FOUNDATIONONE®CDx

PATIENT 03-2024-00108151, UK

TUMOR TYPE Colon adenocarcinoma (CRC)

COUNTRY CODE GB

REPORT DATE 22 Apr 2024

ORDERED TEST # ORD-1864117-01

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** Colon adenocarcinoma (CRC)
- **NAME** 03-2024-00108151, UK
- **DATE OF BIRTH** 06 March 1985
- **SEX** Male
- **MEDICAL RECORD #** X3077596

PHYSICIAN
- **ORDERING PHYSICIAN** Gerlinger, Marco
- **MEDICAL FACILITY** The London Oncology Clinic - LOC Partnership LLP
- **ADDITIONAL RECIPIENT** None
- **MEDICAL FACILITY ID** 200427
- **PATHOLOGIST** Moore, David

SPECIMEN
- **SPECIMEN SITE** Liver
- **SPECIMEN ID** 24S00004299 A1
- **SPECIMEN TYPE** Block
- **DATE OF COLLECTION** 24 January 2024
- **SPECIMEN RECEIVED** 16 April 2024

Genomic Signatures

Microsatellite status - MS-Stable

Tumor Mutational Burden - 6 Muts/Mb

Gene Alterations

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

KRAS wildtype
NRAS wildtype
APC R805*, E1494fs*19
TP53 C238R

4 Disease relevant genes with no reportable alterations: ***BRAF, ERBB2, KRAS, NRAS***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Cetuximab** (p. 8), **Panitumumab** (p. 9)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 10)

GENOMIC SIGNATURES	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Genomic Signatures section
Tumor Mutational Burden - 6 Muts/Mb	**No therapies or clinical trials.** See Genomic Signatures section

GENE ALTERATIONS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
KRAS - wildtype	Cetuximab 2A	none
0 Trials	Panitumumab 2A	
NRAS - wildtype	Cetuximab 2A	none
0 Trials	Panitumumab 2A	
APC - R805*, E1494fs*19	none	none
3 Trials see p. 10		

NCCN category

GENE ALTERATIONS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

Electronically signed by Douglas Lin, M.D. | 22 April 2024
Roche Customer Care | www.rochefoundationmedicine.com

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

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

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

GENOMIC SIGNATURE

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence, MSS tumors are significantly less likely than MSI-H tumors to respond to anti-PD-1 immune checkpoint inhibitors[1-3], including approved therapies nivolumab and pembrolizumab[4-5]. 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)[6]. For patients with chemotherapy-refractory microsatellite-stable (MSS) metastatic colorectal cancer (CRC), a Phase 3 trial reported no OS advantage from the combination of the PD-L1 inhibitor atezolizumab plus cobimetinib relative to regorafenib (8.9 vs. 8.5 months, HR=1.00); atezolizumab monotherapy similarly did not prolong OS (7.1 vs. 8.5 months, HR=1.19)[7]. For patients with MSS CRC, a Phase 2 study combining ipilimumab and nivolumab reported an overall DCR of 25% (10/40)[8]. Two Phase 1 studies for patients with MSS CRC treated with regorafenib and nivolumab reported PFSs of 7.9 months[9] and 5.7 months[10], and a patient with MSS CRC refractory to chemotherapy treated with the PD-1 inhibitor sintilimab and regorafenib reported a CR[11]. The NEST-1 study of neoadjuvant botensilimab in combination with balstilimab for patients with CRC reported pathological responses for 67% (6/9) of patients with MSS tumors[12].

— Nontargeted Approaches —

MSI has not been found to be a predictive biomarker for combination chemotherapy regimens, including FOLFOX[13-14] and FOLFIRI[15-16]. Patients with MSS CRC are more likely to benefit from postsurgical fluorouracil (FU)-based adjuvant therapy[17-18] but less likely to benefit from irinotecan chemotherapy[19].

FREQUENCY & PROGNOSIS

MSS colorectal cancers (CRCs) make up 70-85% of CRC cases[1,20-24]. MSS colorectal cancers are molecularly heterogeneous, driven by diverse mechanisms such as extensive DNA methylation, oncogenic mutations in KRAS or BRAF, or chromosomal instability[22]. Multiple studies have shown that MSS CRCs have a worse prognosis than MSI-high tumors[21,25-31].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA MMR in the tumor[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[24,32-33]. 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[20,34-35]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[20,24,33-34].

GENOMIC SIGNATURE

Tumor Mutational Burden

RESULT
6 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[36-39], anti-PD-1 therapies[37-41], and combination nivolumab and ipilimumab[42-50]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[36-39,41,51-55]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[51]; similar findings were observed in the KEYNOTE 028 and 012 trials[41]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[55]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[56]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[54]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[36] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[38]. In CRC specifically, a retrospective analysis of immune checkpoint inhibitor efficacy reported significantly improved OS for patients with tumors harboring TMB ≥9.8 Muts/MB compared with those with tumors with TMB <9.8 Muts/Mb (~ equivalency <12 Muts/Mb as measured by this assay)[37]. Another retrospective study reported that a TMB ≥12 Muts/Mb cutoff identifies >99% of MSI-High CRC cases but only 3% of MSS cases, indicating the utility of this cutoff for identification of patients with CRC likely to benefit from treatment with immune checkpoint inhibitors[57].

