FOUNDATIONONE®CDx

PATIENT
Chen, Hsiu-Hua

TUMOR TYPE
Duodenum adenocarcinoma
COUNTRY CODE
TW

REPORT DATE
02 May 2022
ORDERED TEST #
ORD-1349720-01

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 Duodenum adenocarcinoma
NAME Chen, Hsiu-Hua
DATE OF BIRTH 03 November 1955
SEX Female
MEDICAL RECORD # 42698293

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

SPECIMEN
SPECIMEN SITE Duodenum
SPECIMEN ID S111-14321C (PF22057)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 08 April 2022
SPECIMEN RECEIVED 25 April 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 3 Muts/Mb

Genomic Findings

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

CCND1 amplification
FGFR2 amplification
C11orf30 (EMSY) amplification
CCND3 amplification - equivocal†
FGF19 amplification
FGF3 amplification
FGF4 amplification
GATA6 amplification
NRAS amplification
TP53 R335fs*10

† See About the Test in appendix for details.

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section	
Tumor Mutational Burden - 3 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)**
***CCND1* -** amplification	none	none
5 Trials *see p. 9*		
***FGFR2* -** amplification	none	none
9 Trials *see p. 11*		

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

For more information regarding biological and clinical significance, including prognostic, diagnostic, germline, and potential chemosensitivity implications, see the Genomic Findings section.

NOTE Genomic alterations detected may be associated with activity of certain approved therapies; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Therapies and the clinical trials listed in this report may not be complete and exhaustive. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type. This report should be regarded and used as a supplementary source of information and not as the single basis for the making of a therapy decision. All treatment decisions remain the full and final responsibility of the treating physician and physicians should refer to approved prescribing information for all therapies.

Therapies contained in this report may have been approved by the US FDA.

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI-H has been frequently reported in carcinomas of the small bowel[6-12], with larger studies reporting a rate of 10.4-19.6% of small intestine carcinomas[13-15]. MSI-H small intestine adenocarcinomas were reported to be higher tumor grade and associated with longer median overall survival (49.6 vs. 23.2 months) than MSS tumors[8,15-17].

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]. 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[21-23]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[18,20,22-23].

BIOMARKER

Tumor Mutational Burden

RESULT
3 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[24-26], anti-PD-1 therapies[24-27], and combination nivolumab and ipilimumab[28-33]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[24-27,34]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[24]. 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[35] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[25]. 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[27,34]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Small intestinal adenocarcinoma harbors a median TMB of 4.5 mutations per megabase (muts/Mb), with 12% of cases exhibiting a TMB ≥10muts/Mb[36] and 8.3-9.5% of cases harboring a TMB >20 muts/Mb[37-38]. In 1 study, small bowel adenocarcinomas were significantly enriched for high TMB relative to colorectal cancer or gastric cancer, and high TMB was more frequent in unspecified small bowel adenocarcinoma than in duodenal adenocarcinoma[38]. Published data investigating the prognostic implications of TMB in small intestinal cancers are generally limited (PubMed, Sep 2021). One study reported that amongst a cohort of patients with small bowel cancer (n=23), high TMB (>10 Mut/Mb) was associated with favorable OS (p<0.05)[39].

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[40-41] and cigarette smoke in lung cancer[42-43], 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]. 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[25-26,34].

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GENE
CCND1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Amplification or overexpression of CCND1 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib[51-56], although as monotherapy these agents have shown limited activity in tumor types other than breast cancer[55,57]. In refractory advanced solid tumors with CCND1 (n=39) or CCND3 (n=1) amplification and retinoblastoma protein expression, palbociclib resulted in SD for 39% (14/36) of patients and a median PFS of 1.8 months in the NCI-MATCH trial[58]; 4 patients (13%, 4/36 overall) with squamous cell carcinomas (lung, esophageal, or laryngeal) or adenoid cystic carcinoma experienced prolonged SD in this study[58]. Among 9 patients with CCND1-amplified advanced solid tumors, 1 patient with bladder cancer responded to ribociclib in a Phase 2 trial[59].

— Potential Resistance —

CCND1 amplification may predict worse outcomes on immune checkpoint inhibitors (anti-PD-1/PD-L1/CTLA-4) in solid tumors on the basis of 2 meta-analyses[60-61]; in these studies, CCND1 amplification was associated with significantly decreased response rate[61] and OS (HR=1.6-2.0)[60-61] across various tumor types and significantly shorter OS specifically in urothelial carcinoma (HR=2.2-3.6), melanoma (HR=1.6-2.5), and solid tumors harboring elevated TMB (HR=2.8)[60-61].

FREQUENCY & PROGNOSIS

In 1 study of small intestinal carcinomas, CCND1 amplification was reported in 3.4% of cases[36]. Cyclin D1 expression has been reported in 33% of small bowel adenocarcinomas and 36% of small bowel adenomas compared with no expression detected in normal mucosa[62]. One study has reported increasing expression of cyclin D in small intestine adenomas and adenocarcinoma tumors; however, increased expression did not correlate with tumor progression[63].

