FOUNDATIONONE® HEME

PATIENT

TUMOR TYPE
Soft tissue Ewing sarcoma
COUNTRY CODE
IN

REPORT DATE

ORDERED TEST #

ABOUT THE TEST FoundationOne® Heme is a comprehensive genomic profiling test designed to identify genomic alterations within hundreds of cancer-related genes in hematologic malignancies and sarcomas.

PATIENT
- DISEASE Soft tissue Ewing sarcoma
- NAME
- DATE OF BIRTH
- SEX
- MEDICAL RECORD #

PHYSICIAN
- ORDERING PHYSICIAN
- MEDICAL FACILITY
- ADDITIONAL RECIPIENT
- MEDICAL FACILITY ID
- PATHOLOGIST

SPECIMEN
- SPECIMEN SITE
- SPECIMEN ID
- SPECIMEN TYPE
- DATE OF COLLECTION
- SPECIMEN RECEIVED

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 2 Muts/Mb

Genomic Findings

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

EWSR1 EWSR1-ERG fusion

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EWSR1*** **EWSR1-ERG fusion** (p. 3)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 4)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section
Tumor Mutational Burden - 2 Muts/Mb	**No therapies or clinical trials.** See Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
EWSR1 **-** EWSR1-ERG fusion	none	none
10 Trials see p. 4		

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

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.

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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

Reports of MSI in sarcomas in the literature are conflicting and varied due to substantial heterogeneity, lack of consensus on the markers and methods used for MSI assessment, and small sample size in most studies[6]. In Ewing sarcoma, MSI at any level has been reported in 6% (1/18) to 48% (11/23) of cases[7-9] or reported as absent[10-11], and high MSI has been observed in 2% (1/55) to 17% (4/23) of cases[8-9]. Studies of small patient cohorts have not shown a significant correlation between MSI status and survival in Ewing sarcoma[8-9].

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[12]. 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[12-14]. 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[15-17]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[12,14,16-17].

BIOMARKER

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[18-20], anti-PD-1 therapies[18-21], and combination nivolumab and ipilimumab[22-27]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[18-21,28-32]. 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[28]; similar findings were observed in the KEYNOTE 028 and 012 trials[21]. 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)[32]. 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[33]. 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[31]. 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[34] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[19].

FREQUENCY & PROGNOSIS

Ewing sarcoma harbors a median TMB of 1.7 mutations per megabase (muts/Mb), and 0.5% of cases have high TMB (>20 muts/Mb)[35]. Published data investigating the prognostic implications of TMB levels in Ewing sarcoma are generally limited (PubMed, Jul 2021). In one study, TMB greater than 11 muts/Mb (as measured in tissue samples) was associated with inferior outcomes for patients with Ewing sarcoma, although these patients also harbored alterations associated with poor prognosis, such as STAG2 and TP53 mutations[36].

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[37-38] and cigarette smoke in lung cancer[39-40], treatment with temozolomide-based chemotherapy in glioma[41-42], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[43-47], and microsatellite instability (MSI)[43,46-47]. 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[19-20,28].

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GENE
EWSR1

ALTERATION
EWSR1-ERG fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapies targeting IGF1R might also be relevant for a patient with an EWSR1-ERG fusion. Phase 2 studies of anti-IGF1R antibodies reported response rates of 6-14.2%[48-50], including a response to the IGF1R inhibitor figitumumab in 1 of 6 Ewing's sarcoma patients with EWS-ERG fusion[49]. However, the presence of EWSR1 fusion alone does not predict response to IGF1R targeted therapies[51]. In preclinical xenograft models, combinations of IGF1R inhibitors with mTOR inhibitors were reported to have better efficacy than IGF1R single agent therapy[52-53]. In a Phase 1 study of the IGF1R inhibitor cixutumumab in combination with the mTOR inhibitor temsirolimus in 17 Ewing's sarcoma patients, 1 patient had a complete response and 4 patients had partial responses[54]. Several preclinical studies have shown that EWSR1-FLI1 sensitizes cells to PARP inhibitors[55-58], and one study reported that EWSR1-ERG driven cell lines were similarly sensitive to PARP inhibitors[56]. However, in a Phase 2 trial in Ewing's sarcoma, 0 of 12 patients responded to single-agent olaparib[59]. The combination of PARP inhibitors with either temozolomide or irinotecan was more effective than single-agent olaparib against EWSR1-FLI1 cells in preclinical studies[56-58].

