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 Stomach carcinoma (NOS)

DATE OF BIRTH 26 September 1959
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

MEDICAL FACILITY Oncosalud- Auna
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 203367
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Stomach
SPECIMEN ID 20-3885
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 12 September 2020
SPECIMEN RECEIVED 24 April 2021

Sensitivity for the detection of alterations and genomic signatures is reduced and the TMB score may be underreported.

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.

KRAS G13D
PIK3R1 M582del
APC N778fs*1
SOX9 R264fs*16
TP53 R175H

1 Disease relevant genes with no reportable alterations: ***ERBB2***

0 Therapies with Clinical Benefit
0 Therapies with Lack of Response
11 Clinical Trials

BIOMARKER FINDINGS	ACTIONABILITY
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 BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
***KRAS* -** G13D	none	none
9 Trials *see p. 6*		
***PIK3R1* -** M582del	none	none
2 Trials *see p. 8*		

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIALS 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.

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

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 tumors reportedly make up 12-35% of sporadic gastric cancers[6-10], 6.6% (5/76) of Barrett esophagus-associated adenocarcinomas[11], and 1.5-4.2% of gastroesophageal cancers[10,12]. In the context of diffuse-type gastric cancer, a higher frequency of MSI-H tumors has been reported in familial (28%, 7/25) versus sporadic (7%, 7/107) tumors; no difference in frequency of MSI-H tumors was observed for intestinal-type gastric cancer[9]. MSI-H tumors have been frequently associated with hypermethylation and loss of MLH1 expression in cancers of the upper gastrointestinal tract, including esophageal, gastroesophageal junction, and gastric adenocarcinomas[9,13-17]. MSI-H gastric cancers are associated with certain clinicopathological and molecular features, including intestinal type differentiation, antral location, advanced age, reduced lymph node metastasis, and better prognosis[7-8,18-21]. A retrospective meta-analysis of the prognostic role of MSI in gastric cancers reported an increased DFS and OS in patients with MSI-H versus MSS/MSI-Low[22]. Conversely, in the same study, MSI-H was a negative predictor of response and MSS/MSI-Low correlated with increased benefit for patients treated with chemotherapy plus surgery as opposed to surgery alone[22]. In gastroesophageal cancer, MSI-H status was associated with shorter PFS compared to MSS patients for patients treated with chemotherapy (mPFS 4.8 months vs 6.9 months, HR=0.4)[23].

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[24]. 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[24-26]. 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[27-29]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[24,26,28-29].

BIOMARKER

Tumor Mutational Burden

RESULT
3 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[30-32], anti-PD-1 therapies[30-33], and combination nivolumab and ipilimumab[34-38]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[30-33,39]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment of patients with 9 types of advanced tumors[30]. 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[40] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[31]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy in patients with solid tumors found significant improvement in ORR in 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[33,39]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors.

FREQUENCY & PROGNOSIS

Gastric adenocarcinoma harbors a median TMB of 3.6 mutations per megabase (muts/Mb), and 5.5% of cases have high TMB (>20 muts/Mb)[41]. However, one study reported high TMB in 20% of intestinal type stomach adenocarcinomas specifically[42]. Another study of patients with gastric cancer reported hypermutation (10-200 muts/Mb) in 16.4% of cases, with significant overrepresentation of samples with microsatellite instability among the hypermutant cases[43]. For patients with gastric cancer, increased TMB is reported to be associated with prolonged OS[44-46]. One study observed that the OS and disease-free survival (DFS) benefits of postoperative chemotherapy were more pronounced in patients with TMB-low gastric cancer (stage Ib/II) compared to those with TMB-high; however, patients with stage III gastric cancer benefitted regardless of TMB level[47]. In esophageal cancer, patients with TMB-high who had not received radiotherapy had significantly reduced OS (p=0.038) compared to those with TMB-low[48].

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[49-50] and cigarette smoke in lung cancer[51-52], treatment with temozolomide-based chemotherapy in glioma[53-54], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[55-59], and microsatellite instability (MSI)[55,58-59]. 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[31-32,39].

