ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Pancreas ductal adenocarcinoma
NAME Chen, Li-Li
DATE OF BIRTH 12 October 1964
SEX Female
MEDICAL RECORD # 48090820

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

SPECIMEN
SPECIMEN SITE Peritoneum
SPECIMEN ID S111-05399A (PF22025)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 11 February 2022
SPECIMEN RECEIVED 01 March 2022

Due to the low tumor purity, sensitivity for the detection of copy number alterations including ERBB2 is reduced due to sample quality. Refer to appendix for limitations statement. Sensitivity for the detection of other alterations and genomic signatures may also be reduced and the TMB score may be underreported.

Biomarker Findings

Microsatellite status - Cannot Be Determined [α]
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

BRCA1 V11fs*12
KRAS G12D
PTEN duplication exon 4
ATR duplication exon 36
DNMT3A P904L
PBRM1 splice site 3049-1G>A

1 Disease relevant genes with no reportable alterations: ***BRCA2***

† See About the Test in appendix for details.
α Patients with Microsatellite status of Cannot Be Determined should be re-tested with an orthogonal (alternative) method.

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Olaparib** (p. 8), **Rucaparib** (p. 9)
- Variants that may inform **nontargeted treatment approaches** (e.g., chemotherapy) in this tumor type: ***BRCA1* V11fs*12** (p. 4)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***DNMT3A* P904L** (p. 7)

REPORT UPDATES

Amended Report 16-Mar-2022

This Amended Report has been issued to reflect a change in Tumor Type from "Unknown primary adenocarcinoma" to "Pancreas ductal adenocarcinoma"; as a result, the therapy olaparib has been moved from "Therapies with Clinical Relevance (In Other Tumor Type)" to "Therapies with Clinical Relevance (In Patient's Tumor Type)" in association with the BRCA1 V11fs*12 alteration, and both olaparib and rucaparib are now listed as NCCN Category 2A. In addition, the Report Highlights table has been updated to account for the updated Tumor Type. Please reach out to Client Services with any questions or concerns. Contact us by phone at 1-888-988-3639 or by email at client.services@foundationmedicine.com.
Original Report Date: 08-Mar-2022

Electronically signed by Erik Williams, M.D. | 16 March 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - Cannot Be Determined	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***BRCA1* -** V11fs*12	Olaparib 2A	Rucaparib 2A
		Niraparib
10 Trials see p. 11		Talazoparib
***KRAS* -** G12D	none	none
2 Trials see p. 13		
***PTEN* -** duplication exon 4	none	none
10 Trials see p. 14		

☐ *NCCN category*

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.

***DNMT3A* -** P904L ..... p. 7

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.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents 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 exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. 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.

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BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of prospective clinical evidence in multiple solid tumor types, microsatellite instability (MSI) and associated increased tumor mutational burden (TMB)[1-2] may predict sensitivity to immune checkpoint inhibitors, including the approved PD-1-targeting agents cemiplimab, dostarlimab, nivolumab (alone or in combination with ipilimumab), and pembrolizumab[3-8] and PD-L1-targeting agents atezolizumab, avelumab, and durvalumab[9-11] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI is rare in pancreatic carcinoma, reported in less than 1% of samples (n=>1,000)[12-16]. The prognostic significance of MSI in pancreatic cancer is unknown (PubMed, Aug 2021).

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[17]. Defective MMR and consequent MSI occur as a result of genetic or epigenetic inactivation of one of the MMR pathway proteins, primarily MLH1, MSH2, MSH6, or PMS2[17-19]. The level of MSI in this sample could not be determined with confidence. Depending on the clinical context, MSI testing of an alternate sample or by another methodology could be considered.

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[20-22], anti-PD-1 therapies[20-23], and combination nivolumab and ipilimumab[24-29]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[20-23,30]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[20]. Analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy, compared with patients with higher TMB treated with chemotherapy[31] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[21]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[23,30]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. As the TMB status of this tumor cannot be determined with confidence, the benefit of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

Pancreatic carcinomas, including ductal and acinar subtypes, have been reported to harbor a median TMB of 2-3 mutations per megabase (muts/Mb), and 0-2% of cases have high TMB (>20 muts/Mb)[32]; TMB has not been assessed in pancreatic mucinous neoplasms (PubMed, Oct 2021). A study of patients with pancreatic ductal adenocarcinoma harboring mismatch repair gene mutations reported improved prognosis for patients with high TMB measured in tissue samples (defined as >50 mutations; survival 69-314 months) compared to those with lower TMB (average of 5.7 mutations; 10-42 months)[33].

FINDING SUMMARY

Tumor mutation burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitution and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[34-35] and cigarette smoke in lung cancer[7,36], treatment with temozolomide-based chemotherapy in glioma[37-38], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[39-43], and microsatellite instability (MSI)[39,42-43]. Elevated TMB has been reported to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors in multiple solid tumor types[21-23,30]. However, the TMB level in this sample could not be determined with confidence.

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GENE
BRCA1

ALTERATION
V11fs*12

TRANSCRIPT ID
NM_007294

CODING SEQUENCE EFFECT
32delT

VARIANT ALLELE FREQUENCY (% VAF)
52.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that inactivate BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors[44-61] or ATR inhibitors[62-64]. Clinical responses to PARP inhibitors have been reported for patients with either germline or somatic BRCA1/2 mutations[45,50,53,60-61] and for patients with platinum-resistant or -refractory disease[44,49,56,59]. A randomized Phase 2 trial evaluating cisplatin and gemcitabine with or without veliparib in 50 patients with advanced pancreatic ductal adenocarcinomas (PDAC) harboring germline BRCA1/2 or PALB2 (gBRCA/PALB2+) mutations reported that the addition of the PARP inhibitor veliparib to chemotherapy did not significantly improve median PFS (10.1 vs. 9.7 months) or median OS (15.5 vs. 16.4 months) relative to chemotherapy alone[65]. In a Phase 1 trial of monotherapy treatment with the ATR inhibitor BAY1895344, 2 patients with deleterious BRCA1 alterations and platinum-refractory ovarian carcinoma experienced a PR or prolonged SD[62]. In other Phase 1 trials of combination approaches, a patient with BRCA1-mutated ovarian carcinoma experienced prolonged SD from the ATR inhibitor berzosertib combined with topotecan[63]; another patient with platinum- and PARP-inhibitory refractory ovarian cancer and an inactivating germline BRCA1 mutation experienced a PR from berzosertib plus carboplatin[66]; and a third patient with BRCA1-mutated triple-negative breast cancer (TNBC) experienced a PR to the ATR inhibitor ceralasertib combined with olaparib[67]. Preclinical studies of BRCA1/2 inactivation in T-cell acute lymphoblastic leukemia (T-ALL)[68], ovarian carcinoma[69], and TNBC[70] showing reduced cell viability and increased DNA damage during ATR treatment further support the sensitivity of BRCA1-deficient cells to ATR inhibitors. The WEE1 inhibitor adavosertib has been evaluated as a monotherapy and in combination with PARP-inhibitor, olaparib. In a Phase 2 study for patients with PARP-resistant ovarian cancer, the combination of olaparib and adavosertib elicited improved clinical benefit (ORR: 29%; DCR: 89%) compared to adavosertib alone (ORR: 23%; DCR: 63%); however, in the BRCA-mutated cohort, no significant difference in clinical benefit was observed between the combination (ORR: 19%) and monotherapy (ORR: 20%) treatments[71]. 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[72].