FREQUENCY & PROGNOSIS

Fusions involving EWSR1 are hallmark driver mutations in some types of sarcoma, including Ewing and clear cell sarcoma[60-62]. EWSR1-ERG fusions have been reported to occur in ~10% of Ewing sarcoma cases[62-65]. Fusions of ERG, as well as other transcription factors in the ETS family, such as the TMPRSS2-ERG fusion, have also been reported in ~50% of patients with prostate cancer[66]. In one study of Ewing sarcoma, the percentage of patients with metastatic disease at diagnosis was higher for patients with EWSR1/FUS-ERG fusions (44%) compared with EWSR1-FLI1 fusions (30%), but OS did not differ between the two fusion groups[67]. Translocations and deletions of ERG are also seen in some acute myeloid leukemias, and ERG overexpression has been associated with poor prognosis[68-69]. Patients with EWSR1-ERG and EWSR1-FLI1 fusions exhibit significant similarities in their pathological and clinical characteristics, as well as progression-free and overall survival[63,70].

FINDING SUMMARY

EWSR1 (Ewing sarcoma breakpoint region 1) encodes the EWS protein, an RNA binding protein of largely unknown function that has been postulated to play a role in the regulation of hematopoietic stem cells[71]. Rearrangements that result in fusions between the EWSR1 transcriptional activation domain and the DNA binding domains of other transcription factors have been shown to be oncogenic[65,72]. Rearrangements leading to fusion between the N-terminus of EWSR1 that mediates transcriptional activation and the C-terminal ETS domain of ERG that binds DNA, such as observed here, are expected to be oncogenic, as proteins with similar domain composition are able to transform cultured cells and drive tumor formation in mouse xenograft models[72-73].

POTENTIAL DIAGNOSTIC IMPLICATIONS

EWSR1 fusions with partners such as FLI1, ERG, FEV, ETV1, E1AF, ZSG, and others are hallmark driver alterations of Ewing sarcoma and other mesenchymal tumors, including chondrosarcomas, round cell tumors, and myoepithelial tumors (NCCN Soft Tissue Sarcoma Guidelines, v3.2021)[61-65,74-75].

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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
EWSR1

ALTERATION
EWSR1-ERG fusion

RATIONALE
Preclinical evidence suggests that cancers with EWSR1-ERG fusion may be sensitive to PARP and IGF1R inhibitors.

NCT05035745

PHASE 1/2

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

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

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

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

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

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

LOCATIONS: Melbourne (Australia)

NCT02264678

PHASE 1/2

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

TARGETS
ATR, PARP, PD-L1

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

NCT04644068

PHASE 1/2

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

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Seoul (Korea, Republic of), Budapest (Hungary), Warszawa (Poland), Brno (Czechia), Gdynia (Poland), Napoli (Italy), Roma (Italy), Grzepnica (Poland), Padova (Italy), Modena (Italy)

CLINICAL TRIALS

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), London (United Kingdom), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), Massachusetts, Rhode Island, Toronto (Canada), New York, Illinois, North Carolina

NCT03784014

PHASE 3

MOLECULAR PROFILING OF ADVANCED SOFT-TISSUE SARCOMAS

TARGETS
ABL, KIT, ROS1, ALK, MET, ERBB2, EGFR, BRAF, MEK, PARP, PD-L1, CDK4, CDK6

LOCATIONS: Marseille (France), Dijon (France), Lyon (France), Clermont-Ferrand (France), Paris (France), Villejuif (France), Bordeaux (France), Saint-Herblain (France)

NCT03907969

PHASE 1/2

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

TARGETS
PARP, DNA-PK

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

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), New York, Tennessee, Oklahoma, Florida, Texas

NCT02769962

PHASE 1/2

Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer

TARGETS
PARP, TOP1

LOCATIONS: Maryland

APPENDIX Variants of Unknown Significance

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. Please note that some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

BRIP1
A745T

CIC
P722L

EWSR1
rearrangement

FANCL
M247V

FLYWCH1
P357R

IGF1R
A257V

KMT2A (MLL)
E1860D and S2319T

LRP1B
R1072H

MYO18A
R691C

PCLO
S4814A and V3204D

RICTOR
E1392del

SPEN
P2067L

WDR90
R1364H

ZNF703
A276P

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APPENDIX Genes Assayed in FoundationOne®Heme