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
KRAS

ALTERATION
G13D

TRANSCRIPT ID
NM_004985

CODING SEQUENCE EFFECT
38G>A

VARIANT ALLELE FREQUENCY (% VAF)
21.0%

POTENTIAL TREATMENT STRATEGIES

Preclinical evidence suggests that KRAS activation may predict sensitivity to MEK inhibitors, such as trametinib, binimetinib, cobimetinib, and selumetinib[60-65]. While clinical responses have been reported for patients with KRAS-mutated ovarian[66-69], cervical small cell neuroendocrine[70], or uterine cancer[68] treated with MEK inhibitor monotherapy, multiple clinical trials have not demonstrated increased response rates for patients with KRAS-altered tumors including KRAS-mutated CRC[71-74], pancreatic cancer[75-77], and NSCLC[72,78-79]. A Phase 2 study of trametinib and uprosertib for patients with recurrent cervical cancer reported no responses for patients with KRAS-mutated (2/2 SDs) or KRAS-amplified (1/1 SD) cancer[80]. Clinical responses have been reported for combination treatment strategies including MEK inhibitors with PI3K or AKT inhibitors for patients with KRAS-mutated ovarian cancer[81-83] and KRAS-mutated endometrioid adenocarcinoma[84]. The reovirus Reolysin targets cells with activated RAS signaling[85-87] and is in clinical trials in patients with some tumor types. Reolysin has demonstrated mixed clinical efficacy, with the highest rate of response reported for patients with head and neck cancer[88-96].

FREQUENCY & PROGNOSIS

KRAS mutations have been reported in 4% of esophageal and 0-10% of gastric adenocarcinomas[21,97-103]. Studies in the literature have reported KRAS mutations in up to 9% of gastric, esophageal, or gastroesophageal junction cancer cases[104-105]. KRAS alterations, including mutations[106] and amplification[107-109] are associated with worse prognosis in patients with gastroesophageal cancer. One study reported that KRAS alteration did not significantly associate with OS in a cohort of patients with gastric, esophageal, or gastroesophageal adenocarcinoma[110]. Published data investigating the prognostic implications of KRAS alterations in esophageal squamous cell carcinoma are limited (PubMed, Sep 2020).

FINDING SUMMARY

KRAS encodes a member of the RAS family of small GTPases. Activating mutations in RAS genes can cause uncontrolled cell proliferation and tumor formation[61,111]. KRAS alterations affecting amino acids G12, G13, Q22, P34, A59, Q61, and A146, as well as mutations G10_A11insG, G10_A11insAG (also reported as G10_A11dup and G12_G13insAG), A18D, L19F, D33E, G60_A66dup/E62_A66dup, E62K, and K117N have been characterized as activating and oncogenic[61,112-133].

GENE
PIK3R1

ALTERATION
M582del

TRANSCRIPT ID
NM_181523

CODING SEQUENCE EFFECT
1742_1744delTGA

VARIANT ALLELE FREQUENCY (% VAF)
20.4%

POTENTIAL TREATMENT STRATEGIES

On the basis of clinical[134-135] and preclinical[136-137] data, PIK3R1 alteration may predict sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors. In patients with PIK3R1 mutation and no other alterations in the PI3K-AKT-mTOR pathway, 2 CRs have been achieved by patients with endometrial cancer treated with the pan-PI3K inhibitor pilaralisib[134], and 1 PR has been achieved by a patient with breast cancer treated with the PI3K-alpha inhibitor alpelisib in combination with ribociclib and letrozole[138]. Limited clinical and preclinical data suggest that PIK3R1 alterations may also be sensitive to inhibitors of mTOR[137,139-142] or AKT[143-144]. One preclinical study reported that PIK3R1 truncation mutations in the 299–370 range confer sensitivity to MEK inhibitors[145].

FREQUENCY & PROGNOSIS

In the TCGA datasets, PIK3R1 mutation is most frequently observed in endometrial carcinoma (33%)[55], glioblastoma (GBM; 11%)[146], uterine carcinosarcoma (11%)(cBioPortal, 2021)[147-148], and lower grade glioma (5%)[149]. PIK3R1 is often inactivated by in-frame insertions or deletions (indels), and the majority of this class of mutation (80%) was observed in endometrial carcinoma[150-152], although PIK3R1 indels have been reported in other cancer types such as GBM, cervical squamous cell carcinoma, and urothelial bladder carcinoma[150]. On the basis of limited clinical data, reduced PIK3R1 expression has been associated with reduced disease-free survival in prostate cancer[153] and metastasis-free survival in breast cancer[154]. PIK3R1 expression is not associated with overall survival in neuroendocrine tumors[155].

FINDING SUMMARY

PIK3R1 encodes the p85-alpha regulatory subunit of phosphatidylinositol 3-kinase (PI3K)[156]. Loss of PIK3R1 has been shown to result in increased PI3K signaling[157-160], promote tumorigenesis[136,143,157], and promote hyperplasia in the context of PTEN-deficiency[161]. Alterations such as seen here may disrupt PIK3R1 function or expression[137,144-145,151-152,162-170].