FINDING SUMMARY

CCND1 encodes cyclin D1, a binding partner of the kinases CDK4 and CDK6, that regulates RB activity and cell cycle progression. Amplification of CCND1 has been positively correlated with cyclin D1 overexpression[64] and may lead to excessive proliferation[65-66].

GENE
FGFR2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGFR2 activating mutations, amplifications, or fusions may confer sensitivity to selective FGFR inhibitors such as erdafitinib[67], pemigatinib[68-69], infigratinib[70], E7090[71], AZD4547[72-74], Debio 1347[75-76], rogaratinib[77], futibatinib[78], ICP192[79], and derazantinib[80] as well as to the multikinase inhibitors pazopanib[81-82] and ponatinib[83]. In a Phase 2 study of the FGFR inhibitor AZD4547, responses were reported in 33% (3/9) of patients with FGFR2-amplified gastroesophageal cancer; in this study, higher-level amplification correlated with higher likelihood of response to FGFR inhibitors[72]. However, a randomized Phase 2 study of AZD4547 compared with paclitaxel for the treatment of patients with advanced stomach adenocarcinoma harboring FGFR2 amplification or polysomy reported no significant increase in median PFS, median OS, or ORR[73].

FREQUENCY & PROGNOSIS

FGFR2 mutation has been reported in 4% (1/28) of small intestine adenocarcinoma cases[6] and in 2% (1/48) of small intestine neuroendocrine tumors[84]. Published data investigating the prognostic implications of FGFR2 alteration in small intestine tumors are limited (PubMed, Mar 2022).

FINDING SUMMARY

FGFR2 encodes a tyrosine kinase cell surface receptor, which plays an important role in cell differentiation, growth, and angiogenesis[85-86]. FGFR2 amplification has been reported in a variety of cancer types[87] and has been shown to correlate with increased mRNA and protein expression[72,88]. Higher level, clonal FGFR2 amplification has been reported to correlate with higher response rates to FGFR inhibitors[72,89].

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GENE
C11orf30 (EMSY)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

EMSY overexpression in breast cancer cell lines has been reported to mimic the effects of inactivating BRCA2 mutations[90]. Unlike BRCA2 inactivation, which predicts sensitivity to DNA repair-associated inhibitors such as the PARP inhibitor olaparib[91-92], EMSY amplification in breast cancer lines was not associated with enhanced sensitivity to this drug in one preclinical study[93]. There are no therapies that target EMSY alterations.

FREQUENCY & PROGNOSIS

In the TCGA datasets, EMSY amplification has been most frequently observed in ovarian carcinoma (8%)[94], breast invasive carcinoma (6%)[95], esophageal carcinoma (5%)(cBioPortal, 2022), and head and neck squamous cell carcinoma (3.5%)[87,96-97]. EMSY overexpression has been primarily reported in breast and high grade ovarian cancers, where it is implicated in BRCA2 inactivation and correlates with poor prognosis or advanced disease[93,98-104]. The consequences of EMSY alterations in other solid tumors or hematologic malignancies have not been studied in detail in the scientific literature (PubMed, 2022).

FINDING SUMMARY

EMSY, also known as C11orf30, encodes a BRCA2-interacting protein with roles in transcriptional regulation[104-105]. Preclinical studies have suggested that EMSY binds to and suppresses the function of BRCA2, and EMSY overexpression may therefore mimic BRCA2 inactivation[90,104]. Amplification of the EMSY gene correlates with increased mRNA expression[93,106], although conflicting data have been reported[107]. The functional consequences of other EMSY alterations have not been extensively studied (PubMed, 2022).

GENE
CCND3

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of preclinical studies, amplification or activation of CCND3 may predict sensitivity to CDK4/6 inhibitors, such as abemaciclib[108] and palbociclib[109-111]; however, 1 preclinical study implicated CCND3 overexpression as a potential mechanism of resistance to palbociclib[112].

FREQUENCY & PROGNOSIS

The frequency of CCND3 amplification in carcinomas of the small intestine has not been evaluated (PubMed, cBioPortal, Jun 2021)[87,97]. Published data investigating the prognostic implications of CCND3 alterations in duodenum and small intestine carcinomas are limited (PubMed, Jun 2021). In a study of 32 mixed gastric carcinomas, overexpression of CCND3 correlated with moderate tumor differentiation and poor survival; CCND3 overexpression was not reported in the gastric-intestinal adenocarcinomas analyzed in this study[113].

FINDING SUMMARY

CCND3 encodes cyclin D3, a G1/S-specific cell cycle regulator. Cyclin D3 interacts with and regulates the cyclin-dependent kinases CDK4 and CDK6, resulting in the phosphorylation and inactivation of Rb and the progression of the cell cycle[114]. CCND3 amplification has been associated with increased cyclin D3 expression[115].