FREQUENCY & PROGNOSIS

Elevated tumor mutational burden (TMB) has been reported in 8-25% of colorectal cancer (CRC) samples[23,58-61]. Multiple studies have reported that up to 90% of hypermutated CRC cases exhibit high levels of microsatellite instability (MSI-H) and MMR deficiency[23,60]. Increased TMB is significantly associated with MSI-H and MMR deficiency, with studies reporting that 100% of MSI-H CRCs harbor elevated TMB and conversely that 100% of tumors with low TMB harbor intact MMR[58-60]. A subset of CRCs that harbor increased TMB but not MSI-H are driven by mutations in POLE, which leads to an "ultramutated" phenotype with especially high TMB[23,60]. Tumors with increased TMB harbor BRAF V600E mutations more frequently than those with low TMB[23,60], whereas TMB-low tumors more frequently harbor mutations in TP53 and APC[23]. The prognostic value of tumor mutational burden (TMB) in colorectal cancer (CRC) is context- and therapy-dependent. A study of tissue TMB (tTMB) in 145 CRC samples showed longer OS in TMB-high samples compared with TMB-low ones[62]. Similarly, for patients with metastatic CRC treated with first-line chemotherapy combined with bevacizumab or cetuximab, high tissue TMB (tTMB-H) was associated with longer OS[63]. For patients treated with adjuvant chemotherapy, tTMB-H was associated with better 5-year relapse-free survival[64]. However, for patients with EGFR/BRAF-inhibitor-treated, BRAF-mutated microsatellite stable (MSS) metastatic CRC, intermediate tTMB was associated with significantly poorer PFS and OS compared with TMB-low status; patients with primary resistance to EGFR/BRAF blockage had higher TMB than those sensitive to these therapies[65]. In a study for 61 patients with metastatic, MSS CRC treated with best standard of care, plasma TMB scores ≥28 Muts/Mb (approximately 14 Muts/Mb as measured by this assay) were associated with reduced OS compared with plasma TMB scores <28 Muts/Mb (3.0 vs. 5.3 months, HR=0.76, p=0.007), whereas tTMB was not found to be prognostic in this population[66-67].

FINDING SUMMARY

Tumor mutational burden (TMB, also known as mutation load) is a measure of the number of somatic protein-coding base substitutions and insertion/deletion mutations occurring in a tumor specimen. TMB is affected by a variety of causes, including exposure to mutagens such as ultraviolet light in melanoma[68-69] and cigarette smoke in lung cancer[70-71], treatment with temozolomide-based chemotherapy in glioma[72-73], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[23,74-77], and microsatellite instability[23,74,77]. This sample harbors a TMB below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[37,51,57].

GENE
KRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— **Targeted Therapies** —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[78-81] or panitumumab[82-84] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v1.2024, Rectal Cancer Guidelines, v1.2024).

FREQUENCY & PROGNOSIS

Approximately 50-65% of colorectal cancers (CRCs) have been reported to lack KRAS mutations[85-93].

Numerous studies have reported that KRAS wild-type status is associated with decreased metastasis, better clinicopathological features, and longer survival of patients with CRC[88-91,94-95].

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[96-97]. No alterations in KRAS were identified in this case.

GENE
NRAS

ALTERATION
wildtype

POTENTIAL TREATMENT STRATEGIES

— **Targeted Therapies** —

Lack of mutations in KRAS or NRAS is associated with clinical benefit of treatment with EGFR-targeting antibodies cetuximab[78-81] or panitumumab[82-84] for patients with CRC. Therefore, these agents are indicated to treat patients with CRC lacking such mutations (NCCN Colon Cancer Guidelines, v1.2024, Rectal Cancer Guidelines, v1.2024).

FREQUENCY & PROGNOSIS

The majority of colorectal cancers (CRCs) (91-98%) have been reported to lack NRAS mutations[23,85,98-103]. NRAS wild-type status has been reported to be associated with decreased frequency of metastasis[85] and longer survival[103-104] of patients with CRC.

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[96]. No alterations in NRAS were identified in this case.

GENE

APC

ALTERATION
R805*, E1494fs*19

HGVS VARIANT
NM_000038.4:c.2413C>T (p.R805*),
NM_000038.4:c.4479_4480del (p.E1494Kfs*19)

VARIANT CHROMOSOMAL POSITION
chr5:112173704, chr5:112175769-112175771

VARIANT ALLELE FREQUENCY (% VAF)
29.5%, 59.4%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no approved drugs targeting APC inactivation in cancer. Loss of APC function leads to the accumulation of beta-catenin and upregulation of WNT pathway transcription programs[105], and potential therapeutic approaches to target this pathway include antagonists that interfere with the ability of beta-catenin to interact with transcriptional co-activator CBP[106-107]. In a Phase 1 trial of the CBP/beta-catenin antagonist E7386, 1 patient with APC-mutated small bowel adenocarcinoma achieved a PR with tumor shrinkage of 69% and response duration of 165 days[108]; preclinical data support sensitivity of APC-deficient gastric or colorectal cancer (CRC) models to E7386[109-110]. Clinical studies have also demonstrated significant responses for patients with APC-mutated desmoid tumors following treatment with the gamma-secretase inhibitors (GSI) nirogacestat and AL101[111-113], suggesting APC mutations may be sensitive to GSIs for this patient population.