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
APC

ALTERATION
N778fs*1

TRANSCRIPT ID
NM_000038

CODING SEQUENCE EFFECT
2332_2335delAATT

VARIANT ALLELE FREQUENCY (% VAF)
13.7%

POTENTIAL TREATMENT STRATEGIES
There are no approved drugs targeted to APC defects or WNT upregulation in solid tumors. Preclinical studies have reported that APC inactivation or beta-catenin activation confer synthetic lethality when TRAIL receptors are upregulated and the TRAIL death receptor program is activated[171]. In addition, the COX-2 inhibitor celecoxib was shown to reduce WNT signaling in cancer cell lines[172-173]. A preclinical study has found that a small-molecule tankyrase inhibitor shows some activity in APC-mutant CRC models[174].

FREQUENCY & PROGNOSIS
APC mutations have been observed in up to 11% of gastroesophageal carcinoma cases, with incidence of up to 13% of gastric carcinomas and up to 8% of esophageal carcinomas (cBioPortal, Jan 2021)[147-148,175-176]. APC mutation has been detected in 2.5-22% of gastric carcinomas in other studies, with a higher frequency in the intestinal type relative to the diffuse type[175-177]. Loss or methylation of APC has been detected in 26-48% of gastric carcinoma cases, and methylation of APC has also been found in 18.2% and 56.3% of low-grade and high-grade gastric adenomas, respectively[178-180]. Loss of APC gene expression, through deletion or methylation, and loss of protein expression have been associated with tumor progression and shorter cancer-specific and overall patient survival in patients with gastric cancer[178,181]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[182].

FINDING SUMMARY
APC (adenomatous polyposis coli) encodes a tumor suppressor with critical roles in regulating cell division and adhesion. APC interacts with beta-catenin and controls signaling in the WNT pathway, which regulates embryonic development and cell differentiation[183]. Alterations such as seen here may disrupt APC function or expression[184-188].

POTENTIAL GERMLINE IMPLICATIONS
Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[189-191]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[192], and in the appropriate clinical context germline testing of APC is recommended.

GENE
SOX9

ALTERATION
R264fs*16

TRANSCRIPT ID
NM_000346

CODING SEQUENCE EFFECT
789_790insGC

VARIANT ALLELE FREQUENCY (% VAF)
21.3%

POTENTIAL TREATMENT STRATEGIES
There are no therapies available to directly address genomic alterations in SOX9.

FREQUENCY & PROGNOSIS
Mutation of SOX9 in cancer is typically rare, but it has been reported in 5-9% of colorectal carcinomas, most of which were truncating or frameshift alterations, and fewer than 4% of other tumor types (cBioPortal, COSMIC, Jan 2021)[147-148,193]. Increased expression of SOX9 has been associated with tumor development and/or increased aggressiveness of prostate cancer, pancreatic ductal adenocarcinoma, ovarian cancer, glioma, and esophageal adenocarcinoma[194-197].

FINDING SUMMARY
SOX9 encodes a transcription factor important for the development and differentiation of multiple tissues, including cartilage, testis, and prostate[198].

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

GENE
TP53

ALTERATION
R175H

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
524G>A

VARIANT ALLELE FREQUENCY (% VAF)
21.1%

POTENTIAL TREATMENT STRATEGIES

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[199-202], or p53 gene therapy and immunotherapeutics such as SGT-53[203-207] and ALT-801[208]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) in patients with TP53 mutations versus 12.1% (4/33) in patients who were TP53 wild-type[209]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR in patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[210]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR in patients with platinum-refractory TP53-mutated ovarian cancer[211]. The combination of adavosertib with paclitaxel and carboplatin in patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[81]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[212]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[213]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel in patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[207]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[214]. Missense mutations leading to TP53 inactivation may also be sensitive to therapies that reactivate mutant p53 such as APR-246[215-217]. In a Phase 1b trial in patients with p53-positive high-grade serous ovarian cancer, APR-246 combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[218]. 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[219-220]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[221-222]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 is frequently mutated in cancers of the gastrointestinal tract, with alterations reported in 34–72% of esophageal, gastroesophageal junction, and gastric adenocarcinomas[21,97,223-224]. Overexpression of p53 protein, which may occur as a result of mutation, has been reported in approximately 36% of gastric cancers, with p53 expression reported to be more frequent in intestinal-type compared with diffuse-type gastric cancer[225-228]. While some studies have reported no association between TP53 mutation status and prognosis in patients with esophageal carcinoma or gastroesophageal junction adenocarcinoma[223-224] others have associated TP53 mutation and elevated p53 expression with poor prognosis for patients with esophageal squamous cell carcinoma[229-230] or stomach cancer[231-233].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[234]. Alterations such as seen here may disrupt TP53 function or expression[235-239].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Mar 2021)[240]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[241-243], including sarcomas[244-245]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[246] to 1:20,000[245]. 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[247]. 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[248-253]. 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[248-249]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[254]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[252,255-256]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

ORDERED TEST # ORD-1078007-01

CLINICAL TRIALS

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

GENE
KRAS

ALTERATION
G13D

RATIONALE
KRAS activating mutations or amplification may predict sensitivity to inhibitors of MAPK pathway components, including MEK inhibitors.

