FOUNDATIONONE® CDx

PATIENT | TUMOR TYPE | REPORT DATE

COUNTRY CODE | ORDERED TEST #

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

PATIENT	PHYSICIAN	SPECIMEN
DISEASE	ORDERING PHYSICIAN	SPECIMEN SITE
NAME	MEDICAL FACILITY	SPECIMEN ID
DATE OF BIRTH		SPECIMEN TYPE
SEX	ADDITIONAL RECIPIENT	DATE OF COLLECTION
MEDICAL RECORD #	MEDICAL FACILITY ID	SPECIMEN RECEIVED
	PATHOLOGIST	

Genomic Signatures

HRD signature - HRDsig Negative
Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Gene Alterations

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

CREBBP I1084fs*3

Report Highlights

- There are no highlights associated with this patient's genomic findings.

For more information on potential biological and clinical significance, see the Genomic Signatures and Gene Alterations sections.

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
HRD signature - HRDsig Negative	**No therapies or clinical trials.** See Genomic Signatures section
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Genomic Signatures section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Genomic Signatures section

No therapies or clinical trials are associated with the Gene Alterations for this sample.

If you have questions or comments about this result, please contact your local Customer Service team (https://www.rochefoundationmedicine.com/#/en/international/ordering-support)

GENE ALTERATIONS 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 Alterations section.

CREBBP - I1084fs*3 ..... p. 4

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 through a centralized EU procedure or a national procedure in an EU Member State. Therapies, including but not limited to the following, have been approved nationally and may not be available in all EU Member States: Tretinoin, Anastrozole, Bicalutamide, Cyproterone, Exemestane, Flutamide, Goserelin, Letrozole, Leuprorelin, Triptorelin.

Electronically signed by J. Keith Killian, M.D. | 28 January 2025
Roche Customer Care | www.rochefoundationmedicine.com

Sample Preparation: Foundation Medicine GmbH, Nonnenwald 2, 82377 Penzberg, Germany
Sample Analysis: Foundation Medicine GmbH, Nonnenwald 2, 82377 Penzberg, Germany

GENOMIC SIGNATURE

HRD signature

RESULT
HRDsig Negative

SCORE
0.03

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical data from real-world clinicogenomic database analyses, HRD signature (HRDsig) Positive status is associated with sensitivity to PARP inhibitors. Multiple studies of patients with either metastatic castration-resistant prostate cancer or metastatic breast cancer treated with PARP inhibitors observed more favorable OS, PFS, and time to treatment discontinuation for patients with HRDsig Positive status compared with patients with HRDsig Negative status[1-3]. Patients with HRDsig Positive platinum-sensitive advanced ovarian cancer who received PARP inhibitor maintenance therapy had more favorable PFS than patients who received no maintenance therapy or patients with HRDsig Negative status[4]. Additionally, in a real-world dataset, HRDsig Positive status was associated with improved outcomes on a platinum chemotherapy-containing regimen in pancreatic cancer[5].

FREQUENCY & PROGNOSIS

HRD signature (HRDsig) Positive status has been identified in multiple solid tumor types, including ovarian (39%), breast (21%), prostate (15%), and pancreas (9%)[2-3,5-6]. A pan-cancer analysis of a large real-world dataset found a strong association between HRDsig Positive status and biallelic inactivation of BRCA1/2 in ovarian, prostate, and pancreatic cancers[3]. Published data investigating the prognostic implications of HRDsig Positive status in solid tumors are limited (PubMed, Jul 2024).

FINDING SUMMARY

Homologous recombination deficiency (HRD) produces characteristic genome-wide changes that accumulate as genomic scars because of incorrect DNA double-strand break repair. HRD signature (HRDsig) is a biomarker developed and validated to classify HRD status in pan-cancer samples using hundreds of copy number (CN) features to capture these genomic changes. HRDsig identifies both genomic and non-genomic mechanisms of HRD and has high sensitivity to detect samples with biallelic genomic alterations in homologous recombination repair (HRR) genes such as BRCA1/2. This sample has a status of HRD signature (HRDsig) Negative, defined as a model score of <0.7.

GENOMIC SIGNATURE

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[7-9], including approved therapies nivolumab and pembrolizumab[10-11]. 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)[12].