FREQUENCY & PROGNOSIS

APC mutations have been found in 73% of tumors in the colorectal adenocarcinoma TCGA dataset[23]. In 1 study, loss of heterozygosity (LOH) of APC was observed in 32% of colorectal cancer (CRC) samples[114]. The prognostic significance of APC mutations in sporadic CRC remains unclear[115]. Solid tumors with WNT/beta-catenin pathway alterations, as seen here, were observed to have significantly less T-cell inflammation in one study[116].

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[117]. Alterations such as seen here may disrupt APC function or expression[118-122].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the APC 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 familial adenomatous polyposis (ClinVar, Mar 2024)[123]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in APC are found in more than 90% of patients with familial adenomatous polyposis (FAP)[124-126]. The prevalence for FAP in the general population is estimated to be 1:8,300 from birth[127], and in the appropriate clinical context germline testing of APC is recommended.

GENE
TP53

ALTERATION
C238R

HGVS VARIANT
NM_000546.4:c.712T>C (p.C238R)

VARIANT CHROMOSOMAL POSITION
chr17:7577569

VARIANT ALLELE FREQUENCY (% VAF)
91.0%

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[128-131] or p53 gene therapy such as SGT53[132-137]. 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[138]. Phase 2 studies of adavosertib in combination with chemotherapy reported ORRs of 32% (30/94) and 41% (12/29) for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[139-140]. For patients with platinum-sensitive TP53-mutated ovarian cancer, the combination of adavosertib with paclitaxel and carboplatin significantly increased PFS compared with paclitaxel and carboplatin alone (9.9 vs. 8.0 months)[141]. 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[142]. 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[143]. 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[144]. 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[137]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[145]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[146].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in up to 75% of colorectal cancer cases[23,147-153]. A study reported p53 expression in 49% of analyzed colorectal cancer cases[154]. TP53 mutation has not been consistently demonstrated to be a significant independent prognostic marker in the context of CRC[147,155].

FINDING SUMMARY

TP53 encodes the tumor suppressor p53, a transcription factor that responds to cellular stresses such as DNA damage or oncogene activation by inducing cell cycle arrest and apoptosis[156]. Alterations such as seen here may disrupt TP53 function or expression[157-161]. Functional loss of p53 is common in aggressive advanced cancers[156].

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 2024)[123]. 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[162-164], including sarcomas[165-166]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[167] to 1:20,000[166]. 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[168]. 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[169-174]. 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[169-170]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[175]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[173,176-177]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

Cetuximab

Assay findings association

KRAS
wildtype

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is available in the EU to treat EGFR-expressing RAS wild-type metastatic colorectal cancer (CRC) as monotherapy or combined with chemotherapy. Cetuximab is also available to treat advanced head and neck squamous cell carcinoma (HNSCC) in combination with other therapies. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including cetuximab, have been shown to have significant clinical activity for patients with CRC[78-81,178-179] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of cetuximab in metastatic CRC (NCCN Colon Cancer Guidelines, v1.2024, NCCN Rectal Cancer Guidelines, v1.2024).

SUPPORTING DATA

Cetuximab has been shown to improve OS, PFS, and response rate for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFIRI, FOLFOX4, or irinotecan[78-79,178-180] and as monotherapy for chemotherapy-refractory patients[81,181] . The Phase 3 study STRATEGIC-1 reported a similar duration of disease control (DDC) for patients with unresectable metastatic CRC (mCRC) and KRAS-, NRAS-, and BRAF-wildtype status treated with mFOLFOX-bevacizumab alternated with a cetuximab regimen in first or second line, respectively (overall DDC 22.5 vs. 23.5 months); in addition, the study reported similar OS (37.8 vs. 34.4 months) and higher numerical ORR for patients treated with cetuximab in the first line followed by mFOLFOX-bevacizumab compared with those receiving EGFR-directed antibodies in the second or third line[182]. A prospective study of cetuximab monotherapy for patients with KRAS-, NRAS-, and BRAF-wildtype mCRC reported 11% (2/19) PRs and 58% (11/19) SDs[183]. The Phase 2 AVETUX trial of cetuximab combined with avelumab and mFOLFOX6 for patients with RAS- and BRAF-wildtype mCRC resulted in an ORR of 81% (4 CR and 27 PRs, n=37) and a DCR of 89%[184]. A study of cetuximab in combination with mFOLFOX6 in the second line for patients with RAS-, NRAS-, and BRAF-wildtype mCRC reported a DCR of 83% (30/36; 24 PR) and median OS and PFS of 32.4 months and 11.1 months, respectively[185]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[186]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[187].

Panitumumab

Assay findings association

KRAS
wildtype

NRAS
wildtype

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is available in the EU to treat patients with RAS wild-type, metastatic colorectal cancer (CRC) combined with chemotherapy as first- or second-line therapy, or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Therapies targeting EGFR, including panitumumab, have been shown to have significant clinical activity for patients with CRC[82,186,188] ; wild-type KRAS and NRAS are predictive biomarkers for the efficacy of panitumumab in metastatic CRC (NCCN Colon Cancer Guidelines v1.2024)(NCCN Rectal Cancers Guidelines, v1.2024).