GENE
FGF19

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

A Phase 1 study of the FGFR4 inhibitor fisogatinib (BLU-554) for patients with advanced hepatocellular carcinoma (HCC) reported a 17% ORR (11/66, 1 CR, ongoing for >1.5 years) and 3.3-month PFS for FGF19 IHC–positive patients; patients with negative or unknown FGF19 IHC scores experienced poorer outcomes (0% ORR, 2.3-month PFS)[116]. A Phase 1/2 study evaluating another FGFR4 inhibitor, FGF401, demonstrated an ORR of 7.5% (4/53) and SD rate of 53% (28/53) for patients with HCC[117]. A Phase 1 study of the FGFR4 inhibitor H3B-6527 reported a 17% ORR (OS of 10.3 months, 46% clinical benefit rate) among patients with HCC; enrollment of patients with intrahepatic cholangiocarcinoma (ICC) was suspended due to efficacy[118]. A retrospective analysis reported that 50% (2/4) of patients with HCC harboring FGF19 amplification experienced a CR to sorafenib[119], though another retrospective study found patients with higher pretreatment serum levels of FGF19 experienced reduced benefit from sorafenib compared with those with lower serum FGF19 (PFS of 86 vs. 139 days, OS of 353 vs. 494 days); no difference was observed for lenvatinib[120]. A patient with head and neck squamous cell carcinoma (HNSCC) with 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) amplification experienced a CR lasting 9 months from a pan-FGFR inhibitor[121].

FREQUENCY & PROGNOSIS

For patients with solid tumors, FGF19 amplification has been reported most frequently in breast cancer (17%), head and neck cancer (12%), lung squamous cell carcinoma (SCC; 12%), and urothelial carcinoma cancer (11%)[122-124]. FGF19 mutations are rare in solid tumors[122]. FGF19 expression or amplification has been associated with poor prognosis in hepatocellular carcinoma (HCC)[125-126], and in prostate cancer following radical prostatectomy[127]. Studies suggest FGF19 expression may also be a poor prognostic indicator in head and neck squamous cell carcinoma (HNSCC)[128] and lung SCC[129].

FINDING SUMMARY

FGF19 encodes fibroblast growth factor 19, an FGFR4 ligand involved with bile acid synthesis and hepatocyte proliferation in the liver[130-131]. FGF19 lies in a region of chromosome 11q13 that also contains FGF3, FGF4, and CCND1; this region is frequently amplified in a diverse range of malignancies[132]. Correlation between FGF19 amplification and protein expression has been reported in hepatocellular carcinoma (HCC)[133], lung squamous cell carcinoma[129,134], and head and neck squamous cell carcinoma (HNSCC)[128], but was not observed in other cancers[120,135].

GENE
FGF3

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies that directly address genomic alterations in FGF3. Inhibitors of FGF receptors, however, are undergoing clinical trials in a number of different cancers. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[136].

FREQUENCY & PROGNOSIS

FGF3 lies in a region of chromosome 11q13 that also contains FGF19, FGF4, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[65].

FINDING SUMMARY

FGF3 encodes fibroblast growth factor 3, a growth factor that plays a central role in development of the inner ear. Germline mutations in FGF3 give rise to an autosomal recessive syndrome characterized by microdontia, deafness, and complete lack of inner ear structures[137].

GENE
FGF4

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

FGF4 amplification and overexpression was associated with cell sensitivity to the multikinase inhibitor sorafenib in preclinical studies[138-139] and amplification of FGF4/FGF3 in HCC significantly correlated with patient response to sorafenib (p=0.006)[138]. Limited data suggest that pan-FGFR inhibitors show activity in FGF amplified cancers; following treatment with a selective pan-FGFR inhibitor, a patient with head and neck squamous cell carcinoma (HNSCC) and amplification of 11q13 (FGF3, FGF4, FGF19) and 12p13 (FGF6 and FGF23) experienced a radiologic CR[136].

FREQUENCY & PROGNOSIS

FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. This chromosomal region is frequently amplified in a diverse range of malignancies[65] including esophageal carcinoma (35%), head and neck squamous cell carcinoma (HNSCC; 24%), breast invasive carcinoma (14%), lung squamous cell carcinoma (13%), cholangiocarcinoma (11%), bladder urothelial carcinoma (10%), stomach adenocarcinoma (7%), skin melanoma (5%), and hepatocellular carcinoma (HCC; 5%), however FGF4 amplification is rare in hematopoietic and lymphoid malignancies, reported in less than 1% of samples analyzed (cBioPortal, Jan 2022)[87,97].

FINDING SUMMARY

FGF4 encodes fibroblast growth factor 4, which plays a central role in development of the teeth[140] and acts synergistically with other FGFs and SHH (sonic hedgehog) to regulate limb outgrowth in vertebrate development[141]. FGF4 lies in a region of chromosome 11q13 that also contains FGF19, FGF3, and CCND1, the latter gene encoding cyclin D1, a key regulator of cell cycle progression. Amplification of FGF4, along with that of FGF3, FGF19, and CCND1, has been reported in a variety of cancers[65,138,142-145] and may confer sensitivity to the multi-kinase inhibitor sorafenib[138].