— Nontargeted Approaches —

Inactivation of BRCA1 may also predict sensitivity to the DNA-damaging agents trabectedin and lurbinectedin[73-82]. Patients with pancreatic cancer and BRCA1/2 or PALB2 mutations may benefit from FOLFIRINOX, or the combination of cisplatin and gemcitabine (NCCN Pancreatic Adenocarcinoma Guidelines v2.2021)[65,83-86].

FREQUENCY & PROGNOSIS

In pancreatic carcinoma datasets, BRCA1 mutation and loss has been respectively reported in 1% and 0-1% of cases[87-88]. Reduced expression of BRCA1 at the mRNA and protein levels has been observed in pancreatic adenocarcinoma, with low or no expression of BRCA1 protein in 50% of cases[89]. Although most cases of pancreatic cancer are sporadic, germline mutations in BRCA1 and BRCA2 have been linked to an increased risk of pancreatic cancer, particularly in families of Ashkenazi Jewish descent[90-94]. Reduced expression of BRCA1 at the mRNA and protein levels has been observed in pancreatic adenocarcinoma, with low or no expression of BRCA1 protein in 50% of cases; reduced or absent BRCA1 expression was found to be associated with poorer 1-year overall survival[89].

FINDING SUMMARY

The protein encoded by BRCA1 is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation[95]. Alterations such as seen here may disrupt BRCA1 function or expression[96-98].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in BRCA1 or BRCA2 are associated with autosomal dominant hereditary breast and ovarian cancer[99-100], and the lifetime risk of breast and ovarian cancer in BRCA1/2 mutation carriers has been estimated to be as high as 87% and 44%, respectively[101]. 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%[91]. 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[101-107]. In the appropriate clinical context, germline testing of BRCA1 is recommended.

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GENE
KRAS

ALTERATION
G12D

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
35G>A

VARIANT ALLELE FREQUENCY (% VAF)
7.9%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[108-113]. Initial Phase 1 monotherapy trials of MEK inhibitors in patients with pancreatic cancer showed promise, with DCR (PR and/or SD) up to 37%[114], response rates up to 25%[114-118], and prolonged PRs in certain patients[115,117,119]. However, subsequent clinical trials combining various MEK inhibitors with gemcitabine reported no additional benefit compared to gemcitabine alone irrespective of KRAS mutation status[120-123], with refametinib and gemcitabine even showing a trend towards worse response and survival in patients with KRAS-mutant pancreatic tumors than in those with KRAS wild-type tumors (OS 6.6 months vs 18.2 months)[120]. Trials combining MEK inhibitors with other targeted therapies, such as EGFR inhibitors[124] or PI3K-AKT pathway inhibitors[125-126], reported no PRs and frequent adverse events in patients with KRAS-mutant pancreatic cancer. Emerging preclinical studies suggest MEK inhibition downstream of KRAS-mutant pancreatic tumors leads to increased autophagy[127-128]. Combination MEK/autophagy inhibitors may therefore be more beneficial. A heavily pretreated patient with pancreatic cancer treated with trametinib plus hydroxychloroquine exhibited a PR[127]. A Phase 2 trial of paclitaxel/carboplatin with or without Reolysin in patients with metastatic pancreatic adenocarcinoma reported no improvement in PFS with addition of Reolysin, regardless of KRAS mutational status[129]; however a Phase 2 study of Reolysin and gemcitabine in patents with pancreatic cancer reported 1 PR, 23 SDs, and 5 PDs in 34 patients with a favorable median OS of 10.2 months[130]. In a Phase 1 study evaluating the MEK-pan-RAF dual inhibitor CH5126766, 6 patients harboring KRAS mutations experienced PRs, including 3 with non-small cell lung cancer (NCSLC), 1 with low-grade serous ovarian carcinoma (LGSOC), 1 with endometrial adenocarcinoma, and 1 with multiple myeloma[131]. Combination of CH5126766 with the FAK inhibitor defactinib elicited PR rates of 50% (4/8) for patients with KRAS-mutated low-grade serous ovarian cancer and 12% (2/17) for patients with KRAS-mutated non-small cell lung cancer (NSCLC) in a Phase 1 study[132-133] . Preclinical and clinical data suggest that KRAS mutations may predict clinical benefit from SHP2 inhibitors[134-135]. A Phase 1 study of RMC-4630 for relapsed/refractory solid tumors reported a DCR of 58% (23/40) for patients with NSCLC and KRAS mutations and a DCR of 75% (12/16) for patients with NSCLC and KRAS G12C mutations[136]. Interim results from a Phase 1/2 study of RMC-4630 plus cobimetinib reported tumor reduction in 3 of 8 patients with KRAS-mutated colorectal cancer[137]. Preclinical data suggest that KRAS mutation may confer sensitivity to SOS1 inhibitors[138-139]. Phase 1 studies of the SOS1 inhibitor BI 1701963 alone or in combination with MEK inhibitors, KRAS G12C inhibitors, or irinotecan are recruiting for patients with solid tumors harboring KRAS mutations[140-141] .

FREQUENCY & PROGNOSIS

KRAS mutations have been observed in 91-95% of pancreatic ductal adenocarcinoma cases[88,142], with the majority of mutations found at codon 12[143-146]. KRAS mutations, particularly G12D, have been associated with decreased median survival time in patients with pancreatic ductal adenocarcinoma[144].

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[109,147]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, E63K, R68S, and K117N have been characterized as activating and oncogenic[109,148-170].