FREQUENCY & PROGNOSIS

Rare instances of MSI have been reported in salivary gland carcinomas[13-14]; however, two larger studies reported no MSI in 58 total salivary gland tumors[15-16]. Published data investigating the prognostic implications of MSI in salivary gland carcinoma are limited (PubMed, Feb 2024). Published data investigating the prognostic implications of MSI in solid tumors has largely been conducted in colon, endometrial, and gastrointestinal cancers due to the higher prevalence in these tumor types. For patients with Stage 2 CRC, deficient DNA MMR and MSI-High status are associated with better prognosis (NCCN Colon Cancer Guidelines, v1.2024, NCCN Rectal Cancer Guidelines, v1.2024)[17-20]; however, the prognostic impact for patients with more advanced cancer is less clear[17,21]. For patients with endometrial cancer, microsatellite status and the presence or absence of pathogenic alterations in POLE and TP53 molecularly defines subpopulations with specific prognostic implications (NCCN Uterine Neoplasms Guidelines, v2.2024)[22-28]. In gastric and gastroesophageal cancers, MSI-High has been associated with certain clinicopathological and molecular features as well as better prognosis[29-35], while MS-Stable and MSI-Low were correlated with increased benefit for patients treated with chemotherapy[35-36].

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 MMR in the tumor[37]. 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[37-39]. 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[40-42]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[37,39,41-42].

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
2 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[43-46], anti-PD-1 therapies[44-48], and combination nivolumab and ipilimumab[49-57]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[43-46,48,58-62]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[58]; similar findings were observed in the KEYNOTE 028 and 012 trials[48]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[62]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[63]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[61]. Similarly, 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[43] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[44].

FREQUENCY & PROGNOSIS

Studies of salivary gland carcinomas reported a median tumor mutational burden (TMB) of 1.7-3.6 Muts/Mb for salivary gland carcinomas, with 13% of salivary gland carcinoma cases harboring a TMB of ≥10 Muts/Mb[64-65]. For patients with salivary gland carcinoma not treated with immunotherapy, no significant association between high levels of tissue tumor mutational burden (TMB) (≥10 mut/Mb) and OS was reported in one study, although OS numerically differed between patients with high and lower TMB (4.5 vs. 15.5 months, adjusted HR=1.20)[65].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions 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[66-67] and cigarette smoke in lung cancer[68-69], treatment with temozolomide-based chemotherapy in glioma[70-71], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[28,72-75], and microsatellite instability[28,72-73]. 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[44-45,58].

GENE
CREBBP

ALTERATION
I1084fs*3

HGVS VARIANT
NM_004380.2:c.3244dup (p.I1084Nfs*3)

VARIANT CHROMOSOMAL POSITION
chr16:3817720

VARIANT ALLELE FREQUENCY (% VAF)
46.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in CREBBP. Limited data suggest that CREBBP mutations may be associated with sensitivity to histone deacetylase inhibitors, although conflicting data have also been reported[76-80].

FREQUENCY & PROGNOSIS

CREBBP mutations have been observed at high frequency in follicular lymphoma (FL, 26%) and diffuse large B-cell lymphoma (DLBCL, 16%), and at lower frequency in acute lymphoblastic leukemia (ALL, 7%), and tumors of the urinary tract (15%), skin (12%), liver (8.7%), endometrium (8.5%), and stomach (8.2%)(COSMIC, Jan 2025)[81]. These mutations include missense substitutions clustered in the CREBBP histone acetyltransferase domain and truncating mutations throughout the gene sequence, suggesting a role for CREBBP inactivation in these diseases. CREBBP mutations have been reported to occur in the transition from prostate acinar carcinoma to squamous cell carcinoma (SCC)[82], which may indicate significance for CREBBP in SCC. In two cases of relapsed pediatric B-cell ALL, CREBBP mutation conferred resistance to glucocorticoid therapy[83]. Reports have found CREBBP mutation in 62-68% of patients with FL[84-85], which was associated with immune evasion[84]. AML with MYST3/CREBBP fusion was reported to occur in 60-80% of cases 9-72 months after adjuvant chemotherapy for breast cancer and was associated with a poor prognosis[86-87].