SUPPORTING DATA

Panitumumab has been shown to improve OS, PFS, and ORR for patients with KRAS-wildtype colorectal cancer (CRC), both in combination with FOLFOX4, FOLFIRI, irinotecan, or best supportive care[82,189-192] , and as monotherapy for chemotherapy-refractory patients[151,186,188] . The Phase 3 PARADIGM trial comparing panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 as first-line treatment for patients with RAS-wildtype left-sided metastatic CRC demonstrated that treatment with panitumumab significantly improved median OS (mOS; 36.2 months vs. 31.3 months, HR=0.84) compared with bevacizumab[193]. A Phase 2 trial reported that, for patients with unresectable RAS-wildtype colorectal adenocarcinoma treated with panitumumab plus FOLFOX4, maintenance with a combination of panitumumab plus fluorouracil and leucovorin was superior to panitumumab monotherapy (10-month PFS OF 59% vs. 49%)[194]. In the Phase 3 ASPECCT study, panitumumab was found to be non-inferior to cetuximab with respect to median OS (10.4 vs. 10.0 months, HR=0.97) for patients with previously treated KRAS exon 2 wildtype metastatic colorectal cancer; median PFS was also similar between the two treatment groups (4.4 vs. 4.1 months, HR=1.00)[186]. In a similar patient population, a Phase 2 study of combination panitumumab and irinotecan versus combination cetuximab and irinotecan also demonstrated non-inferiority with respect to median PFS (5.4 vs. 4.3 months, HR = 0.64) and median OS (14.9 vs. 11.5 months, HR=0.66)[187].

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 listed in this report may not be complete and exhaustive and the therapeutic agents are not ranked in order of potential or predicted efficacy for this patient or in order of level of evidence for this patient's tumor type.

NOTE Clinical trials are ordered by gene and prioritized in the following descending order: Pediatric trial qualification → Geographical proximity → Trial phase → Trial verification within last 2 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. The clinical trials listed in this report may not be complete and exhaustive or may include trials for which the patient does not meet the clinical trial enrollment criteria. For additional information about listed clinical trials or to conduct a search for additional trials, please see clinicaltrials.gov or local registries in your region.

GENE
APC

ALTERATION
R805*, E1494fs*19

RATIONALE
Based on preclinical and limited clinical data, APC inactivation may be associated with sensitivity to CBP/beta-catenin interaction inhibitors.

NCT05091346

PHASE 1/2

A Study of E7386 in Combination With Pembrolizumab in Previously Treated Participants With Selected Solid Tumors

TARGETS
CBP, Beta-catenin, PD-1

LOCATIONS: London (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom), Pamplona (Spain), Barcelona (Spain), Madrid (Spain), Valencia (Spain), Badajoz (Spain), Malaga (Spain), New York

NCT03264664

PHASE 1

Study of E7386 in Participants With Selected Advanced Neoplasms

TARGETS
CBP, Beta-catenin

LOCATIONS: London (United Kingdom), Manchester (United Kingdom), Glasgow (United Kingdom), Minnesota, Florida, Arizona, California

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: Lille (France), Paris (France), Pessac (France), Lyon (France), New York, Tennessee, Florida, Oklahoma, Colorado, Texas