NCT03989115

PHASE 1/2

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

TARGETS
SHP2, MEK

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

NCT03905148

PHASE 1/2

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

TARGETS
RAFs, EGFR, MEK

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

NCT03281369

PHASE 1/2

A Study of Multiple Immunotherapy-Based Treatment Combinations in Patients With Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer (G/GEJ) (Morpheus-Gastric Cancer)

TARGETS
MEK, CXCR4, VEGFRs, PD-L1

LOCATIONS: Texas, Kentucky, New York, California, Glasgow (United Kingdom), Manchester (United Kingdom), Sutton (United Kingdom), London (United Kingdom), Tel-Aviv (Israel), Petach Tikva (Israel)

NCT02079740

PHASE 1/2

Trametinib and Navitoclax in Treating Patients With Advanced or Metastatic Solid Tumors

TARGETS
BCL-W, BCL-XL, BCL2, MEK

LOCATIONS: Massachusetts

NCT03065387

PHASE 1

Study of the Pan-ERBB Inhibitor Neratinib Given in Combination With Everolimus, Palbociclib or Trametinib in Advanced Cancer Subjects With EGFR Mutation/Amplification, HER2 Mutation/Amplification or HER3/4 Mutation

TARGETS
mTOR, EGFR, ERBB2, ERBB4, CDK4, CDK6, MEK

LOCATIONS: Texas

ORDERED TEST # ORD-1078007-01

CLINICAL TRIALS

NCT03162627

PHASE 1

Selumetinib and Olaparib in Solid Tumors

TARGETS
MEK, PARP

LOCATIONS: Texas

NCT02070549

PHASE 1

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

TARGETS
MEK

LOCATIONS: Toronto (Canada)

NCT02407509

PHASE 1

Phase I Trial of RO5126766

TARGETS
RAFs, MEK, mTOR

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

NCT03284502

PHASE 1

Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors

TARGETS
MEK, RAFs

LOCATIONS: Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Seongnam (Korea, Republic of), Pusan (Korea, Republic of), Hwasun (Korea, Republic of)

GENE
PIK3R1

ALTERATION
M582del

RATIONALE
On the basis of clinical and strong preclinical data, PIK3R1 loss or inactivation may indicate sensitivity to pan-PI3K or PI3K-alpha-selective inhibitors.

NCT03711058

PHASE 1/2

Study of PI3Kinase Inhibition (Copanlisib) and Anti-PD-1 Antibody Nivolumab in Relapsed/Refractory Solid Tumors With Expansions in Mismatch-repair Proficient (MSS) Colorectal Cancer

TARGETS
PD-1, PI3K

LOCATIONS: Maryland

NCT03502733

PHASE 1

Copanlisib and Nivolumab in Treating Patients With Metastatic Solid Tumors or Lymphoma

TARGETS
PI3K, PD-1

LOCATIONS: Texas, Maryland

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.

ARFRP1
amplification

ASXL1
amplification

AURKA
amplification

BCL2L1
amplification

GNAS
amplification

SRC
amplification

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

FoundationOne CDx is designed to include genes known to be somatically altered in human solid tumors that are validated targets for therapy, either approved or in clinical trials, and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 324 genes as well as introns of 36 genes involved in rearrangements. The assay will be updated periodically to reflect new knowledge about cancer biology.

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*
AR	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*
AURKB	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*
BCOR	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*
BTK	*C11orf30 (EMSY)*	*C17orf39 (GID4)*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*
CDH1	*CDK12*	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*
CDKN2C	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*
CTCF	*CTNNA1*	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*
DDR2	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FAM46C	*FANCA*	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*
FGF14	*FGF19*	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*
FGFR4	*FH*	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*
GATA4	*GATA6*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3F3A*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11A*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*	*P2RY8*	*PALB2*
PARK2	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*	*PDGFRA*
PDGFRB	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*	*PMS2*
POLD1	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*	*PTCH1*
PTEN	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*	*RAD51B*	*RAD51C*
RAD51D	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*	*REL*	*RET*
RICTOR	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*	*SDHD*	*SETD2*
SF3B1	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SNCAIP*	*SOCS1*
SOX2	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*
SYK	*TBX3*	*TEK*	*TET2*	*TGFBR2*	*TIPARP*	*TNFAIP3*	*TNFRSF14*	*TP53*
TSC1	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*	*VHL*	*WHSC1*	*WT1*	*XPO1*
XRCC2	*ZNF217*	*ZNF703*						