FINDING SUMMARY

CREBBP encodes a ubiquitously expressed transcriptional coregulatory protein that interacts with multiple transcription factors and can couple control of gene expression to chromatin remodeling via its histone acetyltransferase activity. Inherited microdeletions and truncating point mutations in CREBBP are reported to be causal in approximately 20% of cases of Rubinstein-Taybi syndrome[88]. The chromosomal rearrangement t(8;16)(p11;p13) is characteristic of the M4/M5 subtype of acute myeloid leukemia (AML) and results in a chimeric gene fusing MYST3/MOZ (a gene essential for the development of the hematopoietic system and maintenance of hematopoietic stem cells) to CREBBP[89]. CREBBP-BCORL1 fusion has been reported in patients with ossifying fibromyxoid tumors[90-91].

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.

AURKB
NM_004217.2: c.307G>A
(p.V103M)
chr17:8110585
6.7% VAF

ERCC4
NM_005236.2: c.2647G>A
(p.E883K)
chr16:14042100
46.1% VAF

KDR
amplification

KIT
amplification

KMT2D (MLL2)
NM_003482.4: c.15695T>A
(p.I5232N)
chr12:49420054
86.5% VAF

PDGFRA
amplification and
PDGFRA(NM_006206)
rearrangement intron 18

PIK3C2G
NM_004570.4: c.2828G>A
(p.W943*)
chr12:18650617
8.1% VAF

APPENDIX Genes Assayed in FoundationOne®CDx

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 or WTX)*	
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*	*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*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
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	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (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*	*MRE11 (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*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*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*
PRKN (PARK2)	*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*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*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 GENOMIC SIGNATURES

HRD signature (HRDsig)
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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. Foundation Medicine GmbH is accredited by DAkkS according to DIN EN ISO 15189:2014. The accreditation only applies to the scope of accreditation listed in certificate D-ML-21105-01-00. 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: https://www.foundationmedicine.qarad.eifu.online/foundationmedicine/en/foundationmedicine?keycode=286605475.

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, genomic loss of heterozygosity (LOH) score and homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high), 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 PRINCIPLE

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® Sequencing platform (HiSeq 4000 or NovaSeq 6000), 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 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: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

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

Genomic signatures and gene alterations 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 genomic signature or gene alteration. 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. 2023. 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 fraction-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. Homologous recombination deficiency (HRD) produces characteristic genome-wide changes that can be captured by analyzing segmented copy number (CN) profiles. HRD signature (HRDsig) is a biomarker developed and validated to classify HRD status in pan-cancer samples using hundreds of CN features detected by the FoundationOne CDx test. HRDsig may be reported as a laboratory professional service for any solid tumor sample. Samples with score ≥0.7 are reported as "HRDsig Positive" and samples with score <0.7 are reported as "HRDsig Negative." The HRDsig score is not an HRD accumulation or probability score, but rather a model score; it ranges from 0–1 and has a bimodal distribution, with most pan-cancer results falling between 0–0.2 or 0.8–1. The score is provided as additional information but has not been validated as a stand-alone biomarker to support clinical decision making and should be integrated with other patient-specific factors, including cancer type and other genomic findings. HRDsig is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine CN features.
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 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%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). 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 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
ctDNA	Circulating tumor DNA
DCR	Disease control rate
DFS	Disease-free survival
DOR	Duration of response
EFS	Event-free survival
ER	Estrogen receptor
HR +/-	Hormone-receptor positive/negative
ITD	Internal tandem duplication
MR	Molecular response
MMR	Mismatch repair
Muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
mOS	Median overall survival
PD	Progressive disease
PFS	Progression-free survival
mPFS	Median progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
R/R	Relapsed or refractory
SD	Stable disease
TKI	Tyrosine kinase inhibitor
CRC	Colorectal cancer
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
NSCLC	Non-small cell lung cancer
RCC	Renal cell carcinoma
SCC	Squamous cell carcinoma

REFERENCE SEQUENCE INFORMATION

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

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 8.6.0
MR Reporting Config Version 70
Analysis Pipeline Version v3.39.0
Computational Biology Suite Version 6.34.0