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

ARID1A
NM_006015.4: c.4620C>A
(p.N1540K)
chr1:27101338
6.2% VAF

ASXL1
amplification

AURKA
amplification

BCL2L1
amplification

BRD4
NM_058243.2: c.3035C>T
(p.P1012L)
chr19:15353845
53.8% VAF

CSF1R
NM_005211.3: c.2797G>A
(p.G933S)
chr5:149433754
68.4% VAF

CTNNA1
NM_001903.2: c.770A>G
(p.N257S)
chr5:138160400
34.6% VAF

DDR1
NM_001954.4: c.53G>T
(p.G18V)
chr6:30856559
48.4% VAF

GNAS
amplification

KDR
NM_002253.2: c.1379G>T
(p.W460L)
chr4:55973937
36.0% VAF

KMT2D (MLL2)
NM_003482.4: c.8774C>T
(p.A2925V)
chr12:49432365
51.1% VAF

MAP2K1 (MEK1)
NM_002755.3: c.1123C>A
(p.L375I)
chr15:66782894
95.2% VAF

MYCN
NM_005378.4: c.614T>C
(p.V205A)
chr2:16082800
37.1% VAF

NBN
amplification

PDCD1LG2 (PD-L2)
NM_025239.3: c.233A>C
(p.E78A)
chr9:5534922
23.7% VAF

SMO
NM_005631.4: c.1492C>G
(p.L498V)
chr7:128850229
48.0% VAF

SRC
amplification

TSC1
NM_000368.4: c.250G>A
(p.A84T)
chr9:135801087
59.4% VAF

ZNF217
amplification

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

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

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*ALOX12B*	*AMER1 (FAM123B or WTX)*	
APC	*AR*	*ARAF*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*
AURKA	*AURKB*	*AXIN1*	*AXL*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*
BCL6	*BCOR*	*BCORL1*	*BRAF*	*BRCA1*	*BRCA2*	*BRD4*	*BRIP1*	*BTG1*
BTG2	*BTK*	*CALR*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*	*CCND2*
CCND3	*CCNE1*	*CD22*	*CD274 (PD-L1)*	*CD70*	*CD79A*	*CD79B*	*CDC73*	*CDH1*
CDK12	*CDK4*	*CDK6*	*CDK8*	*CDKN1A*	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*
CEBPA	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*	*CRKL*	*CSF1R*	*CSF3R*	*CTCF*
CTNNA1	*CTNNB1*	*CUL3*	*CUL4A*	*CXCR4*	*CYP17A1*	*DAXX*	*DDR1*	*DDR2*
DIS3	*DNMT3A*	*DOT1L*	*EED*	*EGFR*	*EMSY (C11orf30)*	*EP300*	*EPHA3*	*EPHB1*
EPHB4	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC4*	*ERG*	*ERRFI1*	*ESR1*	*EZH2*
FANCA	*FANCC*	*FANCG*	*FANCL*	*FAS*	*FBXW7*	*FGF10*	*FGF12*	*FGF14*
FGF19	*FGF23*	*FGF3*	*FGF4*	*FGF6*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*
FH	*FLCN*	*FLT1*	*FLT3*	*FOXL2*	*FUBP1*	*GABRA6*	*GATA3*	*GATA4*
GATA6	*GID4 (C17orf39)*	*GNA11*	*GNA13*	*GNAQ*	*GNAS*	*GRM3*	*GSK3B*	*H3-3A (H3F3A)*
HDAC1	*HGF*	*HNF1A*	*HRAS*	*HSD3B1*	*ID3*	*IDH1*	*IDH2*	*IGF1R*
IKBKE	*IKZF1*	*INPP4B*	*IRF2*	*IRF4*	*IRS2*	*JAK1*	*JAK2*	*JAK3*
JUN	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KEL*	*KIT*	*KLHL6*
KMT2A (MLL)	*KMT2D (MLL2)*	*KRAS*	*LTK*	*LYN*	*MAF*	*MAP2K1 (MEK1)*	*MAP2K2 (MEK2)*	*MAP2K4*
MAP3K1	*MAP3K13*	*MAPK1*	*MCL1*	*MDM2*	*MDM4*	*MED12*	*MEF2B*	*MEN1*
MERTK	*MET*	*MITF*	*MKNK1*	*MLH1*	*MPL*	*MRE11 (MRE11A)*	*MSH2*	*MSH3*
MSH6	*MST1R*	*MTAP*	*MTOR*	*MUTYH*	*MYC*	*MYCL (MYCL1)*	*MYCN*	*MYD88*
NBN	*NF1*	*NF2*	*NFE2L2*	*NFKBIA*	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*
NPM1	*NRAS*	*NSD2 (WHSC1 or MMSET)*		*NSD3 (WHSC1L1)*	*NT5C2*	*NTRK1*	*NTRK2*	*NTRK3*
P2RY8	*PALB2*	*PARP1*	*PARP2*	*PARP3*	*PAX5*	*PBRM1*	*PDCD1 (PD-1)*	*PDCD1LG2 (PD-L2)*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3C2B*	*PIK3C2G*	*PIK3CA*	*PIK3CB*	*PIK3R1*	*PIM1*
PMS2	*POLD1*	*POLE*	*PPARG*	*PPP2R1A*	*PPP2R2A*	*PRDM1*	*PRKAR1A*	*PRKCI*
PRKN (PARK2)	*PTCH1*	*PTEN*	*PTPN11*	*PTPRO*	*QKI*	*RAC1*	*RAD21*	*RAD51*
RAD51B	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*	*RARA*	*RB1*	*RBM10*
REL	*RET*	*RICTOR*	*RNF43*	*ROS1*	*RPTOR*	*SDHA*	*SDHB*	*SDHC*
SDHD	*SETD2*	*SF3B1*	*SGK1*	*SMAD2*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*
SNCAIP	*SOCS1*	*SOX2*	*SOX9*	*SPEN*	*SPOP*	*SRC*	*STAG2*	*STAT3*
STK11	*SUFU*	*SYK*	*TBX3*	*TEK*	*TENT5C (FAM46C)*		*TET2*	*TGFBR2*
TIPARP	*TNFAIP3*	*TNFRSF14*	*TP53*	*TSC1*	*TSC2*	*TYRO3*	*U2AF1*	*VEGFA*
VHL	*WT1*	*XPO1*	*XRCC2*	*ZNF217*	*ZNF703*			

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER GENOMIC SIGNATURES

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

FoundationOne CDx fulfills the requirements of the European Directive 98/79 EC for in vitro diagnostic medical devices and is registered as a CE-IVD product by Foundation Medicine's EU Authorized Representative, Qarad b.v.b.a, Cipalstraat 3, 2440 Geel, Belgium. Foundation Medicine GmbH is accredited by DAkkS according to DIN EN ISO 15189:2014. The accreditation only applies to the scope of accreditation listed in certificate D-ML-21105-01-00. CE

ABOUT FOUNDATIONONE CDX

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

Please refer to technical information for performance specification details: 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 PRINCIPLE

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

Using an Illumina® Sequencing platform (HiSeq 4000 or NovaSeq 6000), hybrid capture–selected libraries will be sequenced to high uniform depth (targeting >500X median coverage with >99% of exons at coverage >100X). Sequence data will be processed using a customized analysis pipeline designed to accurately detect all classes of genomic alterations, including base substitutions, indels, focal copy number amplifications, homozygous gene deletions, and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including 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: The association of a therapy with a genomic alteration or signature does not necessarily indicate pharmacologic effectiveness (or lack thereof); no association of a therapy with a genomic alteration or signature does not necessarily indicate lack of pharmacologic effectiveness (or effectiveness).