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

ALK	*BCL2*	*BCR*	*BRAF*	*BRCA1*	*BRCA2*	*CD74*	*EGFR*	*ETV4*
ETV5	*ETV6*	*EWSR1*	*EZR*	*FGFR1*	*FGFR2*	*FGFR3*	*KIT*	*KMT2A (MLL)*
MSH2	*MYB*	*MYC*	*NOTCH2*	*NTRK1*	*NTRK2*	*NUTM1*	*PDGFRA*	*RAF1*
RARA	*RET*	*ROS1*	*RSPO2*	*SDC4*	*SLC34A2*	*TERC**	*TERT***	*TMPRSS2*

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

Loss of Heterozygosity (LOH) score
Microsatellite (MS) status
Tumor Mutational Burden (TMB)

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Alterations and Therapies

Biomarker and Genomic Findings

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

Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. The MSI-H/MSS designation by FMI F1CDx test is based on genome wide analysis of 95 microsatellite loci and not based on the 5 or 7 MSI loci described in current clinical practice guidelines. The threshold for MSI-H/MSS was determined by analytical concordance to comparator assays (IHC and PCR) using uterine, cecum and colorectal cancer FFPE tissue. The clinical validity of the qualitative MSI designation has not been established. For Microsatellite Instability (MSI) results, confirmatory testing using a validated orthogonal method should be considered.
2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit.

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.

3. The LOH score is determined by analyzing SNPs spaced at 1Mb intervals across the genome on the FoundationOne CDx test and extrapolating an LOH profile, excluding arm- and chromosome-wide LOH segments. Detection of LOH has been verified only for ovarian cancer patients, and the LOH score result may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas. The LOH score will be reported as "Cannot Be Determined" if the sample is not of sufficient quality to confidently determine LOH. Performance of the LOH classification has not been established for samples below 35% tumor content. There may be potential interference of ethanol with LOH detection. The interfering effects of xylene, hemoglobin, and triglycerides on the LOH score have not been demonstrated.
4. Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. The test does not provide information about susceptibility.
5. Biopsy may pose a risk to the patient when archival tissue is not available for use with the assay. The patient's physician should determine whether the patient is a candidate for biopsy.
6. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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.