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GENE
PTEN

ALTERATION
duplication exon 4

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

PTEN loss or mutation leads to activation of the PI3K-AKT-mTOR pathway and may predict sensitivity to inhibitors of this pathway[171-174]. Across various tissues, most clinical studies have not observed an association between PTEN deficiency and response to inhibitors of the PI3K-AKT-mTOR pathway. However, limited studies in prostate cancer[175-178], renal cell carcinoma[179], breast cancer[180-181], and colorectal cancer[182] have reported an association between PTEN deficiency and response to inhibitors targeting the PI3K-AKT-mTOR pathway. Preclinical data indicate that PTEN loss or inactivation may predict sensitivity to PARP inhibitors[183-187], and clinical benefit has been observed for patients with PTEN-altered breast cancer including triple negative breast cancer[188], ovarian cancer[189], uterine leiomyosarcoma[190], and endometrial cancer[187] treated with PARP inhibitors. However, some studies have reported a lack of association between PTEN mutation and PARP inhibitor sensitivity[49,191].

FREQUENCY & PROGNOSIS

PTEN mutations are rare in pancreatic adenocarcinomas and have been observed in fewer than 1% of cases[88,142]; PTEN homozygous deletion was observed in 1.8% of pancreatic ductal adenocarcinomas[88]. Reduced or loss of PTEN protein expression has been reported in approximately 26% (34/133) to 70% (38/54) of pancreatic ductal adenocarcinoma samples[192-193]. Loss of PTEN protein expression has been associated with local recurrence or distant metastasis as well as poor prognosis in pancreatic ductal adenocarcinoma patients[192].

FINDING SUMMARY

PTEN encodes an inositol phosphatase that functions as a tumor suppressor by negatively regulating the PI3K-AKT-mTOR pathway; loss of PTEN can lead to uncontrolled cell growth and suppression of apoptosis[172]. Alterations such as seen here may disrupt PTEN function or expression[194-235].

POTENTIAL GERMLINE IMPLICATIONS

PTEN mutations underlie several inherited disorders, collectively termed PTEN hamartoma tumor syndrome (PHTS), which include Cowden syndrome (CS) and its variant Lhermitte-Duclos disease (LD), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome[236-237]. The mutation rate for PTEN in these disorders ranges from 20 to 85% of patients[236,238]. The estimated incidence of Cowden syndrome is 1/200,000, which may be an underestimate due to the high variability of this disorder[236]. Given the association between PTEN and these inherited syndromes, in the appropriate clinical context, germline testing for mutations affecting PTEN is recommended.

GENE
ATR

ALTERATION
duplication exon 36

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 2 study reported talazoparib led to a SD lasting over 6 months for a patient with ATR-mutated breast cancer[239]. Based on preclinical evidence, ATR-deficient tumors may be sensitive to PARP inhibitors[240-241].

— Nontargeted Approaches —

ATR inactivation has been associated with increased sensitivity to 5-fluorouracil and cisplatin, but not to oxaliplatin, in cancer cell lines[242-244]; however, this has not been demonstrated clinically.

FREQUENCY & PROGNOSIS

In the Pancreatic Adenocarcinoma TCGA dataset, ATR mutations have been reported in up to 2.2% of cases (cBioPortal, Mar 2021)[245-246]. ATR mutations have been reported in 3% of pancreas carcinoma samples analyzed (COSMIC, Mar 2021)[247]. ATR inactivation, either by mutation or decreased expression, is associated with increased microsatellite instability (MSI) and chromosome instability (CIN) in a variety of tumor types, including colorectal and endometrial cancers[242,248-249]. In one study, expression of phosphorylated ATR positively correlated with histological grade in pancreatic cancer samples but was not predictive of overall survival[250].

FINDING SUMMARY

ATR encodes the protein ataxia telangiectasia and RAD3 related, which phosphorylates the tumor suppressor BRCA1, and several cell cycle checkpoint proteins including CHK1; it plays a key role in maintaining genome integrity via regulation of DNA repair and replication[251-252]. Alterations such as seen here may disrupt ATR function or expression[253].

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GENE
DNMT3A

ALTERATION
P904L

TRANSCRIPT ID
NM_022552

CODING SEQUENCE EFFECT
2711C>T

VARIANT ALLELE FREQUENCY (% VAF)
1.6%

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)[245-246]. 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[254-255]. 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[256-261]. Alterations such as seen here may disrupt DNMT3A function or expression[262-265].

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[266-271]. 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[266-267]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[272]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[270,273-274]. 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
PBRM1

ALTERATION
splice site 3049-1G>A

TRANSCRIPT ID
NM_018313

CODING SEQUENCE EFFECT
3049-1G>A

VARIANT ALLELE FREQUENCY (% VAF)
8.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of significant clinical data from prospective studies, PBRM1 inactivation may predict benefit from PD-1-targeting immune checkpoint inhibitors, such as nivolumab, pembrolizumab, cemiplimab, or dostarlimab, for patients with clear cell renal cell carcinoma and prior anti-angiogenic therapy[275-277]. However, multiple retrospective analyses report that PBRM1 mutation status is not associated with clinical benefit from various immune checkpoint inhibitors in other solid tumor types, including non-small cell lung cancer, urothelial carcinoma, melanoma, or esophagogastric cancer, suggesting that the impact of PBRM1 loss of function may depend on tumor type[278-281].

FREQUENCY & PROGNOSIS

Somatic mutations in PBRM1 are prevalent in clear cell renal cell carcinomas (ccRCC) (41%)[282], intrahepatic cholangiocarcinomas (9-13%)[283-286], and bladder urothelial carcinomas (6-14%)[287-289]. PBRM1 mutations are detected in other tumor types, including in 37% (11/30) of papillary meningiomas and 4% (2/54) of thymic carcinomas[290-291] and in tumors of the skin (7.3%), stomach (5.8%), large intestine (4.8%), lung (2.6%), and soft tissue (2.4%) (COSMIC, Jan 2022)[247]. Preclinical studies have shown that loss of PBRM1 increases the proliferation of ccRCC cell lines[282]. PBRM1 protein loss or mutation is correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC[292-294], extrahepatic cholangiocarcinoma[285], and pancreatic cancer[295]. However, one ccRCC study reported no correlation between PBRM1 mutation and cancer-specific survival[296]. In ccRCC, PBRM1 alterations are generally observed to be mutually exclusive with BAP1 alterations[282,297]; a retrospective analysis of 145 primary ccRCCs found a decreased median overall survival for patients with mutations in both BAP1 and PBRM1 compared with patients having either mutated gene alone[298]. A trend toward worse survival was also seen in patients with intrahepatic cholangiocarcinoma harboring mutations in chromatin modifiers (including BAP1, ARID1A, or PBRM1)[284].

FINDING SUMMARY

PBRM1 (Polybromo-1), also known as BAF180, encodes a subunit of ATP-dependent chromatin-remodeling complexes and a required cofactor for ligand-dependent transactivation by nuclear hormone receptors[299]. Mutation, loss, or inactivation of PBRM1 has been reported in several cancers, suggesting PBRM1 is a tumor suppressor[282,284,300]. Alterations such as seen here may disrupt PBRM1 function or expression[301-306].