GENE
GATA6

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in GATA6. Patients with GATA6-high pancreatic tumors exhibited better clinical outcomes following treatment with adjuvant chemotherapy (p=0.003) or first-line folfirinox (HR=1.90, p=0.025) treatment compared with low GATA6 expressing tumors, while no difference was observed for patients treated with gemcitabine[146-147].

FREQUENCY & PROGNOSIS

Amplification of the GATA6 locus, 18q11.2, has been reported with highest incidences in esophageal adenocarcinomas (21%, 18/85) and pancreatobiliary carcinomas (19%, 7/37)[148-149], and at lower rates in small intestine cancer (5.5%)[36], urothelial bladder carcinoma (3.9%), lung adenocarcinoma (1.7%), and ovarian carcinoma (1.8%)[94,150-151]. While low GATA6 expression correlated with poor prognosis for patients with non-small cell lung cancer (NSCLC)[152], gastric cancer[153], bladder cancer[154], or esophageal adenocarcinomas without neoadjuvant treatment[155], high GATA6 expression has been associated with poor outcome for patients with colon cancer[156], breast cancer[157], ovarian cancer[158], cholangiocarcinoma[159], and NSCLC following EGFR-TKI treatment[160].

FINDING SUMMARY

GATA6 encodes a zinc finger transcription factor, which is involved in the development of several tissues and is expressed in proliferating cells throughout the intestinal tract[161]. GATA6 has been described as both a tumor suppressor and an oncogene, which may be dependent on the tumor type.

GENE
NRAS

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in hematologic malignancies[162-165] and solid tumors[162,166-167] as well as preclinical evidence[168-172], NRAS activating alterations may predict sensitivity to MEK inhibitors, such as trametinib, cobimetinib, and binimetinib. Preclinical data in cancer cell lines indicates that NRAS mutation predicts sensitivity to the PI3K-alpha-specific inhibitor alpelisib[173].

FREQUENCY & PROGNOSIS

NRAS mutation has been observed in 0-3.5% of small intestine adenocarcinomas[6,174]. Published data investigating the prognostic implications of NRAS alteration in small intestine carcinoma are limited (PubMed, Feb 2021).

FINDING SUMMARY

NRAS encodes a member of the RAS family of small GTPases that mediate transduction of growth signals. Activation of RAS signaling causes cell growth, differentiation, and survival by activating the RAF-MAPK-ERK, PI3K, and other pathways[171]. NRAS has been reported to be amplified in cancer[87], and may be biologically relevant in this context[175-176].

GENE
TP53

ALTERATION
R335fs*10

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
1004delG

VARIANT ALLELE FREQUENCY (% VAF)
61.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved therapies to address TP53 mutation or loss. However, tumors with TP53 loss of function alterations may be sensitive to the WEE1 inhibitor adavosertib[177-180], or p53 gene therapy and immunotherapeutics such as SGT-53[181-185] and ALT-801[186]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[187]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[188]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[189]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[190]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[191]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[192]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[193]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[185]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[194-195]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[196-197]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 alterations have been reported in 50-60% of small intestine cancer cases[6], and mutations were observed in 1 of 10 duodenal carcinomas and 3 of 10 jejunal/ileal carcinomas in another study[16]. Loss of 17p heterozygosity, where the TP53 gene resides, has been observed in 20-67% of duodenal and 20% of ileal/jejunal carcinomas[16,198]. Expression of p53 has been observed in 24-53.3% of small intestine carcinomas[12,199-200]. In one study, expression of p53 was more common in poorly differentiated tumors (71%) as compared with well-differentiated cases (30%)[200].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[201]. Alterations such as seen here may disrupt TP53 function or expression[202-206].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[207-209], including sarcomas[210-211]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[212] to 1:20,000[211]. For pathogenic TP53 mutations identified during tumor sequencing, the rate of germline mutations was 1% in the overall population and 6% in tumors arising before age 30[213]. In the appropriate clinical context, germline testing of TP53 is recommended.

POTENTIAL CLONAL HEMATOPOIESIS IMPLICATIONS

Variants seen in this gene have been reported to occur in clonal hematopoiesis (CH), an age-related process in which hematopoietic stem cells acquire somatic mutations that allow for clonal expansion[214-219]. CH in this gene has been associated with increased mortality, risk of coronary heart disease, risk of ischemic stroke, and risk of secondary hematologic malignancy[214-215]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[220]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[218,221-222]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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NOTE Clinical trials are ordered by gene and prioritized by: age range inclusion criteria for pediatric patients, proximity to ordering medical facility, later trial phase, and verification of trial information within the last two months. While every effort is made to ensure the accuracy of the information contained below, the information available in the public domain is continually updated and should be investigated by the physician or research staff. This is not a comprehensive list of all available clinical trials. Foundation Medicine displays a subset of trial options and ranks them in this order of descending priority: Qualification for pediatric trial → Geographical proximity → Later trial phase. Clinical trials listed here may have additional enrollment criteria that may require medical screening to determine final eligibility. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov. Or visit https://www.foundationmedicine.com/genomic-testing#support-services.