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

SELECT ABBREVIATIONS

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

MR Suite Version 4.0.0

The median exon coverage for this sample is 500x

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

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. Hiyama T, et al. J. Gastroenterol. Hepatol. (2004) pmid: 15209621
7. Wu MS, et al. Cancer Res. (1998) pmid: 9537253
8. dos Santos NR, et al. Gastroenterology (1996) pmid: 8536886
9. Fang WL, et al. Biomed Res Int (2013) pmid: 23555086
10. Cancer Genome Atlas Research Network, et al. Nature (2017) pmid: 28052061
11. Farris AB, et al. Am. J. Surg. Pathol. (2011) pmid: 21422910
12. Hall et al., 2016; ASCO Gastrointestinal Cancer Symposium Abstract 528
13. Gu M, et al. Hepatogastroenterology () pmid: 19621725
14. Sasaki S, et al. Oncol Lett (2011) pmid: 22866067
15. Fleisher AS, et al. Cancer Res. (1999) pmid: 10070967
16. Vasavi M, et al. Cancer Biomark (2010) pmid: 21045259
17. Zhang LH, et al. Pathol. Res. Pract. (2013) pmid: 24035280
18. Zhu L, et al. Mol Clin Oncol (2015) pmid: 26137290
19. Leung SY, et al. Cancer Res. (1999) pmid: 9892201
20. Seo JY, et al. World J. Gastroenterol. (2015) pmid: 26078567
21. Nature (2014) pmid: 25079317
22. Pietrantonio F, et al. J. Clin. Oncol. (2019) pmid: 31513484
23. Janjigian YY, et al. Cancer Discov (2018) pmid: 29122777
24. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
25. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
26. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
27. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
28. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
29. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
30. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
31. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
32. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
33. Cristescu R, et al. Science (2018) pmid: 30309915
34. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
35. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
36. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
37. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
38. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
39. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
40. Legrand et al., 2018; ASCO Abstract 12000
41. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
42. Frampton et al., 2016; ASCO Abstract 11558
43. Li X, et al. Cancer Res. (2016) pmid: 26857262
44. Cai L, et al. Cancer Commun (Lond) (2020) pmid: 32141230
45. Zhao DY, et al. World J Gastrointest Oncol (2021) pmid: 33510848
46. Wei XL, et al. Ther Adv Med Oncol (2021) pmid: 33613701
47. Wang D, et al. Gastric Cancer (2021) pmid: 33687617
48. Yuan C, et al. Aging (Albany NY) (2020) pmid: 32165590
49. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
50. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
51. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
52. Rizvi NA, et al. Science (2015) pmid: 25765070
53. Johnson BE, et al. Science (2014) pmid: 24336570
54. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
55. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
56. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
57. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
58. Nature (2012) pmid: 22810696
59. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
60. Nakano H, et al. Proc. Natl. Acad. Sci. U.S.A. (1984) pmid: 6320174
61. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
62. Yamaguchi T, et al. Int. J. Oncol. (2011) pmid: 21523318
63. Watanabe M, et al. Cancer Sci. (2013) pmid: 23438367
64. Gilmartin AG, et al. Clin. Cancer Res. (2011) pmid: 21245089
65. Yeh JJ, et al. Mol. Cancer Ther. (2009) pmid: 19372556
66. Monk BJ, et al. J Clin Oncol (2020) pmid: 32822286
67. Farley J, et al. Lancet Oncol. (2013) pmid: 23261356
68. Slosberg ED, et al. Oncotarget (2018) pmid: 29765547
69. Han C, et al. Gynecol Oncol Rep (2018) pmid: 29946554
70. Lyons YA, et al. Gynecol Oncol Rep (2014) pmid: 26075998
71. Infante JR, et al. Lancet Oncol. (2012) pmid: 22805291
72. Zimmer L, et al. Clin. Cancer Res. (2014) pmid: 24947927