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Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Olaparib

Assay findings association

BRCA1
V11fs*12

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[54-58] as well as strong clinical evidence in multiple other cancer types[44-46,54,57,61,307] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to olaparib.

SUPPORTING DATA

In a Phase 2 study of olaparib plus pembrolizumab for advanced solid tumors, patients with BRCA1 or BRCA2 mutations achieved an ORR of 29% (6/21), whereas patients with mutations in other homologous recombination repair genes achieved an ORR of 6.3% (2/32)[308]. The Phase 3 randomized, placebo-controlled POLO trial investigating maintenance olaparib for patients with platinum-sensitive, germline BRCA1/2-mutated metastatic pancreatic adenocarcinoma reported a significantly longer median PFS compared with placebo (7.4 vs. 3.8 months, HR=0.53)[61]. At 3-year follow-up, an OS of 34% was reported for patients treated with olaparib compared with 18% for patients receiving placebo; however, olaparib maintenance therapy did not impact median OS (19.0 vs. 19.2 months, HR=0.83) relative to placebo[309]. A Phase 2 trial of olaparib monotherapy for patients with germline BRCA1/2-mutated recurrent pancreatic cancer reported a response rate of 22%[44]. Parallel Phase 2 trials reported 2 PRs for patients with platinum-sensitive, DNA damage repair (DDR) deficient, germline BRCA mutation-negative pancreatic ductal adenocarcinoma; no responses were observed in platinum-refractory cases[310].

Niraparib

Assay findings association

BRCA1
V11fs*12

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

On the basis of clinical evidence in ovarian and breast cancers[48-49,311] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to PARP inhibitors such as niraparib.

SUPPORTING DATA

Clinical data on the efficacy of niraparib for the treatment of pancreatic cancer are limited (PubMed, Jan 2022)[312]. Niraparib has been primarily evaluated in the context of ovarian cancer. In a Phase 3 study of patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly increased median PFS, as compared to placebo, in patients with germline BRCA mutations (21 vs. 5.5 months) and in patients without germline BRCA mutations (9.3 vs. 3.9 months) as well as in a subgroup of the patients without germline BRCA mutations with homologous recombination-deficient tumors (12.9 vs. 3.8 months)[48]. In a Phase 1 study of niraparib treatment for patients with solid tumors, 40% (8/20) of patients with ovarian cancer and BRCA mutations and 50% (2/4) of patients with breast cancer and BRCA mutations experienced a PR, and 43% (9/21) of patients with castration-resistant prostate cancer and 100% (2/2) of patients with non-small cell lung cancer achieved SD[49]. A Phase 1 study of the combination of niraparib and bevacizumab in patients with platinum-sensitive, high-grade ovarian cancer reported a DCR of 91% (10/11), with a response rate of 45% (5/11)[313].

Rucaparib

Assay findings association

BRCA1
V11fs*12

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

On the basis of strong clinical evidence in ovarian cancer[50-51,314] , as well as clinical data in other cancer types[51,315-316] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to rucaparib.

SUPPORTING DATA

In the RUCAPANC Phase 2 study, rucaparib elicited an ORR of 15.8% and a DCR of 31.6% in BRCA1/2-mutated advanced or metastatic pancreatic cancer, with 1 CR and 2 PRs confirmed and 1 additional unconfirmed CR out of 19 treated patients[317]. In a Phase 2 study, rucaparib monotherapy elicited 1 CR, 6 PRs, an ORR of 36.8%, and a DCR (CR+PR+SD) of 89.5% in a cohort of 19 patients with advanced pancreatic carcinoma harboring germline or somatic mutations in BRCA or PALB2[318].

Electronically signed by Erik Williams, M.D. | 16 March 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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Talazoparib

Assay findings association

BRCA1
V11fs*12

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

On the basis of strong clinical data in breast cancer[319-321] and additional clinical evidence in ovarian, pancreatic, and prostate cancer[322-325] , loss or inactivation of either BRCA1 or BRCA2 may confer sensitivity to talazoparib.

SUPPORTING DATA

A Phase 1 study of talazoparib reported 2 PRs for patients with pancreatic cancer and a BRCA2 or PALB2 mutation[323]. Talazoparib has been studied primarily in the context of BRCA-mutated, HER2-negative breast cancer, where patients achieved significantly longer median PFS (8.6 vs. 5.6 months, HR=0.54), a higher ORR (62.6% vs. 27.2%), and improved quality of life on talazoparib compared with standard chemotherapy in a Phase 3 study[320-321] . In a Phase 2 study of talazoparib for BRCA1/2-wildtype patients with homologous recombination pathway alterations, the best outcome in non-breast tumors was SD ≥ 6 months for 2/7 patients who had colon cancer with germline ATM alteration or testicular cancer with germline CHEK2 and somatic ATM alteration[239]. Clinical activity of single-agent talazoparib has been observed in numerous other solid tumors, including responses in BRCA-mutated ovarian, pancreatic, prostate, and ampulla of Vater cancers; PALB2-mutated pancreatic and bladder cancers; ATM-mutated cholangiocarcinoma; and small cell lung cancer[322-324,326] .

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

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NOTE 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. 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 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. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
BRCA1

ALTERATION
V11fs*12

RATIONALE
BRCA1 loss or inactivating alterations may predict sensitivity to PARP inhibitors or ATR inhibitors.

NCT04300114

PHASE 3

A Study of Maintenance Treatment With Fluzoparib in gBRCA/PALB2 Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-Based Chemotherapy

TARGETS
PARP

LOCATIONS: Hangzhou (China), Shanghai (China), Nanjing (China), Hefei (China), Guangzhou (China), Wuhan (China), Zhengzhou (China), Jinan (China), Chongqing (China), Tianjin (China)

NCT04768296

PHASE 2

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

TARGETS
TOP1, ATR

LOCATIONS: Hangzhou (China), Nanjing (China), Wuhan (China), Xi'an (China), Osaka (Japan), Beijing (China), Hirakata-shi (Japan), Takatsuki-shi (Japan), Chengdu (China), Chuo-ku (Japan)

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT04228601

PHASE 1/2

A Study of Fluzoparib in Combination With mFOLFIRINOX in Patients With Advanced Pancreatic Cancer

TARGETS
PARP

LOCATIONS: Hangzhou (China), Shanghai (China)

NCT04425876

PHASE 1

A Study of Fluzoparib in Combination With mFOLFIRINOX in Patients With Resectable Pancreatic Cancer

TARGETS
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), Chelyabinsk (Russian Federation), Nedlands (Australia), Kazan (Russian Federation), Arkhangelsk (Russian Federation), Port Macquarie (Australia), Darlinghurst (Australia), Moscow (Russian Federation), Krasnogorsk (Russian Federation)

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)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

GENE
KRAS

ALTERATION
G12D

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors. Multiple clinical studies have reported lack of efficacy of MEK inhibitors as monotherapy for treatment of KRAS-mutant pancreatic cancer. Emerging data suggest patients with KRAS-mutant pancreatic cancer may be sensitive to combination MEK/autophagy inhibitors. Limited clinical and preclinical studies indicate KRAS mutations may predict sensitivity to MEK-pan-RAF dual inhibitors.

