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 Thyroid medullary carcinoma

DATE OF BIRTH 05 September 1993
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN

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

SPECIMEN

SPECIMEN SITE Head and Neck
SPECIMEN ID 20-11477-3
SPECIMEN TYPE Block
DATE OF COLLECTION 04 December 2020
SPECIMEN RECEIVED 08 July 2021

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
Tumor Mutational Burden - Cannot Be Determined

Genomic Findings

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

MAP2K1 (MEK1) I103_K104del

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

2 Therapies with Clinical Benefit
0 Therapies with Lack of Response
6 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
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 BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***MAP2K1 (MEK1)* -** I103_K104del	none	Selumetinib
6 Trials *see p. 5*		Trametinib

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.

Electronically signed by Brennan Decker, M.D., Ph.D. | 18 July 2021
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BIOMARKER

Microsatellite status

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of prospective clinical evidence in multiple solid tumor types, MSI and associated increased mutational burden[1-2] may predict sensitivity to anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors[2-6], including the approved therapies nivolumab (alone or in combination with ipilimumab)[7-9], pembrolizumab[10-11], atezolizumab, avelumab, and durvalumab[3-5] . As the MSI status of this tumor is unknown, the relevance of these therapeutic approaches is unclear.

FREQUENCY & PROGNOSIS

MSI has been reported in 17-65% (n = 17-76) of thyroid cancer cases[12-15]. One study reported MSI positivity in 84% (59/70) of papillary thyroid carcinoma (PTC) cases, with 64% (38/59) being MSI-H and 46% (21/59) being MSI-low (MSI-L), and MSI positivity in 92% (11/12) of follicular thyroid carcinoma (FTC) cases, with 82% (9/11) being MSI-H and 18% (2/11) being MSI-L; MSI-H was not observed in benign thyroid samples[16]. MSI was significantly associated with low risk characteristics in patients with malignant thyroid tumors[15], and MSI positivity at one or more marker sites was significantly associated with improved survival in patients with thyroid cancer[14]. One study reported an increased incidence of MSI in pediatric and adult patients with radiation-associated thyroid cancer, as compared with spontaneous thyroid carcinomas without radiation history[17].

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[18]. 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[18-20]. 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.

POTENTIAL GERMLINE IMPLICATIONS

While approximately 80% of MSI-H tumors arise due to somatic inactivation of an MMR pathway protein, about 20% arise due to germline mutations in one of the MMR genes[18], which are associated with a condition known as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC)[21]. Lynch syndrome leads to an increased risk of colorectal, endometrial, gastric, and other cancers[21-23] and has an estimated prevalence in the general population ranging from 1:600 to 1:2000[24-26]. Therefore, in the appropriate clinical context, germline testing of MLH1, MSH2, MSH6, and PMS2 is recommended.

BIOMARKER

Tumor Mutational Burden

RESULT
Cannot Be Determined

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[27-29], anti-PD-1 therapies[27-30], and combination nivolumab and ipilimumab[31-36]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[27-30,37]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[27]. 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[38] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[28]. 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[30,37]. 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

Median TMB is relatively low in thyroid carcinomas, with 1.8 mutations per megabase (muts/Mb) reported in papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC) and 2.5 muts/Mb reported in anaplastic thyroid carcinoma (ATC)[39]. High TMB (>20 muts/Mb) has been reported in 1% of MTCs and 1.4% of ATCs, but not in any of the PTCs or FTCs analyzed[39]. A whole exome study of 39 follicular thyroid carcinoma tissue samples reported a worse prognosis for those with higher mutational burden (hazard ration 1.4, p=0.02), independent of histopathological classification[40].

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[41-42] and cigarette smoke in lung cancer[11,43], treatment with temozolomide-based chemotherapy in glioma[44-45], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[46-50], and microsatellite instability (MSI)[46,49-50]. 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[28-30,37]. However, the TMB level in this sample could not be determined with confidence.

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GENE
MAP2K1 (MEK1)

ALTERATION
I103_K104del

TRANSCRIPT ID
NM_002755

CODING SEQUENCE EFFECT
306_311delGATCAA

VARIANT ALLELE FREQUENCY (% VAF)
24.2%

POTENTIAL TREATMENT STRATEGIES

Preclinical and clinical data suggest that activating alterations in MAP2K1 may predict sensitivity to MEK inhibitors[51-56] such as cobimetinib, trametinib, and selumetinib. On the basis of clinical[57-61] and preclinical[62-63] data, certain MAP2K1 mutations, including Q56P, K57E, and C121S, are associated with resistance to the BRAF inhibitors dabrafenib and vemurafenib. Combinations of both MEK and BRAF inhibitors were able to overcome drug resistance in BRAF- and MAP2K1-mutated melanoma cell lines in preclinical assays[64].