73. Bennouna J, et al. Invest New Drugs (2011) pmid: 20127139
74. Weekes CD, et al. Clin. Cancer Res. (2013) pmid: 23434733
75. Van Laethem JL, et al. Target Oncol (2017) pmid: 27975152
76. Infante JR, et al. Eur. J. Cancer (2014) pmid: 24915778
77. Van Cutsem E, et al. Int. J. Cancer (2018) pmid: 29756206
78. Blumenschein GR, et al. Ann. Oncol. (2015) pmid: 25722381
79. Leijen S, et al. Clin. Cancer Res. (2012) pmid: 22767668
80. Liu JF, et al. Gynecol. Oncol. (2019) pmid: 31118140
81. Spreafico et al., 2014; ASCO Abstract 5506
82. Juric et al., 2014; ASCO Abstract 9051
83. Banerji et al., 2014; ASCO Abstract e13559
84. Shapiro GI, et al. Invest New Drugs (2019) pmid: 31020608
85. Strong JE, et al. EMBO J. (1998) pmid: 9628872
86. Coffey MC, et al. Science (1998) pmid: 9812900
87. Gong J, et al. Front Oncol (2014) pmid: 25019061
88. Forsyth P, et al. Mol. Ther. (2008) pmid: 18253152
89. Vidal L, et al. Clin. Cancer Res. (2008) pmid: 18981012
90. Gollamudi R, et al. Invest New Drugs (2010) pmid: 19572105
91. Harrington KJ, et al. Clin. Cancer Res. (2010) pmid: 20484020
92. Comins C, et al. Clin. Cancer Res. (2010) pmid: 20926400
93. Lolkema MP, et al. Clin. Cancer Res. (2011) pmid: 21106728
94. Galanis E, et al. Mol. Ther. (2012) pmid: 22871663
95. Karapanagiotou EM, et al. Clin. Cancer Res. (2012) pmid: 22316603
96. Morris DG, et al. Invest New Drugs (2013) pmid: 22886613
97. Dulak AM, et al. Nat. Genet. (2013) pmid: 23525077
98. Wang K, et al. Nat. Genet. (2014) pmid: 24816253
99. Kakiuchi M, et al. Nat. Genet. (2014) pmid: 24816255
100. Wang K, et al. Nat. Genet. (2011) pmid: 22037554
101. Matsubara A, et al. J. Pathol. (2013) pmid: 23208952
102. van Grieken NC, et al. Br. J. Cancer (2013) pmid: 23511561
103. Lee J, et al. Discov Med (2013) pmid: 23911227
104. Luber B, et al. BMC Cancer (2011) pmid: 22152101
105. Wainberg ZA, et al. Br. J. Cancer (2011) pmid: 21811258
106. Warneke VS, et al. Diagn. Mol. Pathol. (2013) pmid: 23846438
107. Wong GS, et al. Nat. Med. (2018) pmid: 29808010
108. Qian Z, et al. Genes Chromosomes Cancer (2014) pmid: 24935174
109. Deng N, et al. Gut (2012) pmid: 22315472
110. Kato S, et al. Clin. Cancer Res. (2018) pmid: 30348637
111. Kahn S, et al. Anticancer Res. () pmid: 3310850
112. Akagi K, et al. Biochem. Biophys. Res. Commun. (2007) pmid: 17150185
113. Bollag G, et al. J. Biol. Chem. (1996) pmid: 8955068
114. Buhrman G, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20194776
115. Sci. STKE (2004) pmid: 15367757
116. Edkins S, et al. Cancer Biol. Ther. (2006) pmid: 16969076
117. Feig LA, et al. Mol. Cell. Biol. (1988) pmid: 3043178
118. Gremer L, et al. Hum. Mutat. (2011) pmid: 20949621
119. Janakiraman M, et al. Cancer Res. (2010) pmid: 20570890
120. Kim E, et al. Cancer Discov (2016) pmid: 27147599
121. Lukman S, et al. PLoS Comput. Biol. (2010) pmid: 20838576
122. Naguib A, et al. J Mol Signal (2011) pmid: 21371307
123. Prior IA, et al. Cancer Res. (2012) pmid: 22589270
124. Privé GG, et al. Proc. Natl. Acad. Sci. U.S.A. (1992) pmid: 1565661
125. Scheffzek K, et al. Science (1997) pmid: 9219684
126. Scholl C, et al. Cell (2009) pmid: 19490892
127. Smith G, et al. Br. J. Cancer (2010) pmid: 20147967
128. Tyner JW, et al. Blood (2009) pmid: 19075190
129. Valencia A, et al. Biochemistry (1991) pmid: 2029511
130. White Y, et al. Nat Commun (2016) pmid: 26854029
131. Wiest JS, et al. Oncogene (1994) pmid: 8058307
132. Angeles AKJ, et al. Oncol Lett (2019) pmid: 31289513
133. Tong JH, et al. Cancer Biol. Ther. (2014) pmid: 24642870
134. Matulonis U, et al. Gynecol. Oncol. (2015) pmid: 25528496
135. Pitz MW, et al. Neuro-oncology (2015) pmid: 25605819
136. Thorpe LM, et al. Proc. Natl. Acad. Sci. U.S.A. (2017) pmid: 28630349
137. Sun M, et al. Proc. Natl. Acad. Sci. U.S.A. (2010) pmid: 20713702
138. Juric et al., 2016; SABCS Abstract P3-14-01
139. Basho RK, et al. JAMA Oncol (2017) pmid: 27893038
140. Myers AP, et al. Gynecol. Oncol. (2016) pmid: 27016228
141. Day TA, et al. Clin. Cancer Res. (2019) pmid: 30420444
142. Ou O, et al. Cancer Lett. (2014) pmid: 25193464
143. Li X, et al. Nat Commun (2019) pmid: 30755611
144. Quayle SN, et al. PLoS ONE (2012) pmid: 23166678

