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, ATM, CBL, CHEK2, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

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. 2022. 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 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.

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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

REFERENCE SEQUENCE INFORMATION

Sequence data is mapped to the human genome, Genome Reference Consortium Human Build 37 (GRCh37), also known as hg19.

MR Suite Version 6.3.0

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1. Gandara DR, et al. Nat. Med. (2018) pmid: 30082870
2. Wang Z, et al. JAMA Oncol (2019) pmid: 30816954
3. Aggarwal C, et al. Clin. Cancer Res. (2020) pmid: 32102950
4. Li et al., 2020; ASCO Abstract 6511
5. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
6. Gao J, et al. Sci Signal (2013) pmid: 23550210
7. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
8. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
9. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
10. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
11. Rizvi NA, et al. Science (2015) pmid: 25765070
12. Johnson BE, et al. Science (2014) pmid: 24336570
13. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
14. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
15. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
16. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
17. Nature (2012) pmid: 22810696
18. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
19. Bronkhorst AJ, et al. Biomol Detect Quantif (2019) pmid: 30923679
20. Raja R, et al. Clin. Cancer Res. (2018) pmid: 30093454
21. Hrebien S, et al. Ann. Oncol. (2019) pmid: 30860573
22. Choudhury AD, et al. JCI Insight (2018) pmid: 30385733
23. Goodall J, et al. Cancer Discov (2017) pmid: 28450425
24. Goldberg SB, et al. Clin. Cancer Res. (2018) pmid: 29330207
25. Bettegowda C, et al. Sci Transl Med (2014) pmid: 24553385
26. Lapin M, et al. J Transl Med (2018) pmid: 30400802
27. Shulman DS, et al. Br. J. Cancer (2018) pmid: 30131550
28. Stover DG, et al. J. Clin. Oncol. (2018) pmid: 29298117
29. Hemming ML, et al. JCO Precis Oncol (2019) pmid: 30793095
30. Egyud M, et al. Ann. Thorac. Surg. (2019) pmid: 31059681
31. Fan G, et al. PLoS ONE (2017) pmid: 28187169
32. Vu et al., 2020; DOI: 10.1200/PO.19.00204
33. Li G, et al. J Gastrointest Oncol (2019) pmid: 31602320
34. Zhang EW, et al. Cancer (2020) pmid: 32757294
35. Butler TM, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 30833418
36. Michels J, et al. Oncogene (2014) pmid: 24037533
37. Bryant HE, et al. Nucleic Acids Res. (2006) pmid: 16556909
38. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
39. Mateo J, et al. Lancet Oncol. (2019) pmid: 31806540
40. Abida W, et al. Clin. Cancer Res. (2020) pmid: 32086346
41. Ma et al., 2022; ASCO GI Abstract 563
42. Dhawan et al., 2020; ASCO Abstract 3513
43. Papageorgiou GI, et al. Front Oncol (2021) pmid: 35004311
44. Olson D, et al. Clin Genitourin Cancer (2016) pmid: 27079472
45. Swisher EM, et al. Nat Commun (2021) pmid: 33941784
46. Zhang W, et al. Oncologist (2020) pmid: 32045060
47. Hussain et al., 2019; ESMO Abstract LBA12PR
48. O'Carrigan et al., 2016; ASCO Abstract 2504
49. Yap TA, et al. Cancer Discov (2021) pmid: 32988960
50. Menezes DL, et al. Mol. Cancer Res. (2015) pmid: 25232030
51. Vendetti FP, et al. Oncotarget (2015) pmid: 26517239
52. Min A, et al. Mol. Cancer Ther. (2017) pmid: 28138034
53. Kwok M, et al. Blood (2016) pmid: 26563132
54. Riabinska A, et al. Sci Transl Med (2013) pmid: 23761041
55. Cheng HH, et al. Eur. Urol. (2016) pmid: 26724258
56. Imyanitov EN, et al. Hered Cancer Clin Pract (2011) pmid: 21819606
57. Mota JM, et al. JCO Precis Oncol (2020) pmid: 32856010
58. Pomerantz MM, et al. Cancer (2017) pmid: 28608931
59. Privé BM, et al. Prostate Cancer Prostatic Dis (2021) pmid: 34253846
60. Crumbaker M, et al. JCO Precis Oncol (2019) pmid: 35100671
61. Satapathy S, et al. Clin Nucl Med (2021) pmid: 33630794
62. Kratochwil C, et al. J Nucl Med (2020) pmid: 31601699
63. Ahmadzadehfar H, et al. Clin Nucl Med (2018) pmid: 29762244
64. De Giorgi U, et al. Br J Cancer (2021) pmid: 34333554
65. Fraser M, et al. Nature (2017) pmid: 28068672
66. Robinson D, et al. Cell (2015) pmid: 26000489
67. Abida W, et al. Proc. Natl. Acad. Sci. U.S.A. (2019) pmid: 31061129
68. Stopsack KH, et al. Clin. Cancer Res. (2020) pmid: 32220891
69. Warner E, et al. Clin Cancer Res (2021) pmid: 33414135