FREQUENCY & PROGNOSIS

MAP2K1 mutation has been observed in 1% of thyroid carcinomas (COSMIC, Apr 2021)[65]. Published data investigating the prognostic implications of MAP2K1 alterations in thyroid carcinoma are limited (PubMed, Apr 2021).

FINDING SUMMARY

MAP2K1 (also known as MEK1) encodes the signaling protein mitogen-activated protein kinase kinase 1 (MKK1 or MEK1). MEK1 phosphorylates the ERK1/2 proteins in the RAS-RAF-MAP kinase pathway, a critical pathway in processes of cell division and differentiation[66]. MAP2K1 alterations, such as observed here, have been characterized as activating and are predicted to be oncogenic[51,53,56,59-60,62-64,67-76].

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Selumetinib

Assay findings association

MAP2K1 (MEK1)
I103_K104del

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Based on preclinical[54] and clinical[52-53,77] evidence, MAP2K1 activating alterations may predict sensitivity to MEK inhibitors. A patient with metastatic low-grade serous (LGS) ovarian cancer harboring an activating MAP2K1 mutation has achieved a durable (greater than 5 years) ongoing complete response to MEK inhibitor selumetinib[53]. Patients with Erdheim-Chester disease harboring MAP2K1 alterations benefited from cobimetinib treatment[52,77] .

SUPPORTING DATA

A Phase 2 trial of selumetinib in radioactive iodine (RAI) refractory papillary thyroid cancer reported 1 PR (3.1%), 21 SD (65.6%), and 11 PD (34.4%) out of 32 evaluable patients, but failed to meet the primary outcome of ORR[78]. In this study, BRAF V600E mutation was associated with longer median PFS (33 weeks) compared to BRAF wild type (11 weeks)[78]. Single-agent selumetinib induced RAI uptake for 12 of 20 patients with RAI-refractory differentiated thyroid cancer, leading to clinical responses for all 8 patients that reached the dosimetry threshold, including all 5 patients with NRAS mutations[79].

Trametinib

Assay findings association

MAP2K1 (MEK1)
I103_K104del

AREAS OF THERAPEUTIC USE

Trametinib is a MEK inhibitor that is FDA approved as a monotherapy to treat patients with melanoma with BRAF V600E or V600K mutations. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of emerging clinical evidence, activating alterations or amplification of MAP2K1 may predict sensitivity to MEK inhibitors such as trametinib. Patients with MAP2K1-mutated histiocytic neoplasms[52,55,80] , MAP2K1-mutated hairy cell leukemia[81], or MAP2K1-amplified triple-negative breast cancer[82] have benefited from treatment with trametinib.

SUPPORTING DATA

Clinical data on the efficacy of trametinib for the treatment of medullary thyroid carcinoma are limited (PubMed, Apr 2021). Clinical data on the efficacy of trametinib for the treatment of medullary thyroid carcinoma are limited (PubMed, Apr 2021). Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[83], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[84].

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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ORDERED TEST # ORD-1139609-01

CLINICAL TRIALS

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
MAP2K1 (MEK1)

RATIONALE
Activating mutation or amplification of MAP2K1 may predict sensitivity to MEK or ERK inhibitors.

ALTERATION
I103_K104del

NCT03989115

PHASE 1/2

Dose-Escalation and Dose-Expansion of RMC-4630 and Cobimetinib in Relapsed/Refractory Solid Tumors

TARGETS
SHP2, MEK

LOCATIONS: Florida, Georgia, Texas, North Carolina, Tennessee, Virginia, Oklahoma, Maryland, Pennsylvania, Ohio

NCT03905148

PHASE 1/2

Study of the Safety and Pharmacokinetics of BGB-283 and PD-0325901 in Patients With Advanced or Refractory Solid Tumors

TARGETS
RAFs, EGFR, MEK

LOCATIONS: Texas, Randwick (Australia), Blacktown (Australia), Melbourne (Australia), Nedlands (Australia)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

LOCATIONS: Sutton (United Kingdom), London (United Kingdom)

NCT04803318

PHASE 2

Trametinib Combined With Everolimus and Lenvatinib for Recurrent/Refractory Advanced Solid Tumors

TARGETS
mTOR, FGFRs, KIT, PDGFRA, RET, VEGFRs, MEK

LOCATIONS: Guangzhou (China)

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

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ORDERED TEST # ORD-1139609-01

CLINICAL TRIALS

NCT02070549

PHASE 1

Trametinib in Treating Patients With Advanced Cancer With or Without Hepatic Dysfunction

TARGETS
MEK

LOCATIONS: Toronto (Canada)

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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.

BRCA1
H888Y

BRCA2
Y3092C

KDR
S515C

LTK
F639L

MAP3K1
L78P

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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 Alterations and Therapies

Biomarker and Genomic Findings

Therapies are ranked based on the following criteria: Therapies with clinical benefit in patient's tumor type (ranked alphabetically within each NCCN category) followed by therapies with clinical benefit in other tumor type (ranked alphabetically within each NCCN category).

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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.

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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%.