FoundationOne Heme is designed to include genes known to be somatically altered in human hematologic malignancies and sarcomas 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 utilizes DNA sequencing to interrogate 406 genes as well as selected introns of 31 genes involved in rearrangements, in addition to RNA sequencing of 265 genes. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACTB*	*ADGRA2 (GPR124)*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*AMER1 (FAM123B or WTX)*	
APC	*APH1A*	*AR*	*ARAF*	*ARFRP1*	*ARHGAP26 (GRAF)*		*ARID1A*	*ARID2*
ASMTL	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXL*
B2M	*BAP1*	*BARD1*	*BCL10*	*BCL11B*	*BCL2*	*BCL2L2*	*BCL6*	*BCL7A*
BCOR	*BCORL1*	*BIRC3*	*BLM*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*
BRSK1	*BTG2*	*BTK*	*BTLA*	*CAD*	*CALR**	*CARD11*	*CBFB*	*CBL*
CCN6 (WISP3)	*CCND1*	*CCND2*	*CCND3*	*CCNE1*	*CCT6B*	*CD22*	*CD274 (PD-L1)*	*CD36*
CD58	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*	*CDK12*	*CDK4*	*CDK6*
CDK8	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHD2*	*CHEK1*	*CHEK2*
CIC	*CIITA*	*CKS1B*	*CPS1*	*CREBBP*	*CRKL*	*CRLF2*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUX1*	*CXCR4*	*DAXX*	*DDR2*	*DDX3X*	*DNM2*
DNMT3A	*DOT1L*	*DTX1*	*DUSP2*	*DUSP9*	*EBF1*	*ECT2L*	*EED*	*EGFR*
ELP2	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHA5*	*EPHA7*	*EPHB1*	*ERBB2*	*ERBB3*
ERBB4	*ERG*	*ESR1*	*ETS1*	*ETV6*	*EXOSC6*	*EZH2*	*FAF1*	*FANCA*
FANCC	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FAS (TNFRSF6)*	*FBXO11*	*FBXO31*
FBXW7	*FGF10*	*FGF14*	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*
FGFR2	*FGFR3*	*FGFR4*	*FHIT*	*FLCN*	*FLT1*	*FLT3*	*FLT4*	*FLYWCH1*
FOXL2	*FOXO1*	*FOXO3*	*FOXP1*	*FRS2*	*GADD45B*	*GATA1*	*GATA2*	*GATA3*
GID4 (C17orf39)	*GNA11*	*GNA12*	*GNA13*	*GNAQ*	*GNAS*	*GRIN2A*	*GSK3B*	*GTSE1*
HDAC1	*HDAC4*	*HDAC7*	*HGF*	*H1-2 (HIST1H1C)*		*H1-3 (HIST1H1D)*		
H1-4 (HIST1H1E)		*H2AC6 (HIST1H2AC)*		*H2AC11 (HIST1H2AG)*		*H2AC16 (HIST1H2AL)*		
H2AC17 (HIST1H2AM)		*H2BC4 (HIST1H2BC)*		*H2BC11 (HIST1H2BJ)*		*H2BC12 (HIST1H2BK)*		
H2BC17 (HIST1H2BO)		*H3C2 (HIST1H3B)*		*HNF1A*	*HRAS*	*HSP90AA1*	*ICK*	*ID3*
IDH1	*IDH2*	*IGF1R*	*IKBKE*	*IKZF1*	*IKZF2*	*IKZF3*	*IL7R*	*INHBA*
INPP4B	*INPP5D (SHIP)*	*IRF1*	*IRF4*	*IRF8*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JARID2	*JUN*	*KAT6A (MYST3)*	*KDM2B*	*KDM4C*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*
KEAP1	*KIT*	*KLHL6*	*KMT2A (MLL)*	*KMT2C (MLL3)*	*KMT2D (MLL2)*	*KRAS*	*LEF1*	*LRP1B*
LRRK2	*MAF*	*MAFB*	*MAGED1*	*MALT1*	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*
MAP3K14	*MAP3K6*	*MAP3K7*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*
MEF2C	*MEN1*	*MET*	*MIB1*	*MITF*	*MKI67*	*MLH1*	*MPL*	*MRE11 (MRE11A)*
MSH2	*MSH3*	*MSH6*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
MYO18A	*NCOR2*	*NCSTN*	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOD1*
NOTCH1	*NOTCH2*	*NPM1*	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NT5C2*	*NTRK1*	*NTRK2*
NTRK3	*NUP93*	*NUP98*	*P2RY8*	*PAG1*	*PAK3*	*PALB2*	*PASK*	*PAX5*
PBRM1	*PC*	*PCBP1*	*PCLO*	*PDCD1*	*PDCD11*	*PDCD1LG2 (PD-L2)*		*PDGFRA*
PDGFRB	*PDK1*	*PHF6*	*PIK3CA*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PIM1*	*PLCG2*
POT1	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PRKDC*	*PRSS8*	*PTCH1*	*PTEN*	*PTPN11*
PTPN2	*PTPN6 (SHP-1)*	*PTPRO*	*RAD21*	*RAD50*	*RAD51*	*RAF1*	*RARA*	*RASGEF1A*
RB1	*RELN*	*RET*	*RHOA*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*RUNX1*
S1PR2	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SERP2*	*SETBP1*	*SETD2*	*SF3B1*
SGK1	*SMAD2*	*SMAD4*	*SMARCA1*	*SMARCA4*	*SMARCB1*	*SMC1A*	*SMC3*	*SMO*
SOCS1	*SOCS2*	*SOCS3*	*SOX10*	*SOX2*	*SPEN*	*SPOP*	*SRC*	*SRSF2*
STAG2	*STAT3*	*STAT4*	*STAT5A*	*STAT5B*	*STAT6*	*STK11*	*SUFU*	*SUZ12*
TAF1	*TBL1XR1*	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TENT5C (FAM46C)*	*TET2*	*TGFBR2*	*TLL2*	*TMEM30A*
TMSB4XP8 (TMSL3)		*TNFAIP3*	*TNFRSF11A*	*TNFRSF14*	*TNFRSF17*	*TOP1*	*TP53*	*TP63*
TRAF2	*TRAF3*	*TRAF5*	*TSC1*	*TSC2*	*TSHR*	*TUSC3*	*TYK2*	*U2AF1*