NCT03825289

PHASE 1

Trametinib and Hydroxychloroquine in Treating Patients With Pancreatic Cancer

TARGETS
MEK

LOCATIONS: Utah

NCT04132505

PHASE 1

Binimetinib and Hydroxychloroquine in Treating Patients With KRAS Mutant Metastatic Pancreatic Cancer

TARGETS
MEK

LOCATIONS: Texas

GENE
PTEN

ALTERATION
duplication exon 4

RATIONALE
PTEN loss or inactivating mutations may lead to increased activation of the PI3K-AKT-mTOR pathway and may indicate sensitivity to inhibitors of this pathway. PTEN loss or inactivation may also predict sensitivity to PARP inhibitors.

NCT04425876

PHASE 1

A Study of Fluzoparib in Combination With mFOLFIRINOX in Patients With Resectable Pancreatic Cancer

TARGETS
PARP

LOCATIONS: Shanghai (China)

NCT04337463

PHASE NULL

ATG-008 Combined With Toripalimab in Advanced Solid Tumors

TARGETS
mTORC1, mTORC2, PD-1

LOCATIONS: Chongqing (China), Chengdu (China)

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)

NCT04001569

PHASE 1/2

AZD8186 and Paclitaxel in Advanced Gastric Cancer

TARGETS
PI3K-beta

LOCATIONS: Seongnam-si (Korea, Republic of)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04632992

PHASE 2

A Study Evaluating Targeted Therapies in Participants Who Have Advanced Solid Tumors With Genomic Alterations or Protein Expression Patterns Predictive of Response

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, PD-L1, ERBB2, PI3K-alpha, RET, AKTs

LOCATIONS: Alaska, Washington, Oregon, California, Idaho

NCT03907969

PHASE 1/2

A Clinical Trial to Evaluate AZD7648 Alone and in Combination With Other Anti-cancer Agents in Patients With Advanced Cancers

TARGETS
PARP, DNA-PK

LOCATIONS: Newcastle upon Tyne (United Kingdom), London (United Kingdom), Connecticut, Texas

NCT03994796

PHASE 2

Genetic Testing in Guiding Treatment for Patients With Brain Metastases

TARGETS
TRKB, ALK, TRKC, ROS1, TRKA, CDK4, CDK6, PI3K, mTOR

LOCATIONS: Washington, Oregon, Idaho, Montana

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.

ERCC4
C723*

FGFR3
G44S

GNAS
A436_P447del and R4H

MAP3K13
G107E

NOTCH2
R2298Q

NOTCH3
D2106Y

POLE
H2264Q

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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Foundation Medicine, Inc. | 1.888.988.3639

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FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

DNA GENE LIST: ENTIRE CODING SEQUENCE FOR THE DETECTION OF BASE SUBSTITUTIONS, INSERTION/DELETIONS, AND COPY NUMBER ALTERATIONS

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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FoundationOne 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. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne 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: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and for selected forms of ovarian cancer, loss of heterozygosity (LOH) score, using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. The test is intended as a companion diagnostic to identify patients who may benefit from treatment with therapies in accordance with approved therapeutic product labeling. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes. Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

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. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. 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.

Diagnostic Significance

FoundationOne CDx identifies alterations to select cancer-associated genes or portions of genes (biomarkers). In some cases, the Report also highlights selected negative test results regarding biomarkers of clinical significance.

Qualified Alteration Calls (Equivocal and Subclonal)

An alteration denoted as "amplification – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence that the copy number of a gene exceeds the threshold for identifying copy number amplification. The threshold used in FoundationOne CDx for identifying a copy number amplification is four (4) for ERBB2 and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that the FoundationOne CDx assay data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that the FoundationOne CDx analytical methodology has identified as being present in <10% of the assayed tumor DNA.

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. 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.

Limitations

1. In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-

Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

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.

VARIANT ALLELE FREQUENCY

Variant Allele Frequency (VAF) represents the fraction of sequencing reads in which the variant is observed. This attribute is not taken into account for therapy inclusion, clinical trial matching, or interpretive content. Caution is recommended in interpreting VAF to indicate the potential germline or somatic origin of an alteration, recognizing that tumor fraction and tumor ploidy of samples may vary.

Precision of VAF for base substitutions and indels

BASE SUBSTITUTIONS	%CV*
Repeatability	5.11 - 10.40
Reproducibility	5.95 - 12.31
INDELS	**%CV***
Repeatability	6.29 - 10.00
Reproducibility	7.33 - 11.71

**Interquartile Range = 1st Quartile to 3rd Quartile*

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 >10%, 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, CBL, 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

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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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.

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 CDx.

TREATMENT DECISIONS ARE 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 or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