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

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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 4.2.0

The median exon coverage for this sample is 981x

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1. Histopathology (2007) pmid: 17204026
2. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
3. Hochster et al., 2017; ASCO Abstract 673
4. Fleming et al., 2018; ASCO Abstract 5585
5. Bang et al., 2018; ASCO Abstract 92
6. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
7. Overman MJ, et al. Lancet Oncol. (2017) pmid: 28734759
8. Overman MJ, et al. J. Clin. Oncol. (2018) pmid: 29355075
9. Lipson EJ, et al. Clin. Cancer Res. (2013) pmid: 23169436
10. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
11. Rizvi NA, et al. Science (2015) pmid: 25765070
12. Soares P, et al. Eur. J. Cancer (1997) pmid: 9135503
13. Lazzereschi D, et al. Br. J. Cancer (1999) pmid: 9888478
14. Onda M, et al. Clin. Cancer Res. (2001) pmid: 11705861
15. Vaish M, et al. Exp. Mol. Med. (2004) pmid: 15150440
16. Santos JC, et al. BMC Cancer (2013) pmid: 23414134
17. Richter HE, et al. Carcinogenesis (1999) pmid: 10590215
18. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
19. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
20. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
21. Lynch HT, et al. Clin. Genet. (2009) pmid: 19659756
22. Pande M, et al. Fam. Cancer (2012) pmid: 22714864
23. Kastrinos F, et al. Semin. Oncol. (2007) pmid: 17920897
24. Silva FC, et al. Sao Paulo Med J (2009) pmid: 19466295
25. Sehgal R, et al. Genes (Basel) (2014) pmid: 24978665
26. Fam. Cancer (2005) pmid: 16136383
27. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
28. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
29. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
30. Cristescu R, et al. Science (2018) pmid: 30309915
31. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
32. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
33. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
34. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
35. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
36. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
37. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
38. Legrand et al., 2018; ASCO Abstract 12000
39. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
40. Nicolson NG, et al. J. Clin. Endocrinol. Metab. (2018) pmid: 29726952
41. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
42. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
43. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
44. Johnson BE, et al. Science (2014) pmid: 24336570
45. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
46. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
47. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
48. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
49. Nature (2012) pmid: 22810696
50. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
51. Choi YL, et al. Carcinogenesis (2012) pmid: 22327936
52. Diamond EL, et al. Cancer Discov (2016) pmid: 26566875
53. Grisham RN, et al. J. Clin. Oncol. (2015) pmid: 26324360
54. Marks JL, et al. Cancer Res. (2008) pmid: 18632602
55. Gounder MM, et al. N. Engl. J. Med. (2018) pmid: 29768143
56. Hanrahan AJ, et al. Cancer Res (2020) pmid: 32641410
57. Long GV, et al. Nat Commun (2014) pmid: 25452114
58. Rizos H, et al. Clin. Cancer Res. (2014) pmid: 24463458
59. Trunzer K, et al. J. Clin. Oncol. (2013) pmid: 23569304
60. Van Allen EM, et al. Cancer Discov (2014) pmid: 24265153
61. Shi H, et al. Cancer Discov (2014) pmid: 24265155
62. Carlino MS, et al. Clin. Cancer Res. (2015) pmid: 25370473
63. Greger JG, et al. Mol. Cancer Ther. (2012) pmid: 22389471
64. Shi H, et al. Cancer Discov (2012) pmid: 22588879
65. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
66. Burgermeister E, et al. Mol. Cell. Biol. (2007) pmid: 17101779
67. Arcila ME, et al. Clin. Cancer Res. (2015) pmid: 25351745
68. Brown NA, et al. Blood (2014) pmid: 24982505
69. Chakraborty R, et al. Blood (2014) pmid: 25202140
70. Emery CM, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915144
71. Nelson DS, et al. Genes Chromosomes Cancer (2015) pmid: 25899310
72. Nikolaev SI, et al. Nat. Genet. (2011) pmid: 22197931
73. Sogabe S, et al. Mol. Cancer Ther. (2014) pmid: 25253779
74. Wang H, et al. Cancer Res. (2011) pmid: 21705440
75. Gao Y, et al. Cancer Discov (2018) pmid: 29483135
76. Sato H, et al. Clin Cancer Res (2020) pmid: 32122926
77. Diamond EL, et al. Nature (2019) pmid: 30867592
78. Hayes DN, et al. Clin. Cancer Res. (2012) pmid: 22241789
79. Ho AL, et al. N. Engl. J. Med. (2013) pmid: 23406027
80. Kumamoto T, et al. Int. J. Hematol. (2019) pmid: 30361829
81. Andritsos et al., 2016; ASH Abstract 5598
82. Parsons HA, et al. Clin. Cancer Res. (2017) pmid: 27489289
83. Tolcher AW, et al. Ann. Oncol. (2015) pmid: 25344362
84. Patterson et al., 2018; AACR Abstract 3891

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