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U2AF2	*VHL*	*WDR90*	*WT1*	*XBP1*	*XPO1*	*YY1AP1*	*ZMYM3*	*ZNF217*
ZNF24 (ZSCAN3)	*ZNF703*	*ZRSR2*						

*Note: the assay was updated on 11/8/2016 to include the detection of alterations in CALR

HEMATOLOGICAL MALIGNANCY DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCL6*	*BCR*	*BRAF*	*CCND1*	*CRLF2*	*EGFR*	*EPOR*
ETV1	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FGFR2*	*IGH*	*IGK*	*IGL*
JAK1	*JAK2*	*KMT2A (MLL)*	*MYC*	*NTRK1*	*PDGFRA*	*PDGFRB*	*RAF1*	*RARA*
RET	*ROS1*	*TMPRSS2*	*TRG*					

HEMATOLOGICAL MALIGNANCY RNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS*

ABI1	*ABL1*	*ABL2*	*ACSL6*	*AFDN (MLLT4 or AF6)*		*AFF1*	*AFF4*	*ALK*
ARHGAP26 (GRAF)		*ARHGEF12*	*ARID1A*	*ARNT*	*ASXL1*	*ATF1*	*ATG5*	*ATIC*
BCL10	*BCL11A*	*BCL11B*	*BCL2*	*BCL3*	*BCL6*	*BCL7A*	*BCL9*	*BCOR*
BCR	*BIRC3*	*BRAF*	*BTG1*	*CAMTA1*	*CARS1 (CARS)*	*CBFA2T3*	*CBFB*	*CBL*
CCND1	*CCND2*	*CCND3*	*CD274 (PD-L1)*	*CDK6*	*CDX2*	*CEP43 (FGFR1OP)*	*CHIC2*	*CHN1*
CIC	*CIITA*	*CLP1*	*CLTC*	*CLTCL1*	*CNTRL (CEP110)*	*COL1A1*	*CREB3L1*	*CREB3L2*
CREBBP	*CRLF2*	*CSF1*	*CTNNB1*	*DDIT3*	*DDX10*	*DDX6*	*DEK*	*DUSP22*
EGFR	*EIF4A2*	*ELF4*	*ELL*	*ELN*	*EML4*	*EP300*	*EPOR*	*EPS15*
ERBB2	*ERG*	*ETS1*	*ETV1*	*ETV4*	*ETV5*	*ETV6*	*EWSR1*	*FCGR2B*
FCRL4	*FEV*	*FGFR1*	*FGFR2*	*FGFR3*	*FLI1*	*FNBP1*	*FOXO1*	*FOXO3*
FOXO4	*FOXP1*	*FSTL3*	*FUS*	*GAS7*	*GLI1*	*GMPS*	*GPHN*	*H4C9 (HIST1H4I)*
HERPUD1	*HEY1*	*HIP1*	*HLF*	*HMGA1*	*HMGA2*	*HOXA11*	*HOXA13*	*HOXA3*
HOXA9	*HOXC11*	*HOXC13*	*HOXD11*	*HOXD13*	*HSP90AA1*	*HSP90AB1*	*IGH*	*IGK*