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Genomic signatures and gene alterations detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each genomic signature or gene alteration. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Limitations

1. In the fraction-based MSI algorithm, a tumor specimen will be categorized as MSI-H, MSS, or MS-Equivocal according to the fraction of microsatellite loci determined to be altered or unstable (i.e., the fraction unstable loci score). In the F1CDx assay, MSI is evaluated based on a genome-wide analysis across >2000 microsatellite loci. For a given microsatellite locus, non-somatic alleles are discarded, and the microsatellite is categorized as unstable if remaining alleles differ from the reference

genome. The final fraction unstable loci score is calculated as the number of unstable microsatellite loci divided by the number of evaluable microsatellite loci. The MSI-H and MSS cut-off thresholds were determined by analytical concordance to a PCR comparator assay using a pan-tumor FFPE tissue sample set. Patients with results categorized as "MS-Stable" with median exon coverage <300X, "MS-Equivocal," or "Cannot Be Determined" should receive confirmatory testing using a validated orthogonal (alternative) method.

2. TMB by F1CDx is determined by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater (after filtering) and the total number is reported as mutations per megabase (mut/Mb) unit. Observed TMB is dependent on characteristics of the specific tumor focus tested for a patient (e.g., primary vs. metastatic, tumor content) and the testing platform used for the detection; therefore, observed TMB results may vary between different specimens for the same patient and between detection methodologies employed on the same sample. The TMB calculation may differ from TMB calculations used by other assays depending on variables such as the amount of genome interrogated, percentage of tumor, assay limit of detection (LoD), filtering of alterations included in the score, and the read depth and other bioinformatic test specifications. Refer to the SSED for a detailed description of these variables in FMI's TMB calculation https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019B.pdf. The clinical validity of TMB defined by this panel has been established for TMB as a qualitative output for a cut-off of 10 mutations per megabase but has not been established for TMB as a quantitative score.
3. Homologous Recombination status may be reported for epithelial ovarian, peritoneal, or Fallopian tube carcinomas (Coleman et al., 2017; 28916367). Samples with deleterious *BRCA1/2* alteration and/or Loss of Heterozygosity (LOH) score ≥ 16% will be reported as "HRD Positive" and samples with absence of these findings will be reported as "HRD Not Detected," agnostic of potential secondary *BRCA1/2* reversion alterations. Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be classified as deleterious and, in the absence of an elevated LOH profile, samples with such mutations may be classified as "HRD Not Detected." A result of "HRD Not Detected" does not rule out the presence of a *BRCA1/2* alteration or an elevated LOH profile outside the assay performance characteristic limitations.
4. 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.
5. 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.
6. 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.
7. Reflex testing to an alternative FDA approved companion diagnostic should be performed for patients who have an *ERBB2* amplification result detected with copy number equal to 4 (baseline ploidy of tumor +2) for confirmatory testing. While this result is considered negative by FoundationOne®CDx (F1CDx), in a clinical concordance study with an FDA approved FISH test, 70% (7 out of 10 samples) were positive, and 30% (3 out 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. HER2 overexpression occurs in 18-20% of breast cancers (Owens et al. 2004 [PMID: 15140287]; Salmon et al. 1987 [PMID: 3798106]; Yaziji et al. 2004 [PMID: 15113815]). Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

The variants indicated for consideration of follow-up germline testing are 1) limited to reportable short variants with a protein effect listed in the ClinVar genomic database (Landrum et al., 2018; 29165669) as Pathogenic, Pathogenic/Likely Pathogenic, or Likely Pathogenic (by an expert panel or multiple submitters), 2) associated with hereditary cancer-predisposing disorder(s), 3) detected at an allele frequency of >10%, and 4) in select genes reported by the ESMO Precision Medicine Working Group (Mandelker et al., 2019; 31050713) to have a greater than 10% probability of germline origin if identified during tumor sequencing. The selected genes are *ATM, BAP1, BRCA1, BRCA2, BRIP1, CHEK2, FH, FLCN, MLH1, MSH2, MSH6, MUTYH, PALB2, PMS2, POLE, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD,*

TSC2, and *VHL*, and are not inclusive of all cancer susceptibility genes. The content in this report should not substitute for genetic counseling or follow-up germline testing, which is needed to distinguish whether a finding in this patient's tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

SOFTWARE VERSION INFORMATION

MR Suite Version (RG) 7.18.0
MR Reporting Config Version Config 55
Analysis Pipeline Version v3.32.0
Computational Biology Suite Version 6.30.3