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531

145. Cheung LW, et al. Cancer Cell (2014) pmid: 25284480
146. Brennan CW, et al. Cell (2013) pmid: 24120142
147. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
148. Gao J, et al. Sci Signal (2013) pmid: 23550210
149. Cancer Genome Atlas Research Network, et al. N. Engl. J. Med. (2015) pmid: 26061751
150. Ye K, et al. Nat. Med. (2016) pmid: 26657142
151. Cheung LW, et al. Cancer Discov (2011) pmid: 21984976
152. Urick ME, et al. Cancer Res. (2011) pmid: 21478295
153. Munkley J, et al. Oncoscience (2015) pmid: 26501081
154. Cizkova M, et al. BMC Cancer (2013) pmid: 24229379
155. Qian ZR, et al. J. Clin. Oncol. (2013) pmid: 23980085
156. Huang CH, et al. Cell Cycle (2008) pmid: 18418043
157. Taniguchi CM, et al. Cancer Res. (2010) pmid: 20530665
158. Luo J, et al. Cell Metab. (2006) pmid: 16679293
159. Ueki K, et al. J. Biol. Chem. (2003) pmid: 14504291
160. Mauvais-Jarvis F, et al. J. Clin. Invest. (2002) pmid: 11781359
161. Luo J, et al. Proc. Natl. Acad. Sci. U.S.A. (2005) pmid: 16006513
162. Jaiswal BS, et al. Cancer Cell (2009) pmid: 19962665
163. Ko HR, et al. Cell Death Dis (2014) pmid: 24651434
164. Wu H, et al. Proc. Natl. Acad. Sci. U.S.A. (2009) pmid: 19915146
165. Huang CH, et al. Science (2007) pmid: 18079394
166. Bousquet C, et al. EMBO J. (2006) pmid: 16917505
167. Oliver MD, et al. Biosci. Rep. (2017) pmid: 28143957
168. Philp AJ, et al. Cancer Res. (2001) pmid: 11606375
169. Lucas CL, et al. J. Exp. Med. (2014) pmid: 25488983
170. Chen L, et al. Nat Commun (2018) pmid: 29636477
171. Zhang L, et al. Nature (2010) pmid: 20348907
172. Lu W, et al. Eur. J. Pharmacol. (2009) pmid: 19026633
173. Tuynman JB, et al. Cancer Res. (2008) pmid: 18281498
174. Lau T, et al. Cancer Res. (2013) pmid: 23539443
175. Fang DC, et al. World J. Gastroenterol. (2002) pmid: 12378616
176. Horii A, et al. Cancer Res. (1992) pmid: 1317264
177. Lee J, et al. PLoS ONE (2012) pmid: 22723903
178. Fang Z, et al. Clin Transl Oncol (2012) pmid: 22262720
179. Liu JB, et al. World J. Gastroenterol. (2012) pmid: 23049225
180. Wang ZK, et al. J. Gastroenterol. Hepatol. (2012) pmid: 22741528
181. Bria E, et al. Ann. Oncol. (2013) pmid: 23131390
182. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
183. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
184. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
185. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
186. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
187. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
188. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
189. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
190. Annu Rev Pathol (2011) pmid: 21090969
191. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
192. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
193. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
194. Kopp JL, et al. Cancer Cell (2012) pmid: 23201164
195. Zhong WD, et al. BMC Cancer (2012) pmid: 22703285
196. Wang L, et al. Med. Oncol. (2012) pmid: 22714060
197. Clemons NJ, et al. Am. J. Physiol. Gastrointest. Liver Physiol. (2012) pmid: 23064761
198. Pritchett J, et al. Trends Mol Med (2011) pmid: 21237710
199. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
200. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
201. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
202. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
203. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
204. Xu L, et al. Mol. Med. (2001) pmid: 11713371
205. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
206. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
207. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
208. Hajdenberg et al., 2012; ASCO Abstract e15010
209. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
210. Moore et al., 2019; ASCO Abstract 5513
211. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
212. Lee J, et al. Cancer Discov (2019) pmid: 31315834
213. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
214. Ma CX, et al. J. Clin. Invest. (2012) pmid: 22446188
215. Lehmann S, et al. J. Clin. Oncol. (2012) pmid: 22965953
216. Mohell N, et al. Cell Death Dis (2015) pmid: 26086967
217. Fransson Å, et al. J Ovarian Res (2016) pmid: 27179933
218. Gourley et al., 2016; ASCO Abstract 5571
219. Kwok M, et al. Blood (2016) pmid: 26563132
220. Boudny M, et al. Haematologica (2019) pmid: 30975914
221. Dillon MT, et al. Mol. Cancer Ther. (2017) pmid: 28062704
222. Middleton FK, et al. Cancers (Basel) (2018) pmid: 30127241
223. Sengpiel C, et al. Cancer Invest. (2009) pmid: 19160092
224. Pühringer-Oppermann F, et al. J. Cancer Res. Clin. Oncol. (2006) pmid: 16538517
225. Lee HE, et al. Pathobiology (2014) pmid: 23969480
226. Sezer C, et al. J BUON () pmid: 23613399
227. Victorzon M, et al. Eur. J. Cancer (1996) pmid: 8664030
228. Gonçalves AR, et al. Pathol. Oncol. Res. (2011) pmid: 21116760
229. Han U, et al. Dis. Esophagus (2007) pmid: 17760650
230. Yamasaki M, et al. Ann. Surg. Oncol. (2010) pmid: 19941080
231. Liu X, et al. PLoS ONE (2012) pmid: 23285001
232. Wiksten JP, et al. Anticancer Res. () pmid: 18751407
233. Migliavacca M, et al. J. Cell. Physiol. (2004) pmid: 15254976
234. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
235. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
236. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
237. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
238. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
239. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
240. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
241. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
242. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
243. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
244. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
245. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
246. Lalloo F, et al. Lancet (2003) pmid: 12672316
247. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
248. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
249. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
250. Xie M, et al. Nat. Med. (2014) pmid: 25326804
251. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
252. Severson EA, et al. Blood (2018) pmid: 29678827
253. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
254. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
255. Chabon JJ, et al. Nature (2020) pmid: 32269342
256. Razavi P, et al. Nat. Med. (2019) pmid: 31768066

Electronically signed by Eric Severson, M.D., Ph.D., M.M.Sc. | 19 May 2021
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Shakti Ramkissoon, M.D., Ph.D., M.M. Sc, Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Sample Analysis: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
Post-Sequencing Analysis: 150 Second St., 1st Floor. Cambridge, MA 02141 · CLIA: 22D2027531