GENE
CCND1

ALTERATION
amplification

RATIONALE
CCND1 amplification or overexpression may activate CDK4/6 and may predict sensitivity to single-agent CDK4/6 inhibitors.

NCT04282031

PHASE 1/2

A Study of BPI-1178 in Patients With Advanced Solid Tumor and HR+/HER2- Breast Cancer

TARGETS
CDK6, CDK4, ER, Aromatase

LOCATIONS: Shanghai (China)

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)

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

TARGETS
VEGFRs, ABL, SRC, ALK, ROS1, AXL, TRKA, MET, TRKC, DDR2, KIT, EGFR, PD-1, CTLA-4, PARP, CDK4, CDK6, FLT3, CSF1R, RET, mTOR, ERBB2, MEK, BRAF, SMO

LOCATIONS: Vancouver (Canada), Edmonton (Canada), Saskatoon (Canada), Regina (Canada), Ottawa (Canada), Montreal (Canada), Toronto (Canada), Kingston (Canada), London (Canada)

NCT05252416

PHASE 1/2

(VELA) Study of BLU-222 in Advanced Solid Tumors

TARGETS
ER, CDK4, CDK6, CDK2

LOCATIONS: Massachusetts

NCT02896335

PHASE 2

Palbociclib In Progressive Brain Metastases

TARGETS
CDK4, CDK6

LOCATIONS: Massachusetts

GENE
FGFR2

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR2.

ALTERATION
amplification

NCT04977453

PHASE 1/2

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1, CTLA-4

LOCATIONS: Daejeon (Korea, Republic of), Suwon-si (Korea, Republic of), Seoul (Korea, Republic of)

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT03564691

PHASE 1

Study of MK-4830 as Monotherapy and in Combination With Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-4830-001)

TARGETS
ITL4, FGFRs, RET, PDGFRA, VEGFRs, KIT, PD-1

LOCATIONS: Seoul (Korea, Republic of), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland), Heraklion (Greece), Washington, Hospitalet de Llobregat (Spain)

NCT04008797

PHASE 1

A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor

TARGETS
CBP, Beta-catenin, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Osakasayama (Japan), Chuo-Ku (Japan), Kashiwa (Japan)

NCT04565275

PHASE 1/2

A Study of ICP-192 in Patients With Advanced Solid Tumors

TARGETS
FGFR2, FGFR1, FGFR3, FGFR4

LOCATIONS: Macquarie Park (Australia), Melbourne (Australia), Clayton (Australia), Frankston (Australia), Colorado, Minnesota, Arizona, Ohio, Florida

NCT04965818

PHASE 1/2

Phase 1b/2 Study of Futibatinib in Combination With Binimetinib in Patients With Advanced KRAS Mutant Cancer

TARGETS
MEK, FGFRs

LOCATIONS: California, Indiana, Texas

NCT04729348

PHASE 2

Pembrolizumab And Lenvatinib In Leptomeningeal Metastases

TARGETS
PD-1, KIT, VEGFRs, FGFRs, PDGFRA, RET

LOCATIONS: Massachusetts

NCT02856425

PHASE 1

Trial Of Pembrolizumab And Nintedanib

TARGETS
FGFR1, LCK, SRC, VEGFRs, FGFR2, FGFR3, FLT3, LYN, PD-1

LOCATIONS: Villejuif (France)

NCT01543763

PHASE 1

Phase I Tolerability, Efficacy, and Safety Study of Pazopanib in Combination With PCI-24781 in Patients With Metastatic Solid Tumors

TARGETS
HDAC, FGFR3, KIT, FGFR1, VEGFRs, FGFR2

LOCATIONS: California

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.

BRD4 V228I	***CUL3*** M454V	***DAXX*** E457del	***FLCN*** P28R
MYC S298del	***SDHB*** C22S	***SMAD4*** A39G	***SOCS1*** T15I

Electronically signed by Erik Williams, M.D. | 02 May 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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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*	*ETV1*
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)

Electronically signed by Erik Williams, M.D. | 02 May 2022
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FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. CE

ABOUT FOUNDATIONONE CDX

FoundationOne CDx was developed and its performance characteristics determined by Foundation Medicine, Inc. (Foundation Medicine). FoundationOne CDx may be used for clinical purposes and should not be regarded as purely investigational or for research only. Foundation Medicine's clinical reference laboratories are qualified to perform high-complexity clinical testing.

Please refer to technical information for performance specification details: www.rochefoundationmedicine.com/f1cdxtech.

INTENDED USE

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

TEST PRINCIPLES

FoundationOne CDx will be performed exclusively as a laboratory service using DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples. The proposed assay will employ a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which will undergo whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, one promoter region, one non-coding (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons. The assay therefore includes detection of alterations in a total of 324 genes.