IGL	*IKZF1*	*IL21R*	*IL3*	*IRF4*	*ITK*	*JAK1*	*JAK2*	*JAK3*
JAZF1	*KAT6A (MYST3)*	*KDSR*	*KIF5B*	*KMT2A (MLL)*	*LASP1*	*LCP1*	*LMO1*	*LMO2*
LPP	*LYL1*	*MAF*	*MAFB*	*MALT1*	*MDS2*	*MECOM*	*MLF1*	*MLLT1 (ENL)*
MLLT10 (AF10)	*MLLT3*	*MLLT6*	*MN1*	*MNX1*	*MRTFA (MKL1)*	*MSI2*	*MSN*	*MUC1*
MYB	*MYC*	*MYH11*	*MYH9*	*NACA*	*NBEAP1 (BCL8)*	*NCOA2*	*NDRG1*	*NF1*
NF2	*NFKB2*	*NIN*	*NOTCH1*	*NPM1*	*NR4A3*	*NSD1*	*NSD2 (WHSC1 or MMSET)*	
NSD3 (WHSC1L1)	*NTRK1*	*NTRK2*	*NTRK3*	*NUMA1*	*NUP214*	*NUP98*	*NUTM2A*	*OMD*
P2RY8	*PAFAH1B2*	*PAX3*	*PAX5*	*PAX7*	*PBX1*	*PCM1*	*PCSK7*	*PDCD1LG2 (PD-L2)*
PDE4DIP	*PDGFB*	*PDGFRA*	*PDGFRB*	*PER1*	*PHF1*	*PICALM*	*PIM1*	*PLAG1*
PML	*POU2AF1*	*PPP1CB*	*PRDM1*	*PRDM16*	*PRRX1*	*PSIP1*	*PTCH1*	*PTK7*
RABEP1	*RAF1*	*RALGDS*	*RAP1GDS1*	*RARA*	*RBM15*	*RET*	*RHOH*	*RNF213*
RNF217-AS1 (STL)		*ROS1*	*RPL22*	*RPN1*	*RUNX1*	*RUNX1T1 (ETO)*	*RUNX2*	*SEC31A*
SEPTIN5 (SEPT5)	*SEPTIN6 (SEPT6)*	*SEPTIN9 (SEPT9)*	*SET*	*SH3GL1*	*SLC1A2*	*SNX29 (RUNDC2A)*		*SRSF3*
SS18	*SSX1*	*SSX2*	*SSX4*	*STAT6*	*SYK*	*TAF15*	*TAL1*	*TAL2*
TBL1XR1	*TCF3 (E2A)*	*TCL1A (TCL1)*	*TEC*	*TET1*	*TFE3*	*TFG*	*TFPT*	*TFRC*
TLX1	*TLX3*	*TMPRSS2*	*TNFRSF11A*	*TOP1*	*TP63*	*TPM3*	*TPM4*	*TRIM24*
TRIP11	*TTL*	*TYK2*	*USP6*		*YPEL5*	*ZBTB16*	*ZMYM2*	*ZNF384*
ZNF521								

*Note: some VUS rearrangements between targeted genes and unknown fusion partners or intergenic regions detected by RNA sequencing may not be reported.

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Microsatellite (MS) status
Tumor Mutational Burden (TMB)

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The median exon coverage for this sample is 904x