The median exon coverage for this sample is 1,108x

1. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
2. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
3. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
4. Overman et al., 2016; ASCO Abstract 3501
5. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
6. Ayers et al., 2016; ASCO-SITC Abstract P60
7. Ciardiello et al., 2018; ESMO Abstract LBA-004
8. Parikh et al., 2021; DOI: 10.1038/s43018-021-00269-7
9. Fukuoka S, et al. J. Clin. Oncol. (2020) pmid: 32343640
10. Kim et al., 2020; DOI: 10.1016/j.annonc.2020.04.073
11. Zhang Y, et al. BMC Gastroenterol (2021) pmid: 34688262
12. Kasi et al., 2024; ASCO GI Abstract 117
13. Sinicrope FA, et al. J. Clin. Oncol. (2013) pmid: 24019539
14. Gavin PG, et al. Clin. Cancer Res. (2012) pmid: 23045248
15. Bertagnolli MM, et al. J. Clin. Oncol. (2009) pmid: 19273709
16. Van Cutsem E, et al. J. Clin. Oncol. (2009) pmid: 19451425
17. Ribic CM, et al. N. Engl. J. Med. (2003) pmid: 12867608
18. Sargent DJ, et al. J. Clin. Oncol. (2010) pmid: 20498393
19. Fallik D, et al. Cancer Res. (2003) pmid: 14522894
20. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
21. Guastadisegni C, et al. Eur. J. Cancer (2010) pmid: 20627535
22. Histopathology (2007) pmid: 17204026
23. Nature (2012) pmid: 22810696
24. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
25. Samowitz WS, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11535541
26. Elsaleh H, et al. Clin Colorectal Cancer (2001) pmid: 12445368
27. Brueckl WM, et al. Anticancer Res. () pmid: 12820457
28. Guidoboni M, et al. Am. J. Pathol. (2001) pmid: 11438476
29. Gryfe R, et al. N. Engl. J. Med. (2000) pmid: 10631274
30. Sinicrope FA, et al. Gastroenterology (2006) pmid: 16952542
31. Laghi L, et al. Dig Dis (2012) pmid: 22722556
32. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
33. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
34. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
35. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
36. Legrand et al., 2018; ASCO Abstract 12000
37. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
38. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
39. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
40. Marabelle et al., 2019; ESMO Abstract 11920
41. Cristescu R, et al. Science (2018) pmid: 30309915
42. Hodi et al., 2019; AACR abstract CT037
43. Lee et al., 2019; ASCO Abstract 641
44. Rizvi et al., 2017; WCLC Abstract 1106
45. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
46. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
47. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
48. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
49. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
50. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
51. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
52. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
53. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
54. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
55. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
56. Schenker et al., 2022; AACR Abstract 7845
57. Fabrizio DA, et al. J Gastrointest Oncol (2018) pmid: 30151257
58. George et al., 2016; ASCO Abstract 3587
59. Nagahashi et al., 2016; ASCO Abstract e15103
60. Stadler ZK, et al. J. Clin. Oncol. (2016) pmid: 27022117
61. Shao C, et al. JAMA Netw Open (2020) pmid: 33119110
62. Schwartz et al., 2018; ASCO Abstract 572
63. Innocenti F, et al. J Clin Oncol (2019) pmid: 30865548
64. Lee DW, et al. Clin Cancer Res (2019) pmid: 31285374
65. Randon G, et al. Eur J Cancer (2022) pmid: 34933155
66. Loree et al., 2021; ASCO GI Abstract 61
67. Chen EX, et al. JAMA Oncol (2020) pmid: 32379280
68. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
69. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
70. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
71. Rizvi NA, et al. Science (2015) pmid: 25765070
72. Johnson BE, et al. Science (2014) pmid: 24336570
73. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
74. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
75. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
76. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
77. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
78. Van Cutsem E, et al. J. Clin. Oncol. (2011) pmid: 21502544
79. Bokemeyer C, et al. Ann. Oncol. (2011) pmid: 21228335
80. Karapetis CS, et al. N. Engl. J. Med. (2008) pmid: 18946061
81. De Roock W, et al. Ann. Oncol. (2008) pmid: 17998284
82. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
83. Douillard JY, et al. N. Engl. J. Med. (2013) pmid: 24024839
84. Amado RG, et al. J. Clin. Oncol. (2008) pmid: 18316791
85. Guo F, et al. Sci Rep (2018) pmid: 29666387
86. Lièvre A, et al. Cancer Res. (2006) pmid: 16618717
87. De Roock W, et al. Lancet Oncol. (2011) pmid: 21163703
88. Chen J, et al. BMC Cancer (2014) pmid: 25367198
89. Li W, et al. BMC Cancer (2015) pmid: 25929517
90. Hu J, et al. Medicine (Baltimore) (2016) pmid: 27977612
91. Zekri J, et al. Genet. Mol. Res. (2017) pmid: 28218784
92. Staudacher JJ, et al. Clin Transl Gastroenterol (2017) pmid: 29048416
93. Wang Y, et al. Virchows Arch. (2018) pmid: 29705968
94. Mármol I, et al. Int J Mol Sci (2017) pmid: 28106826
95. Kwak MS, et al. Medicine (Baltimore) (2017) pmid: 28858102
96. Pylayeva-Gupta Y, et al. Nat. Rev. Cancer (2011) pmid: 21993244
97. Kahn S, et al. Anticancer Res. () pmid: 3310850
98. Pentheroudakis G, et al. BMC Cancer (2013) pmid: 23374602
99. Vaughn CP, et al. Genes Chromosomes Cancer (2011) pmid: 21305640
100. Janku F, et al. Target Oncol (2013) pmid: 23400451
101. De Roock W, et al. Lancet Oncol. (2010) pmid: 20619739
102. Irahara N, et al. Diagn. Mol. Pathol. (2010) pmid: 20736745
103. Schirripa M, et al. Int. J. Cancer (2015) pmid: 24806288
104. Cercek A, et al. Clin. Cancer Res. (2017) pmid: 28446505
105. Zhan T, et al. Oncogene (2017) pmid: 27617575
106. Jung YS, et al. Exp Mol Med (2020) pmid: 32037398
107. Krishnamurthy N, et al. Cancer Treat Rev (2018) pmid: 29169144
108. Kawazoe et al., 2021; ESMO Abstract 473P
109. Yamada K, et al. Cancer Res (2021) pmid: 33408116
110. Kanda Y, et al. Biochem Biophys Res Commun (2022) pmid: 34837838
111. Gounder M, et al. N Engl J Med (2023) pmid: 36884323
112. Kummar S, et al. J Clin Oncol (2017) pmid: 28350521
113. Chan D, et al. Curr Oncol (2021) pmid: 34590610
114. Christie M, et al. Oncogene (2013) pmid: 23085758
115. Quyn AJ, et al. Surgeon (2008) pmid: 19110823
116. Luke JJ, et al. Clin Cancer Res (2019) pmid: 30635339
117. Logan CY, et al. Annu. Rev. Cell Dev. Biol. (2004) pmid: 15473860
118. Eklof Spink K, et al. EMBO J. (2001) pmid: 11707392
119. Liu J, et al. J. Mol. Biol. (2006) pmid: 16753179
120. Dikovskaya D, et al. J. Cell. Sci. (2010) pmid: 20144988
121. Murphy SJ, et al. Dig. Dis. Sci. (2007) pmid: 17410430
122. Aretz S, et al. Hum. Mutat. (2004) pmid: 15459959
123. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
124. Kerr SE, et al. J Mol Diagn (2013) pmid: 23159591
125. Annu Rev Pathol (2011) pmid: 21090969
126. Kastritis E, et al. Int. J. Cancer (2009) pmid: 18844223
127. Half E, et al. Orphanet J Rare Dis (2009) pmid: 19822006
128. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
129. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
130. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
131. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
132. Leung et al., 2021; ASCO Abstract 4139
133. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
134. Xu L, et al. Mol. Med. (2001) pmid: 11713371
135. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
136. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
137. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
138. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
139. Moore et al., 2019; ASCO Abstract 5513
140. Embaby A, et al. Gynecol Oncol (2023) pmid: 37236033
141. Oza et al., 2015; ASCO Abstract 5506
142. Lee J, et al. Cancer Discov (2019) pmid: 31315834
143. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
144. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
145. Gourley et al., 2016; ASCO Abstract 5571
146. Park H, et al. ESMO Open (2022) pmid: 36084396
147. Fong et al., 2022; ASCO GI Abstract 57
148. Goh HS, et al. Cancer Res. (1995) pmid: 7585578
149. Berg M, et al. PLoS ONE (2010) pmid: 21103049
150. Han SW, et al. PLoS ONE (2013) pmid: 23700467
151. Peeters M, et al. Clin. Cancer Res. (2013) pmid: 23325582