The median exon coverage for this sample is 2,638x

1. Triner et al., 2024; ASCO GU Abstract 186
2. Batalini F, et al. JCO Precis Oncol (2023) pmid: 37992259
3. Moore JA, et al. JCO Precis Oncol (2023) pmid: 37769224
4. Richardson DL, et al. Clin Cancer Res (2024) pmid: 39078736
5. Chen KT, et al. Oncologist (2023) pmid: 37354528
6. Richardson et al., 2023; ASCO Abstract 5583
7. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
8. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
9. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
10. Overman et al., 2016; ASCO Abstract 3501
11. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
12. Ayers et al., 2016; ASCO-SITC Abstract P60
13. Suzuki H, et al. Diagn. Mol. Pathol. (1998) pmid: 9917133
14. Moore A, et al. Head Neck (2020) pmid: 31762146
15. Ohki K, et al. Int J Oral Maxillofac Surg (2001) pmid: 11829237
16. Nakano T, et al. Oral Oncol. (2019) pmid: 30846173
17. Argilés G, et al. Ann Oncol (2020) pmid: 32702383
18. Ribic CM, et al. N. Engl. J. Med. (2003) pmid: 12867608
19. Sargent DJ, et al. J. Clin. Oncol. (2010) pmid: 20498393
20. Sinicrope FA, et al. J Natl Cancer Inst (2011) pmid: 21597022
21. Van Cutsem E, et al. Ann Oncol (2014) pmid: 25190710
22. Wu et al., 2022;36357827
23. McCluggage WG, et al. Histopathology (2022) pmid: 34996131
24. Oaknin A, et al. Ann Oncol (2022) pmid: 35690222
25. Talhouk A, et al. Br J Cancer (2015) pmid: 26172027
26. Concin N, et al. Virchows Arch (2021) pmid: 33604759
27. León-Castillo A, et al. J Clin Oncol (2020) pmid: 32749941
28. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
29. Zhu L, et al. Mol Clin Oncol (2015) pmid: 26137290
30. Leung SY, et al. Cancer Res. (1999) pmid: 9892201
31. dos Santos NR, et al. Gastroenterology (1996) pmid: 8536886
32. Wu MS, et al. Cancer Res. (1998) pmid: 9537253
33. Seo JY, et al. World J. Gastroenterol. (2015) pmid: 26078567
34. Nature (2014) pmid: 25079317
35. Pietrantonio F, et al. J. Clin. Oncol. (2019) pmid: 31513484
36. Janjigian YY, et al. Cancer Discov (2018) pmid: 29122777
37. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
38. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
39. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
40. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
41. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
42. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
43. Legrand et al., 2018; ASCO Abstract 12000
44. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
45. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
46. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
47. Marabelle et al., 2019; ESMO Abstract 11920
48. Cristescu R, et al. Science (2018) pmid: 30309915
49. Hodi et al., 2019; AACR abstract CT037
50. Lee et al., 2019; ASCO Abstract 641
51. Rizvi et al., 2017; WCLC Abstract 1106
52. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
53. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
54. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
55. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
56. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
57. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
58. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
59. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
60. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
61. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
62. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
63. Schenker at al., 2022; AACR Abstract 7845
64. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
65. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
66. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
67. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
68. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
69. Rizvi NA, et al. Science (2015) pmid: 25765070
70. Johnson BE, et al. Science (2014) pmid: 24336570
71. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
72. Nature (2012) pmid: 22810696
73. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
74. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
75. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
76. Mullighan CG, et al. Nature (2011) pmid: 21390130
77. Andersen CL, et al. Leuk Res Rep (2012) pmid: 24371765
78. Mensah AA, et al. Oncotarget (2015) pmid: 25671298
79. Zhang MC, et al. Clin Epigenetics (2020) pmid: 33097085
80. Sun Y, et al. Cancer Lett (2021) pmid: 34481935
81. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
82. Grasso CS, et al. Ann. Oncol. (2015) pmid: 25735316
83. Ma X, et al. Nat Commun (2015) pmid: 25790293
84. Green MR, et al. Proc. Natl. Acad. Sci. U.S.A. (2015) pmid: 25713363
85. Loeffler M, et al. Leukemia (2015) pmid: 25027518
86. Gervais C, et al. Leukemia (2008) pmid: 18528428
87. Haferlach T, et al. Leukemia (2009) pmid: 19194466
88. Petrij F, et al. J. Med. Genet. (2000) pmid: 10699051
89. Borrow J, et al. Nat. Genet. (1996) pmid: 8782817
90. Kao YC, et al. Genes Chromosomes Cancer (2017) pmid: 27537276
91. Hofvander J, et al. Mod. Pathol. (2020) pmid: 31932680