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 Unknown primary carcinoma (NOS)
NAME
DATE OF BIRTH
SEX
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN
MEDICAL FACILITY Arias Stella
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 317319
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Kidney
SPECIMEN ID H21 05309-1A
SPECIMEN TYPE Block
DATE OF COLLECTION 06 July 2021
SPECIMEN RECEIVED 29 July 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 8 Muts/Mb

Genomic Findings

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

PBRM1 D18fs*27
SETD2 Q7*
VHL N141fs*3

0 Therapies with Clinical Benefit
0 Therapies with Resistance
0 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 8 Muts/Mb

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials are associated with the Genomic Findings for this sample.

If you have questions or comments about this result, please contact your Foundation Medicine customer support representative.

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VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

VHL - N141fs*3 ..... p. 5

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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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
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4]. In a retrospective analysis of 361 patients with solid tumors treated with pembrolizumab, 3% were MSI-H and experienced a significantly higher ORR compared with non-MSI-H cases (70% vs. 12%, p=0.001)[5].

FREQUENCY & PROGNOSIS

MSI-high (MSI-H) has been observed at high frequency in endometrial cancers (14-33%)[6-13], colorectal cancers (CRCs; 10-15%)[3,14-17], and gastric cancers (12-35%)[18-21] and at lower frequencies in many other tumor types, including esophageal[22], small bowel[23-27], hepatobiliary[28-34], prostate[35-37], and urinary tract carcinomas[38-40]. In one study, MSI-H status was associated with a positive prognostic effect in patients with gastric cancer treated with surgery alone and a negative predictive effect in patients treated with chemotherapy[41]. Data regarding the role of MSI-H on prognosis and survival in endometrial cancer are conflicting[6,9-10,12,42-44]. However, studies specifically analyzing early stage endometrial cancer have reported a correlation between MSI-H and decreased survival[8,11,13,43], thereby suggesting that MSI-H predicts for poor prognosis in this subset of endometrial tumors.

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[16]. 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[16,45-46]. This sample is microsatellite-stable (MSS), equivalent to the clinical definition of an MSS tumor: one with mutations in none of the tested microsatellite markers[15,47-48]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15-16,46,48].

BIOMARKER

Tumor Mutational Burden

RESULT
8 Muts/Mb

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[49-51], anti-PD-1 therapies[49-52], and combination nivolumab and ipilimumab[53-58]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[49-52,59]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[49]. 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[60] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[50]. 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[52,59]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Carcinomas that have been reported to harbor the highest frequencies of elevated TMB include colorectal (CRC) (8-25%)[17,61], endometrial (7-24%)[62], intestinal type gastric (20%)[63], and non-small cell lung carcinoma (NSCLC; 8-13%)[64-65] . In patients with NSCLC, increased TMB is associated with higher tumor grade and poor prognosis[66], as well as with a decreased frequency of known driver mutations in EGFR, ALK, ROS1, or MET (1% of high-TMB samples each), but not BRAF (10.3%) or KRAS (9.4%)[64]. Although some studies have reported a lack of association between smoking and increased TMB in NSCLC[66-67], several other large studies did find a strong link[68-71]. In CRC, elevated TMB is associated with a higher frequency of BRAF V600E driver mutations[17,61] and with microsatellite instability (MSI)[61], which in turn has been reported to correlate with better prognosis[14,72-78]. Although increased TMB is associated with increased tumor grade in endometrioid endometrial carcinoma[62,79-81] and bladder cancer[82], it is also linked with improved prognosis in patients with these tumor types[62].

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[83-84] and cigarette smoke in lung cancer[85-86], treatment with temozolomide-based chemotherapy in glioma[87-88], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[17,62,89-91], and microsatellite instability (MSI)[17,62,91]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[50-51,59].

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GENE
PBRM1

ALTERATION
D18fs*27

TRANSCRIPT ID
NM_018313

CODING SEQUENCE EFFECT
52delG

VARIANT ALLELE FREQUENCY (% VAF)
27.2%

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[92-94]. 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[95-98].

FREQUENCY & PROGNOSIS

Somatic mutations in PBRM1 are prevalent in clear cell renal cell carcinomas (ccRCC) (41%)[99], intrahepatic cholangiocarcinomas (9-13%)[100-103], and bladder urothelial carcinomas (6-14%)[104-106]. PBRM1 mutations are detected in other tumor types, including in 37% (11/30) of papillary meningiomas and 4% (2/54) of thymic carcinomas[107-108] and in skin (6%), large intestine (5%), stomach (5%), soft tissue (3%), and lung (2%) (COSMIC, 2021)[109]. Preclinical studies have shown that loss of PBRM1 increases the proliferation of ccRCC cell lines[99]. PBRM1 protein loss or mutation is correlated with late tumor stage, low differentiation grade, and/or poor patient prognosis in ccRCC[110-112], extrahepatic cholangiocarcinoma[102], and pancreatic cancer[113]. However, one ccRCC study reported no correlation between PBRM1 mutation and cancer-specific survival[114]. In ccRCC, PBRM1 alterations are generally observed to be mutually exclusive with BAP1 alterations[99,115]; 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[116]. A trend toward worse survival was also seen in patients with intrahepatic cholangiocarcinoma harboring mutations in chromatin modifiers (including BAP1, ARID1A, or PBRM1)[101].