152. Malhotra P, et al. Tumour Biol. (2013) pmid: 23526092
153. Di Bartolomeo M, et al. Target Oncol (2014) pmid: 23821376
154. Wangefjord S, et al. Diagn Pathol (2013) pmid: 23337059
155. Russo A, et al. J. Clin. Oncol. (2005) pmid: 16172461
156. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
157. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
158. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
159. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
160. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
161. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
162. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
163. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
164. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
165. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
166. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
167. Lalloo F, et al. Lancet (2003) pmid: 12672316
168. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
169. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
170. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
171. Xie M, et al. Nat. Med. (2014) pmid: 25326804
172. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
173. Severson EA, et al. Blood (2018) pmid: 29678827
174. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
175. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
176. Chabon JJ, et al. Nature (2020) pmid: 32269342
177. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
178. Cunningham D, et al. N. Engl. J. Med. (2004) pmid: 15269313
179. Jonker DJ, et al. N. Engl. J. Med. (2007) pmid: 18003960
180. Papamichael D, et al. Eur J Cancer (2022) pmid: 35033994
181. Karapetis CS, et al. Clin. Cancer Res. (2014) pmid: 24218517
182. Chibaudel et al., 2022; ASCO Abstract 3504
183. Moiseyenko VM, et al. Clin Drug Investig (2018) pmid: 29470838
184. Stein A, et al. J Immunother Cancer (2021) pmid: 34315821
185. Kang S, et al. J Cancer Res Clin Oncol (2023) pmid: 37031435
186. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
187. Sakai D, et al. Eur J Cancer (2020) pmid: 32526634
188. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
189. Peeters M, et al. Clin. Cancer Res. (2015) pmid: 26341920
190. Watanabe J, et al. Int J Cancer (2022) pmid: 35723084
191. Kim TW, et al. Clin Colorectal Cancer (2018) pmid: 29703606
192. Shitara K, et al. Cancer Sci (2016) pmid: 27712015
193. Watanabe J, et al. JAMA (2023) pmid: 37071094
194. Pietrantonio F, et al. JAMA Oncol (2019) pmid: 31268481