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

MR Suite Version 6.0.0

The median exon coverage for this sample is 740x

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1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
4. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
5. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
6. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
7. Rizvi NA, et al. Science (2015) pmid: 25765070
8. Oaknin A, et al. JAMA Oncol (2020) pmid: 33001143
9. Hochster et al., 2017; ASCO Abstract 673
10. Fleming et al., 2018; ASCO Abstract 5585
11. Bang et al., 2018; ASCO Abstract 92
12. Hu ZI, et al. Clin. Cancer Res. (2018) pmid: 29367431
13. Campbell BB, et al. Cell (2017) pmid: 29056344
14. Pihlak R, et al. Cancers (Basel) (2018) pmid: 29329208
15. Salem ME, et al. Mol. Cancer Res. (2018) pmid: 29523759
16. Laghi L, et al. PLoS ONE (2012) pmid: 23029359
17. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
18. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
19. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
20. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
21. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
22. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
23. Cristescu R, et al. Science (2018) pmid: 30309915
24. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
25. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
26. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
27. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
28. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
29. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
30. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
31. Legrand et al., 2018; ASCO Abstract 12000
32. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
33. Hu et al., 2017; ASCO Abstract e15791
34. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
35. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
36. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
37. Johnson BE, et al. Science (2014) pmid: 24336570
38. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
39. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
40. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
41. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
42. Nature (2012) pmid: 22810696
43. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
44. Kaufman B, et al. J. Clin. Oncol. (2015) pmid: 25366685
45. Mateo J, et al. N. Engl. J. Med. (2015) pmid: 26510020
46. Tutt A, et al. Lancet (2010) pmid: 20609467
47. Robson M, et al. N. Engl. J. Med. (2017) pmid: 28578601
48. Mirza MR, et al. N. Engl. J. Med. (2016) pmid: 27717299
49. Sandhu SK, et al. Lancet Oncol. (2013) pmid: 23810788
50. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
51. Drew Y, et al. Br. J. Cancer (2016) pmid: 27002934
52. Pujade-Lauraine E, et al. Lancet Oncol. (2017) pmid: 28754483
53. Ledermann JA, et al. Lancet Oncol. (2016) pmid: 27617661
54. Fong PC, et al. N. Engl. J. Med. (2009) pmid: 19553641
55. Audeh MW, et al. Lancet (2010) pmid: 20609468
56. Fong PC, et al. J. Clin. Oncol. (2010) pmid: 20406929
57. Gelmon KA, et al. Lancet Oncol. (2011) pmid: 21862407
58. Kaye SB, et al. J. Clin. Oncol. (2012) pmid: 22203755
59. Domchek SM, et al. Gynecol. Oncol. (2016) pmid: 26723501
60. Moore K, et al. N. Engl. J. Med. (2018) pmid: 30345884
61. Golan T, et al. N. Engl. J. Med. (2019) pmid: 31157963
62. Yap TA, et al. Cancer Discov (2021) pmid: 32988960
63. Thomas A, et al. J. Clin. Oncol. (2018) pmid: 29252124
64. Saito YD, et al. Cancer Treat Res Commun (2018) pmid: 31299005
65. O'Reilly EM, et al. J. Clin. Oncol. (2020) pmid: 31976786
66. O'Carrigan et al., 2016; ASCO Abstract 2504
67. Yap et al., 2016; AACR-NCI-EORTC Abstract 1LBA
68. Pouliot GP, et al. PLoS ONE (2019) pmid: 31721781
69. Kim H, et al. Clin. Cancer Res. (2017) pmid: 27993965
70. Jin J, et al. Neoplasia (2018) pmid: 29605721
71. Westin et al., 2021; ASCO Abstract 5505
72. Do K, et al. J. Clin. Oncol. (2015) pmid: 25964244
73. Cruz C, et al. J. Clin. Oncol. (2018) pmid: 30240327
74. Poveda A, et al. Ann. Oncol. (2017) pmid: 28368437
75. García MJ, et al. Mol. Cancer Ther. (2013) pmid: 23364677
76. Schöffski P, et al. Eur. J. Cancer (2011) pmid: 21376569
77. Italiano A, et al. Cancer (2011) pmid: 21287534
78. Laroche-Clary A, et al. Br. J. Cancer (2015) pmid: 25602962
79. Ghouadni A, et al. Breast (2017) pmid: 28467918
80. Monk BJ, et al. Ann. Oncol. (2015) pmid: 25722380
81. Monk BJ, et al. Gynecol. Oncol. (2020) pmid: 31924332
82. Yasui H, et al. J Chemother (2016) pmid: 27077926
83. Conroy T, et al. N Engl J Med (2011) pmid: 21561347
84. Fogelman D, et al. Cancer Chemother Pharmacol (2015) pmid: 26126726
85. Wattenberg MM, et al. Br J Cancer (2020) pmid: 31787751
86. Golan T, et al. Br J Cancer (2014) pmid: 25072261
87. Bailey P, et al. Nature (2016) pmid: 26909576
88. Witkiewicz AK, et al. Nat Commun (2015) pmid: 25855536
89. Beger C, et al. Clin. Cancer Res. (2004) pmid: 15173085
90. Lucas AL, et al. Clin. Cancer Res. (2013) pmid: 23658460
91. MedGenMed (2005) pmid: 16369438
92. Kim R, et al. JOP (2012) pmid: 22406596
93. Naderi A, et al. Int J Gastrointest Cancer (2002) pmid: 12622420
94. Stadler ZK, et al. Cancer (2012) pmid: 21598239
95. O'Donovan PJ, et al. Carcinogenesis (2010) pmid: 20400477
96. Nelson AC, et al. Radiat. Res. (2010) pmid: 20681793
97. Silver DP, et al. Cancer Discov (2012) pmid: 22843421
98. Ludwig T, et al. Genes Dev. (2001) pmid: 11358863
99. Miki Y, et al. Science (1994) pmid: 7545954
100. Wooster R, et al. Nature () pmid: 8524414
101. Ford D, et al. Lancet (1994) pmid: 7907678
102. Whittemore AS, et al. Am. J. Hum. Genet. (1997) pmid: 9042908
103. Claus EB, et al. Cancer (1996) pmid: 8635102
104. Struewing JP, et al. N. Engl. J. Med. (1997) pmid: 9145676
105. Oddoux C, et al. Nat. Genet. (1996) pmid: 8841192
106. King MC, et al. Science (2003) pmid: 14576434
107. Hall MJ, et al. Cancer (2009) pmid: 19241424
108. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
109. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
110. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
111. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
112. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
113. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
114. Bodoky G, et al. Invest New Drugs (2012) pmid: 21594619
115. Rinehart J, et al. J. Clin. Oncol. (2004) pmid: 15483017
116. Lorusso PM, et al. J. Clin. Oncol. (2005) pmid: 16009947
117. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
118. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
119. Garrido-Laguna I, et al. Oncoscience (2015) pmid: 25897431
120. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152
121. Infante JR, et al. Eur. J. Cancer (2013) pmid: 23583440
122. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
123. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
124. Ko AH, et al. Clin. Cancer Res. (2016) pmid: 26251290
125. Chung V, et al. JAMA Oncol (2017) pmid: 27978579
126. Bedard PL, et al. Clin. Cancer Res. (2015) pmid: 25500057
127. Kinsey CG, et al. Nat. Med. (2019) pmid: 30833748
128. Bryant KL, et al. Nat. Med. (2019) pmid: 30833752
129. Noonan AM, et al. Mol. Ther. (2016) pmid: 27039845
130. Mahalingam D, et al. Cancers (Basel) (2018) pmid: 29799479
131. Guo C, et al. Lancet Oncol (2020) pmid: 33128873
132. Krebs et al., 2021; AACR Abstract CT019
133. Shinde et al., 2020; AACR Abstract CT143
134. Lu H, et al. Mol Cancer Ther (2019) pmid: 31068384
135. Mainardi S, et al. Nat Med (2018) pmid: 29808006
136. Koczywas et al., 2021; AACR Abstract LB001
137. Bendell et al., 2020; EORTC-NCI-AACR Abstract 5
138. Hillig RC, et al. Proc Natl Acad Sci U S A (2019) pmid: 30683722
139. Hofmann MH, et al. Cancer Discov (2021) pmid: 32816843
140. Hofmann et al., 2021; AACR Abstract CT210
141. Gort et al., 2020; ASCO Abstract TPS3651
142. Biankin AV, et al. Nature (2012) pmid: 23103869
143. Feldmann G, et al. J Hepatobiliary Pancreat Surg (2007) pmid: 17520196
144. Rachakonda PS, et al. PLoS ONE (2013) pmid: 23565280
145. Hruban RH, et al. Am. J. Pathol. (1993) pmid: 8342602
146. Maitra A, et al. Best Pract Res Clin Gastroenterol (2006) pmid: 16549325
147. Kahn S, et al. Anticancer Res. () pmid: 3310850
148. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
149. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
150. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
151. Sci. STKE (2004) pmid: 15367757
152. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
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153. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
154. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
155. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
156. Kim E, et al. Cancer Discov (2016) pmid: 27147599
157. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
158. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
159. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
160. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
161. Scheffzek K, et al. Science (1997) pmid: 9219684
162. Scholl C, et al. Cell (2009) pmid: 19490892
163. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
164. Tyner JW, et al. Blood (2009) pmid: 19075190
165. Valencia A, et al. Biochemistry (1991) pmid: 2029511
166. White Y, et al. Nat Commun (2016) pmid: 26854029
167. Wiest JS, et al. Oncogene (1994) pmid: 8058307
168. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
169. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
170. Loree JM, et al. Clin Cancer Res (2021) pmid: 34117033
171. Courtney KD, et al. J. Clin. Oncol. (2010) pmid: 20085938
172. Simpson L, et al. Exp. Cell Res. (2001) pmid: 11237521
173. Patnaik A, et al. Ann. Oncol. (2016) pmid: 27672108
174. Milella M, et al. Sci Rep (2017) pmid: 28220839
175. Templeton AJ, et al. Eur. Urol. (2013) pmid: 23582881
176. Sweeney C, et al. Lancet (2021) pmid: 34246347
177. de Bono JS, et al. Clin. Cancer Res. (2019) pmid: 30037818
178. Saura C, et al. Cancer Discov (2017) pmid: 27872130
179. Voss MH, et al. Clin. Cancer Res. (2018) pmid: 30327302
180. André F, et al. J. Clin. Oncol. (2016) pmid: 27091708
181. Schmid P, et al. J. Clin. Oncol. (2019) pmid: 31841354
182. Weldon Gilcrease G, et al. Invest New Drugs (2019) pmid: 30302599
183. Mendes-Pereira AM, et al. EMBO Mol Med (2009) pmid: 20049735
184. Shen Y, et al. Clin. Cancer Res. (2013) pmid: 23881923
185. Chatterjee P, et al. PLoS ONE (2013) pmid: 23565244
186. McCormick A, et al. Int. J. Gynecol. Cancer (2016) pmid: 26905328
187. Forster MD, et al. Nat Rev Clin Oncol (2011) pmid: 21468130
188. Eikesdal HP, et al. Ann Oncol (2021) pmid: 33242536
189. Dougherty et al., 2014; ASCO Abstract 5536
190. Pan M, et al. Perm J (2021) pmid: 33970096
191. Romero I, et al. Gynecol Oncol (2020) pmid: 32988624
192. Foo WC, et al. Hum. Pathol. (2013) pmid: 23260327
193. Ying H, et al. Cancer Discov (2011) pmid: 21984975
194. Campbell RB, et al. J. Biol. Chem. (2003) pmid: 12857747
195. Rodríguez-Escudero I, et al. Hum. Mol. Genet. (2011) pmid: 21828076
196. He X, et al. Cancer Res. (2013) pmid: 23475934
197. Han SY, et al. Cancer Res. (2000) pmid: 10866302
198. Myers MP, et al. Proc. Natl. Acad. Sci. U.S.A. (1998) pmid: 9811831
199. Pradella LM, et al. BMC Cancer (2014) pmid: 24498881
200. Kim JS, et al. Mol. Cell. Biol. (2011) pmid: 21536651
201. Denning G, et al. Oncogene (2007) pmid: 17213812
202. Hlobilkova A, et al. Anticancer Res. () pmid: 16619501
203. Redfern RE, et al. Protein Sci. (2010) pmid: 20718038
204. Shenoy S, et al. PLoS ONE (2012) pmid: 22505997
205. Wang Y, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19329485
206. Okumura K, et al. J. Biol. Chem. (2006) pmid: 16829519
207. Lee JO, et al. Cell (1999) pmid: 10555148
208. Maxwell GL, et al. Cancer Res. (1998) pmid: 9635567
209. Risinger JI, et al. Clin. Cancer Res. (1998) pmid: 9865913
210. Kato H, et al. Clin. Cancer Res. (2000) pmid: 11051241
211. Fenton TR, et al. Proc. Natl. Acad. Sci. U.S.A. (2012) pmid: 22891331
212. Ngeow J, et al. J. Clin. Endocrinol. Metab. (2012) pmid: 23066114
213. Lobo GP, et al. Hum. Mol. Genet. (2009) pmid: 19457929
214. Liu J, et al. Oncogene (2014) pmid: 23995781
215. Maehama T, et al. Annu. Rev. Biochem. (2001) pmid: 11395408
216. De Vivo I, et al. J. Med. Genet. (2000) pmid: 10807691
217. Ramaswamy S, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10051603