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[117]. Mutation, loss, or inactivation of PBRM1 has been reported in several cancers, suggesting PBRM1 is a tumor suppressor[99,101,118]. Alterations such as seen here may disrupt PBRM1 function or expression[119-124].

GENE
SETD2

ALTERATION
Q7*

TRANSCRIPT ID
NM_014159

CODING SEQUENCE EFFECT
19C>T

VARIANT ALLELE FREQUENCY (% VAF)
35.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in SETD2.

FREQUENCY & PROGNOSIS

Somatic inactivating alterations of SETD2 are documented to occur at low frequency in a number of solid tumors, most commonly in renal carcinoma[99]. SETD2 has been associated with favorable prognosis in gastric cancer[125]. SETD2 has also been associated with poor prognosis in RCC and MDS[126], while data in other tumor types is limited (PubMed, Jun 2021).

FINDING SUMMARY

SETD2 encodes a histone lysine-36 methyltransferase[127] that preferentially interacts with the expanded N-terminal polyglutamine tracts present in mutant huntingtin, implicating it in the pathogenesis of Huntington disease[128]. SETD2 mRNA expression has been observed to be consistently reduced in breast tumors relative to adjacent non-tumor tissue, suggesting a potential tumor suppressor role[129]. SETD2 alterations such as observed here have been shown to be inactivating[130-135].

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GENE
VHL

ALTERATION
N141fs*3

TRANSCRIPT ID
NM_000551

CODING SEQUENCE EFFECT
420_421insC

VARIANT ALLELE FREQUENCY (% VAF)
24.2%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Various strategies are under clinical investigation to block pathways downstream of inactivated VHL, including HIF, VEGF, and mTOR. The multikinase inhibitor sunitinib, which has activity against VEGFRs and other targets, is approved to treat several tumor types and has shown strong efficacy in patients with VHL disease[136-140]. Several clinical trials found response rates up to 64% and disease control rates up to 90%[141-142]. However, multiple clinical studies of sunitinib in patients with renal cell carcinoma reported that mutation or inactivation of the VHL gene is not significantly associated with therapeutic response or survival[143-145]. Other agents that inhibit VEGFRs, including the multikinase inhibitors sorafenib, axitinib, pazopanib, regorafenib, cabozantinib, and vandetanib; the anti-VEGFR2 antibody ramucirumab; and the mTOR inhibitors everolimus and temsirolimus, are also approved in multiple tumor types. However, studies have similarly shown that VHL mutation or inactivation does not correlate with responses to these agents[144,146-147]. Therefore, it is unclear whether these therapeutic strategies would be beneficial in this case. The HIF2a inhibitor belzutifan achieved an ORR of 36% in a clinical trial for VHL disease-associated clear cell renal cell carcinoma[148]. Responses were also seen in other VHL mutation-associated tumor types, including CNS hemangioblastomas and pancreatic neuroendocrine tumors; however, it was not determined whether VHL inactivation was significantly associated with these responses[148].

FREQUENCY & PROGNOSIS

VHL mutations have been reported in 4.5% of all tumor samples analyzed in COSMIC, including 51% of renal clear cell carcinomas, 35% of hemangioblastomas, and 6.4% of pheochromocytomas (Feb 2021)[109]. Studies exploring the prognostic value of VHL mutation in RCC have given mixed results[149]. In colorectal cancer, increased pVHL expression has been observed at the invading tumor margin and correlated with worse disease-free survival[150]. In contrast, VHL has been reported to be hypermethylated and downregulated in non-small cell lung cancer[151], and VHL copy number loss was associated with poor survival in this tumor type[152].

FINDING SUMMARY

VHL encodes the protein pVHL (von Hippel-Lindau tumor suppressor), which is frequently inactivated, either via mutation or hypermethylation, in clear cell renal cell carcinoma (ccRCC) and plays an important role in its pathogenesis[153]. Inactivating mutations in VHL lead to dysregulation of critical downstream growth regulators, especially members of the HIF family and VEGF[154-155]. Alterations such as seen here may disrupt VHL function or expression[156-194].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the VHL variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with von Hippel-Lindau syndrome (ClinVar, Mar 2021)[195]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in VHL underlie von Hippel-Lindau syndrome, a rare but highly penetrant autosomal dominant syndrome occurring in 1/36,000 live births that predisposes to the development of several types of cancer, including clear cell renal cell carcinomas and pancreatic neuroendocrine tumors, as well as retinal and central nervous system hemangioblastomas[196-198]. In the appropriate clinical context, germline testing of VHL is recommended.

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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.

AXL
R190C

FLT1
R1045Q

GATA4
P80S

KMT2A (MLL)
A53V

MSH2
R929Q

TSC1
K587R

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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. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
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

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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%.

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 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

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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 5.0.0

The median exon coverage for this sample is 966x

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