Using an Illumina® HiSeq platform, hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g.,gene fusions). Additionally, genomic signatures including loss of heterozygosity (LOH), microsatellite instability (MSI) and tumor mutational burden (TMB) will be reported.

THE REPORT

Incorporates analyses of peer-reviewed studies and other publicly available information identified by Foundation Medicine; these analyses and information may include associations between a molecular alteration (or lack of alteration) and one or more drugs with potential clinical benefit (or potential lack of clinical benefit), including drug candidates that are being studied in clinical research. The F1CDx report may be used as an aid to inform molecular eligibility for clinical trials. Note: A finding of biomarker alteration does not necessarily indicate pharmacologic effectiveness (or lack thereof) of any drug or treatment regimen; a finding of no biomarker alteration does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness) of any drug or treatment regimen.

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, TSC2,* and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

Variants that may represent clonal hematopoiesis (CH) are limited to select reportable short variants in defined genes identified in solid tumors only. Variant selection was determined based on gene tumor-suppressor or oncogene status, known role in solid tumors versus hematological malignancies, and literature prevalence. The defined genes are *ASXL1, CBL, DNMT3A, IDH2, JAK2, KMT2D (MLL2), MPL, MYD88, SF3B1, TET2,* and *U2AF1* and are not inclusive of all CH genes. The content in this report should not substitute for dedicated hematological workup. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH. Patient-matched peripheral blood mononuclear

cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH. Interpretation should be based on clinical context.

LEVEL OF EVIDENCE NOT PROVIDED

Drugs with potential clinical benefit (or potential lack of clinical benefit) are not evaluated for source or level of published evidence.

NO GUARANTEE OF CLINICAL BENEFIT

This Report makes no promises or guarantees that a particular drug will be effective in the treatment of disease in any patient. This Report also makes no promises or guarantees that a drug with potential lack of clinical benefit will in fact provide no clinical benefit.

NO GUARANTEE OF REIMBURSEMENT

Foundation Medicine makes no promises or guarantees that a healthcare provider, insurer or other third party payor, whether private or governmental, will reimburse a patient for the cost of FoundationOne CDx.

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

Drugs referenced in this Report may not be suitable for a particular patient. The selection of any, all or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) resides entirely within the discretion of the treating physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 6.1.0