70. Tukachinsky 2021; 33558422
71. Darst et al., 2022; AACR Abstract 688
72. Shiloh Y, et al. Nat. Rev. Mol. Cell Biol. (2013) pmid: 23847781
73. Cremona CA, et al. Oncogene (2014) pmid: 23851492
74. Jiang X, et al. J. Biol. Chem. (2006) pmid: 16603769
75. Fernandes N, et al. J. Biol. Chem. (2005) pmid: 15713674
76. Scott SP, et al. Proc. Natl. Acad. Sci. U.S.A. (2002) pmid: 11805335
77. van Os NJ, et al. Clin Genet (2016) pmid: 26662178
78. Rothblum-Oviatt C, et al. Orphanet J Rare Dis (2016) pmid: 27884168
79. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
80. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
81. Xie M, et al. Nat. Med. (2014) pmid: 25326804
82. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
83. Severson EA, et al. Blood (2018) pmid: 29678827
84. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
85. Chabon JJ, et al. Nature (2020) pmid: 32269342
86. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
87. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
88. Prog Mol Biol Transl Sci (2011) pmid: 21507354
89. Yang J, et al. Mol Med Rep () pmid: 21887466
90. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
91. Daskalos A, et al. Cancer (2011) pmid: 21351083
92. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
93. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
94. Kim MS, et al. APMIS (2013) pmid: 23031157
95. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
96. Guo X, et al. Nature (2015) pmid: 25383530
97. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
98. Zhang ZM, et al. Nature (2018) pmid: 29414941
99. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
100. Yen WC, et al. Clin. Cancer Res. (2015) pmid: 25934888
101. Hu W, et al. Cancer Res. (2014) pmid: 24743243
102. Konishi J, et al. Cancer Res. (2007) pmid: 17804716
103. Xiao Y, et al. Oncogene (2011) pmid: 20838375
104. Ferrarotto et al., 2020; ESMO Abstract 919MO
105. Hu ZI, et al. Cancer Med (2019) pmid: 31347292
106. Grasso CS, et al. Nature (2012) pmid: 22722839
107. Cell (2015) pmid: 26544944
108. Barbieri CE, et al. Nat. Genet. (2012) pmid: 22610119
109. Carvalho FL, et al. Prostate (2014) pmid: 24737393
110. Kim AR, et al. Int J Clin Exp Pathol (2019) pmid: 31934201
111. Penton AL, et al. Semin. Cell Dev. Biol. (2012) pmid: 22306179
112. Kopan R, et al. Cell (2009) pmid: 19379690
113. Liu KW, et al. J. Clin. Invest. (2011) pmid: 21393858
114. Feng H, et al. Oncogene (2012) pmid: 21996738
115. Wang S, et al. J. Biol. Chem. (2009) pmid: 19008228
116. Zhou XD, et al. Cell Death Differ. (2008) pmid: 18421299
117. Voruz S, et al. Haematologica (2018) pmid: 29097496
118. Tasian SK, et al. Leukemia (2019) pmid: 29884903
119. Krenz M, et al. Circ. Res. (2005) pmid: 16166557
120. Nakamura T, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19706403
121. Taylor BS, et al. Cancer Cell (2010) pmid: 20579941
122. Tassidis H, et al. Tumour Biol. (2013) pmid: 23192641
123. Grossmann KS, et al. Adv. Cancer Res. (2010) pmid: 20399956
124. Tartaglia M, et al. Nat. Genet. (2003) pmid: 12717436
125. Bard-Chapeau EA, et al. Cancer Cell (2011) pmid: 21575863
126. Sturla LM, et al. Br. J. Cancer (2011) pmid: 21934682
127. Brasil AS, et al. Genet Test Mol Biomarkers (2010) pmid: 20578946
128. Horm. Res. (2009) pmid: 20029231
129. Chen Y, et al. Genes Chromosomes Cancer (2006) pmid: 16518851
130. Tartaglia M, et al. Am. J. Hum. Genet. (2006) pmid: 16358218
131. Pierpont EI, et al. Genes Brain Behav. (2009) pmid: 19077116
132. Mathur D, et al. Fetal Pediatr Pathol (2014) pmid: 24754368
133. de Bono et al., 2020; ASCO GU Abstract 119
134. de Bono J, et al. N. Engl. J. Med. (2020) pmid: 32343890
135. Hussain M, et al. (2020) pmid: 32955174
136. Antonarakis et al., 2019; ASCO Abstract 5045
137. Price MJ, et al. JCO Precis Oncol (2022) pmid: 35476551
138. Saad et al., 2022; ASCO GU Abstract 11
139. Karzai F, et al. J Immunother Cancer (2018) pmid: 30514390
140. Yu et al., 2019; ASCO GU Abstract 145
141. Yu et al., 2020; ASCO GU Abstract 100
142. Reichert et al., 2022; ASCO GU Abstract 88
143. Abida W, et al. J. Clin. Oncol. (2020) pmid: 32795228
144. Carneiro et al., 2022; ASCO GU Abstract 128
145. Pook et al., 2022; ASCO GU Abstract 95
146. Smith MR, et al. Lancet Oncol (2022) pmid: 35131040
147. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
148. Chi et al., 2022; ASCO GU Abstract 12
149. de Bono JS, et al. Lancet Oncol (2021) pmid: 34388386
150. Dorff et al., 2022; ASCO GU Abstract 157

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