ACCURACY		
Sensitivity: Base Substitutions	At ≥5% Minor Allele Frequency	>99.0%
Sensitivity: Insertions/Deletions (1-40bp)	At ≥10% Minor Allele Frequency	98.0%
Sensitivity: Focal Copy Number Alterations (Homozygous Deletions or Amplifications)	At ≥8 copies	>95.0%
Sensitivity: Microsatellite Instability-High (MSI-H) status	Positive Predictive Agreement (PPA)	100.0% (87.54%-100.00%)*
Sensitivity: Microsatellite Stable (MSS) status	Positive Predictive Agreement (PPA)	89.66% (81.50%, 94.46%)*
Sensitivity: Known Gene Fusions	>95.0%	
Specificity: Base Substitutions, Insertions/Deletions, and Focal Copy Number Alterations	Positive Predictive Value (PPV)	>99.0%
Specificity: Known Gene Fusions	Positive Predictive Value (PPV)	>95.0%
Specificity: Microsatellite Instability-High (MSI-H) status	Negative Predictive Agreement (NPA)	97.44% (91.12%-99.29%)*
Specificity: Microsatellite Stable (MSS) status	Negative Predictive Agreement (NPA)	94.44% (86.57%, 97.82%)*
Accuracy: Tumor Mutation Burden	At ≥20% tumor nuclei	>90.0%
Reproducibility (average concordance between replicates)	97.0% inter-batch precision 97.0% intra-batch precision 95.0% microsatellite status precision 96.0% tumor mutation burden precision	

*95% Confidence Interval

Assay specifications were determined for typical median exon coverage of approximately 500X. For additional information regarding the validation of FoundationOne®Heme, please refer to the article He, J. et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting, Blood (2016 Jun. 16).

In the fractional-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the FoundationOne Heme 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 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.

Tumor Mutational Burden (TMB) is determined by measuring the number of somatic mutations in sequenced genes on the FoundationOne Heme test and extrapolating to the genome as a whole. TMB is assayed for all FoundationOne Heme samples and is reported as the number of mutations per megabase (Muts/Mb). Tumor Mutational Burden is reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine Tumor Mutational Burden.

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ABOUT FOUNDATIONONE HEME

FoundationOne®Heme is a comprehensive genomic profiling test for hematologic malignancies and sarcomas. The test is designed to provide physicians with clinically actionable information to help with diagnostic sub-classification, prognosis assessment, and targeted therapeutic selection. Test results provide information about clinically significant alterations, potential targeted therapies, available clinical trials, and quantitative markers that may support immunotherapy clinical trial enrollment. FoundationOne Heme is analytically validated to detect all classes of genomic alterations in more than 400 cancer-related genes. In addition to DNA sequencing, FoundationOne Heme employs RNA sequencing across 265 genes to capture a broad range of gene fusions, common drivers of hematologic malignancies and sarcomas.

FoundationOne Heme was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne Heme has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. FoundationOne Heme may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

FoundationOne Heme 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 FoundationOne Heme 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 Heme for identifying a copy number amplification is five (5) for *ERBB2* and six (6) for all other genes. Conversely, an alteration denoted as "loss – equivocal" implies that FoundationOne Heme data provide some, but not unambiguous, evidence for homozygous deletion of the gene in question. An alteration denoted as "subclonal" is one that FoundationOne Heme analytical methodology has identified as being present in <10% of the assayed tumor DNA.

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

Therapies are ranked based on the following criteria: Therapies with clinical benefit (ranked alphabetically within each evidence category), followed by therapies associated with resistance (when applicable).

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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 Heme.

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. These include: subclonal alterations in heterogeneous samples, low sample quality or with homozygous losses of <3 exons; and deletions and insertions >40bp, or in repetitive/high homology sequences. FoundationOne Heme is performed using DNA and RNA derived from tumor, and as such germline events may not be reported.

The following targets typically have low coverage resulting in a reduction in sensitivity: SDHD exon 4, TNFRSF11A exon1, and TP53 exon 1.

FoundationOne Heme fulfills the requirements of the European Directive 98/79 EC for in vitro

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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

REPORT HIGHLIGHTS

The Report Highlights includes select genomic and therapeutic information with potential impact on patient care and treatment that is specific to the genomics and tumor type of the sample analyzed. This section may highlight information including targeted therapies with potential sensitivity or resistance; evidence-matched clinical trials; and variants with potential diagnostic, prognostic, nontargeted treatment, germline, or clonal hematopoiesis implications. Information included in the Report Highlights is expected to evolve with advances in scientific and clinical research. Findings included in the Report Highlights should be considered in the context of all other information in this report and other relevant patient information. Decisions on patient care and treatment are the responsibility of the treating physician.

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >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, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, 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.

SELECT ABBREVIATIONS

ABBREVIATION	DEFINITION
CR	Complete response
DCR	Disease control rate
DNMT	DNA methyltransferase
HR	Hazard ratio
ITD	Internal tandem duplication
MMR	Mismatch repair
muts/Mb	Mutations per megabase
NOS	Not otherwise specified
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TKI	Tyrosine kinase inhibitor

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 6.3.0

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