The median exon coverage for this sample is 848x

Electronically signed by Erik Williams, M.D. | 02 May 2022
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1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Alvi MA, et al. Oncotarget (2015) pmid: 26315110
7. Bläker H, et al. Oncogene (2002) pmid: 11791187
8. Brueckl WM, et al. Cancer Lett. (2004) pmid: 14732226
9. Hibi K, et al. Jpn. J. Cancer Res. (1995) pmid: 7775257
10. Overman MJ, et al. Br. J. Cancer (2010) pmid: 19935793
11. Rashid A, et al. Gastroenterology (1997) pmid: 9207270
12. Wheeler JM, et al. Gut (2002) pmid: 11788563
13. Planck M, et al. Cancer (2003) pmid: 12627520
14. Michel S, et al. Mol. Carcinog. (2010) pmid: 19852062
15. Ruemmele P, et al. Am. J. Surg. Pathol. (2009) pmid: 19252434
16. Muneyuki T, et al. Dig. Dis. Sci. (2000) pmid: 11117578
17. Agaram NP, et al. Am. J. Clin. Pathol. (2010) pmid: 20395525
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. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
22. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
23. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
24. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
25. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
26. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
27. Cristescu R, et al. Science (2018) pmid: 30309915
28. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
29. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
30. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
31. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
32. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
33. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
34. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
35. Legrand et al., 2018; ASCO Abstract 12000
36. Takeda et al., 2022; ASCO GI Abstract 642
37. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
38. Schrock AB, et al. JAMA Oncol (2017) pmid: 28617917
39. Tsuboi A, et al. PLoS One (2021) pmid: 34014970
40. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
41. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
42. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
43. Rizvi NA, et al. Science (2015) pmid: 25765070
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. Morschhauser F, et al. Haematologica (2020) pmid: 32381571
52. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
53. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
54. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
55. Patnaik A, et al. Cancer Discov (2016) pmid: 27217383
56. Leonard JP, et al. Blood (2012) pmid: 22383795
57. Dickler MN, et al. Clin. Cancer Res. (2017) pmid: 28533223
58. Clark et al., 2019; AACR Abstract LB-010/2
59. Peguero et al., 2016; ASCO Abstract 2528
60. Chen Y, et al. Front Immunol (2020) pmid: 32903763
61. Litchfield K, et al. Cell (2021) pmid: 33508232
62. Arber N, et al. Cancer Epidemiol. Biomarkers Prev. (1997) pmid: 9298583
63. Arber N, et al. Cancer Epidemiol. Biomarkers Prev. (1999) pmid: 10613343
64. Elsheikh S, et al. Breast Cancer Res. Treat. (2008) pmid: 17653856
65. Fu M, et al. Endocrinology (2004) pmid: 15331580
66. Takahashi-Yanaga F, et al. Cell. Signal. (2008) pmid: 18023328
67. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
68. Krook MA, et al. Cold Spring Harb Mol Case Stud (2019) pmid: 31371345
69. Abou-Alfa GK, et al. Lancet Oncol. (2020) pmid: 32203698
70. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
71. Morizane et al., 2020; ASCO GI Abstract 538
72. Pearson A, et al. Cancer Discov (2016) pmid: 27179038
73. Van Cutsem E, et al. Ann. Oncol. (2017) pmid: 29177434
74. Aggarwal C, et al. J Thorac Oncol (2019) pmid: 31195180
75. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
76. Cleary JM, et al. Cancer Discov (2021) pmid: 33926920
77. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
78. Goyal L, et al. Cancer Discov (2019) pmid: 31109923
79. Guo et al., 2021; ASCO Abstract 4092
80. Mazzaferro V, et al. Br. J. Cancer (2019) pmid: 30420614
81. Borad MJ, et al. PLoS Genet. (2014) pmid: 24550739
82. Liao RG, et al. Cancer Res. (2013) pmid: 23786770
83. Gozgit JM, et al. Mol. Cancer Ther. (2012) pmid: 22238366
84. Banck MS, et al. J. Clin. Invest. (2013) pmid: 23676460
85. Powers CJ, et al. Endocr. Relat. Cancer (2000) pmid: 11021964
86. Turner N, et al. Nat. Rev. Cancer (2010) pmid: 20094046
87. Gao J, et al. Sci Signal (2013) pmid: 23550210
88. Tokunaga R, et al. Oncotarget (2016) pmid: 26933914
89. André F, et al. Clin. Cancer Res. (2013) pmid: 23658459
90. Cousineau I, et al. Mol. Genet. Genomics (2011) pmid: 21409565
91. Dedes KJ, et al. Cell Cycle (2011) pmid: 21487248
92. Ihnen M, et al. Mol. Cancer Ther. (2013) pmid: 23729402
93. Wilkerson PM, et al. J. Pathol. (2011) pmid: 21735447
94. Nature (2011) pmid: 21720365
95. Nature (2012) pmid: 23000897
96. Nature (2015) pmid: 25631445
97. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
98. Brown LA, et al. Genes Chromosomes Cancer (2008) pmid: 18314909
99. Brown LA, et al. Breast Cancer Res. Treat. (2010) pmid: 19636701
100. Altinisik J, et al. Mol. Biol. Rep. (2011) pmid: 20349280
101. Madjd Z, et al. Asian Pac. J. Cancer Prev. (2014) pmid: 24641409
102. Bane AL, et al. Breast Cancer Res. Treat. (2011) pmid: 21327470
103. Rodriguez C, et al. Clin. Cancer Res. (2004) pmid: 15355907
104. Hughes-Davies L, et al. Cell (2003) pmid: 14651845
105. Varier RA, et al. J. Biol. Chem. (2016) pmid: 26841866
106. van Hattem WA, et al. Int J Clin Exp Pathol (2008) pmid: 18787609
107. Shih IeM, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 16172393
108. Tanaka Y, et al. Cancer Sci (2020) pmid: 31849147
109. Schmitz R, et al. Nature (2012) pmid: 22885699
110. Choi YJ, et al. Cancer Cell (2012) pmid: 23079655
111. Sawai CM, et al. Cancer Cell (2012) pmid: 23079656
112. Ketzer F, et al. Oncogenesis (2022) pmid: 35013097
113. Shan YS, et al. Oncol Lett (2017) pmid: 28943959
114. Sridhar J, et al. AAPS J (2006) pmid: 16584130
115. Kasugai Y, et al. Clin. Cancer Res. (2005) pmid: 16322284
116. Kim RD, et al. Cancer Discov (2019) pmid: 31575541
117. Chan et al., 2017; AACR Abstract CT106
118. Macarulla et al., 2021; ASCO Abstract 4090
119. Kaibori M, et al. Oncotarget (2016) pmid: 27384874
120. Kanzaki H, et al. Sci Rep (2021) pmid: 33674622
121. Dumbrava EI, et al. JCO Precis Oncol (2018) pmid: 31123723
122. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
123. Nature (2012) pmid: 22960745
124. Robertson AG, et al. Cell (2017) pmid: 28988769
125. Miura S, et al. BMC Cancer (2012) pmid: 22309595
126. Kang HJ, et al. Liver Cancer (2019) pmid: 30815392
127. Nagamatsu H, et al. Prostate (2015) pmid: 25854696
128. Gao L, et al. Oncogene (2019) pmid: 30518874
129. Li F, et al. Oncogene (2020) pmid: 32111983
130. Xie MH, et al. Cytokine (1999) pmid: 10525310
131. Hagel M, et al. Cancer Discov (2015) pmid: 25776529
132. Int. J. Oncol. (2002) pmid: 12429977
133. Kan Z, et al. Genome Res. (2013) pmid: 23788652
134. Caruso S, et al. Gastroenterology (2019) pmid: 31063779
135. Sawey ET, et al. Cancer Cell (2011) pmid: 21397858
136. Dumbrava et al., 2018; doi/full/10.1200/PO.18.00100
137. Tekin M, et al. Am. J. Hum. Genet. (2007) pmid: 17236138
138. Arao T, et al. Hepatology (2013) pmid: 22890726
139. Yamada T, et al. BMC Cancer (2015) pmid: 25885470
140. Kratochwil K, et al. Genes Dev. (2002) pmid: 12502739
141. Scherz PJ, et al. Science (2004) pmid: 15256670
142. Zaharieva BM, et al. J. Pathol. (2003) pmid: 14648664
143. Arai H, et al. Cancer Genet. Cytogenet. (2003) pmid: 14499691
144. Ribeiro IP, et al. Tumour Biol. (2014) pmid: 24477574
145. Schulze K, et al. Nat. Genet. (2015) pmid: 25822088
146. Duan K, et al. Sci Rep (2021) pmid: 34294813
147. Martinelli P, et al. Gut (2017) pmid: 27325420
148. Lin L, et al. Proc Natl Acad Sci U S A (2012) pmid: 22375031
149. Kwei KA, et al. PLoS Genet. (2008) pmid: 18535672
150. Nature (2014) pmid: 24476821
151. Nature (2014) pmid: 25079552
152. Chen W, et al. Front Oncol (2020) pmid: 32596145
153. Liu H, et al. Cell Death Dis (2019) pmid: 30674866