218. Liu JL, et al. Mol. Cell. Biol. (2005) pmid: 15988030
219. Karoui M, et al. Br. J. Cancer (2004) pmid: 15026806
220. Gil A, et al. PLoS ONE (2015) pmid: 25875300
221. Furnari FB, et al. Cancer Res. (1998) pmid: 9823298
222. Spinelli L, et al. J. Med. Genet. (2015) pmid: 25527629
223. Mingo J, et al. Eur. J. Hum. Genet. (2018) pmid: 29706633
224. Wang Q, et al. J. Mol. Graph. Model. (2010) pmid: 20538496
225. Andrés-Pons A, et al. Cancer Res. (2007) pmid: 17942903
226. Butler MG, et al. J. Med. Genet. (2005) pmid: 15805158
227. Georgescu MM, et al. Proc. Natl. Acad. Sci. U.S.A. (1999) pmid: 10468583
228. Staal FJ, et al. Br. J. Cancer (2002) pmid: 12085208
229. Nguyen HN, et al. Oncogene (2014) pmid: 24292679
230. Rahdar M, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19114656
231. Das S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12808147
232. Wang X, et al. Biochem. J. (2008) pmid: 18498243
233. Valiente M, et al. J. Biol. Chem. (2005) pmid: 15951562
234. Nguyen HN, et al. Oncogene (2015) pmid: 25263454
235. Shan L, et al. Cell Discov (2020) pmid: 32704382
236. Blumenthal GM, et al. Eur. J. Hum. Genet. (2008) pmid: 18781191
237. Orloff MS, et al. Oncogene (2008) pmid: 18794875
238. Zbuk KM, et al. Nat. Rev. Cancer (2007) pmid: 17167516
239. Gruber et al., 2019; ASCO Abstract 3006
240. Peasland A, et al. Br. J. Cancer (2011) pmid: 21730979
241. McCabe N, et al. Cancer Res. (2006) pmid: 16912188
242. Jardim MJ, et al. Mol. Biol. Cell (2009) pmid: 19570909
243. Harefuah (1991) pmid: 1937255
244. Sangster-Guity N, et al. Oncogene (2011) pmid: 21258400
245. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
246. Gao J, et al. Sci Signal (2013) pmid: 23550210
247. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
248. Vassileva V, et al. Cancer Res. (2002) pmid: 12124347
249. Miquel C, et al. Oncogene (2007) pmid: 17384679
250. Zhou Y, et al. Biochem Biophys Res Commun (2020) pmid: 32456796
251. Ha K, et al. Mol. Cancer Ther. (2011) pmid: 21566061
252. Liang Y, et al. World J Surg (2009) pmid: 19034564
253. Mordes DA, et al. Genes Dev. (2008) pmid: 18519640
254. Trowbridge JJ, et al. Nat. Genet. (2011) pmid: 22200773
255. Prog Mol Biol Transl Sci (2011) pmid: 21507354
256. Yang J, et al. Mol Med Rep () pmid: 21887466
257. Vallböhmer D, et al. Clin Lung Cancer (2006) pmid: 16870044
258. Daskalos A, et al. Cancer (2011) pmid: 21351083
259. Fabbri M, et al. Proc. Natl. Acad. Sci. U.S.A. (2007) pmid: 17890317
260. Gao Q, et al. Proc. Natl. Acad. Sci. U.S.A. (2011) pmid: 22011581
261. Kim MS, et al. APMIS (2013) pmid: 23031157
262. Chen ZX, et al. J. Cell. Biochem. (2005) pmid: 15861382
263. Guo X, et al. Nature (2015) pmid: 25383530
264. Sandoval JE, et al. J. Biol. Chem. (2019) pmid: 30705090
265. Zhang ZM, et al. Nature (2018) pmid: 29414941
266. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
267. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
268. Xie M, et al. Nat. Med. (2014) pmid: 25326804
269. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
270. Severson EA, et al. Blood (2018) pmid: 29678827
271. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
272. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
273. Chabon JJ, et al. Nature (2020) pmid: 32269342
274. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
275. Braun DA, et al. JAMA Oncol (2019) pmid: 31486842
276. Braun DA, et al. Nat Med (2020) pmid: 32472114
277. Miao D, et al. Science (2018) pmid: 29301960
278. Abou Alaiwi S, et al. Cancer Immunol Res (2020) pmid: 32321774
279. Hakimi AA, et al. Nat Commun (2020) pmid: 32820162
280. Miao D, et al. Nat. Genet. (2018) pmid: 30150660
281. Yang Q, et al. Ann Transl Med (2021) pmid: 33850862
282. Varela I, et al. Nature (2011) pmid: 21248752
283. Fujimoto A, et al. Nat Commun (2015) pmid: 25636086
284. Jiao Y, et al. Nat. Genet. (2013) pmid: 24185509
285. Churi CR, et al. PLoS ONE (2014) pmid: 25536104
286. Simbolo M, et al. Oncotarget (2014) pmid: 24867389
287. Nature (2014) pmid: 24476821
288. Robertson AG, et al. Cell (2017) pmid: 28988769
289. Pietzak EJ, et al. Eur. Urol. (2017) pmid: 28583311
290. Williams EA, et al. Acta Neuropathol. (2020) pmid: 32405805
291. Petrini I, et al. Nat. Genet. (2014) pmid: 24974848
292. da Costa WH, et al. BJU Int. (2014) pmid: 24053427
293. Pawłowski R, et al. Int. J. Cancer (2013) pmid: 22949125
294. Hakimi AA, et al. Eur. Urol. (2013) pmid: 23036577
295. Numata M, et al. Int. J. Oncol. (2013) pmid: 23229642
296. Hakimi AA, et al. Clin. Cancer Res. (2013) pmid: 23620406
297. Peña-Llopis S, et al. Nat. Genet. (2012) pmid: 22683710
298. Kapur P, et al. Lancet Oncol. (2013) pmid: 23333114
299. Lemon B, et al. Nature () pmid: 11780067
300. Xia W, et al. Cancer Res. (2008) pmid: 18339845
301. Hopson S, et al. ACS Chem. Biol. (2017) pmid: 28921948
302. Porter EG, et al. J. Biol. Chem. (2017) pmid: 28053089
303. Niimi A, et al. Mutat. Res. (2015) pmid: 26117423
304. Brownlee PM, et al. Cell Rep (2014) pmid: 24613357
305. Kakarougkas A, et al. Mol. Cell (2014) pmid: 25066234
306. Gao W, et al. Proc. Natl. Acad. Sci. U.S.A. (2017) pmid: 28082722
307. Del Conte G, et al. Br. J. Cancer (2014) pmid: 25025963
308. Maio et al., 2021; AACR Abstract CT178
309. Golan et al., 2021; ASCO Abstract 378
310. Golan et al., 2018; ASCO Abstract 297
311. Konstantinopolous et al., 2018; ASCO Abstract 106

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

312. Chi J, et al. Therap Adv Gastroenterol (2021) pmid: 34025781
313. Mirza et al., 2016; ASCO Abstract 5555
314. Shapira-Frommer et al., 2015; ASCO Abstract 5513
315. Kristeleit et al., 2014; ASCO Abstract 2573
316. Domcheck et al., 2016; ASCO Abstract 4110
317. Shroff RT, et al. JCO Precis Oncol (2018) pmid: 30051098
318. Binder et al., 2019; AACR Abstract CT234
319. Turner et al., 2017; ASCO Abstract 1007
320. Litton JK, et al. N. Engl. J. Med. (2018) pmid: 30110579
321. Ettl J, et al. Ann. Oncol. (2018) pmid: 30124753
322. Meehan et al., 2017; AACR Abstract 4687
323. de Bono J, et al. Cancer Discov (2017) pmid: 28242752
324. Lu E, et al. J Natl Compr Canc Netw (2018) pmid: 30099369
325. De Bono et al., 2020; ASCO Abstract 5566
326. Piha-Paul et al., 2017; EORTC-NCI-AACR Abstract A096

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