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154. Wang C, et al. FASEB J (2020) pmid: 32103545
155. Plum PS, et al. J Cancer Res Clin Oncol (2021) pmid: 33300112
156. Shen F, et al. Oncol. Rep. (2013) pmid: 23784465
157. Song Y, et al. Exp Mol Pathol (2015) pmid: 26505174
158. Shen W, et al. Hum Pathol (2019) pmid: 30633927
159. Tian F, et al. Eur J Cancer (2013) pmid: 23313142
160. Ma R, et al. Cancer Biol Ther (2019) pmid: 31092103
161. Zheng R, et al. Genes Cancer (2010) pmid: 21779441
162. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
163. Ravandi F, et al. Blood Cancer J (2015) pmid: 26657199
164. Maiti A, et al. Clin Lymphoma Myeloma Leuk (2019) pmid: 30635233
165. Khanna V, et al. Cureus (2015) pmid: 26870618
166. Dummer R, et al. Lancet Oncol. (2017) pmid: 28284557
167. Ascierto PA, et al. Lancet Oncol. (2013) pmid: 23414587
168. Burgess MR, et al. Blood (2014) pmid: 25361812
169. Ohashi K, et al. Clin. Cancer Res. (2013) pmid: 23515407
170. Posch C, et al. J. Invest. Dermatol. (2015) pmid: 26016894
171. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
172. Vogel CJ, et al. Pigment Cell Melanoma Res (2015) pmid: 25728708
173. Fritsch C, et al. Mol. Cancer Ther. (2014) pmid: 24608574
174. Younes N, et al. Cancer (1997) pmid: 9128999
175. Zack TI, et al. Nat. Genet. (2013) pmid: 24071852
176. Beroukhim R, et al. Nature (2010) pmid: 20164920
177. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
178. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
179. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
180. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
181. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
182. Xu L, et al. Mol. Med. (2001) pmid: 11713371
183. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
184. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
185. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
186. Hajdenberg et al., 2012; ASCO Abstract e15010
187. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
188. Moore et al., 2019; ASCO Abstract 5513
189. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
190. Oza et al., 2015; ASCO Abstract 5506
191. Lee J, et al. Cancer Discov (2019) pmid: 31315834
192. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
193. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
194. Kwok M, et al. Blood (2016) pmid: 26563132
195. Boudny M, et al. Haematologica (2019) pmid: 30975914
196. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
197. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
198. Achille A, et al. Br. J. Cancer (1998) pmid: 9514055
199. Arai M, et al. Int. J. Cancer (1997) pmid: 9033644
200. Nishiyama K, et al. Oncol. Rep. () pmid: 11836595
201. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
202. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
203. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
204. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
205. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
206. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
207. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
208. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
209. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
210. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
211. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
212. Lalloo F, et al. Lancet (2003) pmid: 12672316
213. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
214. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
215. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
216. Xie M, et al. Nat. Med. (2014) pmid: 25326804
217. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
218. Severson EA, et al. Blood (2018) pmid: 29678827
219. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
220. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
221. Chabon JJ, et al. Nature (2020) pmid: 32269342
222. Razavi P, et al. Nat. Med. (2019) pmid: 31768066

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