FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Chu, Li Li	Skin melanoma	14 Jun 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1645065-01

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 Skin melanoma
NAME Chu, Li Li
DATE OF BIRTH 08 May 1968
SEX Female
MEDICAL RECORD # 21193099

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

SPECIMEN
SPECIMEN SITE Lymph Node
SPECIMEN ID S112-23173 A (PF23073)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 19 May 2023
SPECIMEN RECEIVED 05 June 2023

Biomarker Findings

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

Genomic Findings

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

BRAF BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion
CTNNB1 Y30_D56del
BCOR rearrangement intron 9
CDKN2A/B p16INK4a loss and p14ARF loss exons 2-3

2 Disease relevant genes with no reportable alterations: ***KIT, NRAS***

Report Highlights

- Targeted therapies with **NCCN categories of evidence** in this tumor type: **Trametinib** (p. 7)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 9)

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

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
BRAF **-** BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion	Trametinib 2A	Cobimetinib Selumetinib
10 Trials see p. 9		
CTNNB1 **-** Y30_D56del	none	none
4 Trials see p. 11		

2A *NCCN category*

Electronically signed by Erik Williams, M.D. | 14 June 2023
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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

GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

BCOR - rearrangement intron 9 ..... p. 5 exons 2-3 ..... p. 6

CDKN2A/B - p16INK4a loss and p14ARF loss

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.

BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI has been detected in 16-32% of cutaneous melanomas in several small datasets, with the majority exhibiting MSI-low[6]. A higher frequency of MSI (low and high) has been reported in metastatic tumors (20-77%) compared to primary tumors (2-30%)[7]. No association between MSI status and clinicopathological features of patients with melanoma was reported in one study[8].

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[9]. 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[9-11]. 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[12-14]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[9,11,13-14].

BIOMARKER

Tumor Mutational Burden

RESULT
2 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[15-17], anti-PD-1 therapies[15-18], and combination nivolumab and ipilimumab[19-24]. In multiple studies of immune checkpoint inhibitors in melanoma, higher TMB has corresponded with clinical benefit from treatment with anti-PD-1 or anti-PD-L1 treatments[18,25-26]. Increased TMB has been associated with longer PFS and OS for patients with melanoma treated with nivolumab, with studies reporting increased benefit for patients with a mutational load above 162 missense mutations per tumor (~equivalency >8 Muts/Mb as measured by this assay)[27]. Increased TMB (~equivalency >10.8 Muts/Mb as measured by this assay) has also been associated with longer PFS and OS for patients with melanoma treated with combination nivolumab and ipilumumab[27]. Improved PFS and OS of patients with melanoma treated with ipilumumab has been observed across all TMB levels[28].

FREQUENCY & PROGNOSIS

A large-scale genomic analysis found that various melanoma subtypes harbored median TMBs between 6.3 and 14.4 Muts/Mb, and 25% to 40% of cases had elevated TMBs of greater than 20 Muts/Mb[29]. Malignant melanoma has been reported to have a high prevalence of somatic mutations compared with other tumor types[30], with desmoplastic melanoma ranking among the highest of melanoma subtypes (median TMB of 62 Muts/Mb)[31]. Higher mutational load has been reported in NF1-mutant melanoma samples compared with BRAF-mutant, NRAS-mutant, or BRAF/NRAS/NF1 wild-type samples[25]. In 1 study, elevated TMB correlated with PD-L1 positive status and increased OS in tissue specimens from patients with Stage 3 melanoma[32]. In another study, elevated tissue TMB (>20 Muts/Mb) was associated with longer PFS and OS in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy as compared with patients with lower TMB[25]. Increased TMB has also been associated with histologic stage and cumulative sun exposure[33].

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[34-35] and cigarette smoke in lung cancer[36-37], treatment with temozolomide-based chemotherapy in glioma[38-39], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[40-44], and microsatellite instability (MSI)[40,43-44]. 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[15-16,18,25,45-48].

GENE
BRAF

ALTERATION
BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Based on limited clinical data in low-grade glioma and sarcoma, patients with tumors harboring RAF fusions may benefit from treatment with type-II RAF inhibitors such as tovorafenib[49]. In a retrospective genomic screen, 3 patients with BRAF fusions in melanomas responded to consecutive CTLA-4 inhibitor ipilimumab and immune checkpoint inhibitor pembrolizumab treatments, with 2 patients reported to be disease free following ipilimumab and pembrolizumab and 1 patient progressing on ipilimumab and then responding on pembrolizumab[50]. The MEK inhibitor trametinib has also been reported to benefit patients with BRAF fusions in melanomas in case reports and basket trials[51-53]. Individual case reports have also observed benefit for patients with the pan-RAF inhibitor sorafenib[54-56]. Second-generation BRAF inhibitors are in development; 1 patient with melanoma and a BRAF fusion treated with PLX8394 achieved a CR, which was the best overall response in a basket trial otherwise consisting of BRAF exon 15 missense mutations[57]. Targeting extracellular signal-regulated kinase (ERK) downstream of BRAF with ulixertinib resulted in 1 SD for the 1 patient with a BRAF fusion in another basket trial[58]. Single-agent BRAF V600-targeting treatments such as vemurafenib are not predicted to confer benefit in melanomas with BRAF fusions in the absence of BRAF V600 mutation; a report showed no tumor response for a patient with a BRAF fusion[59], although a combination of dabrafenib and trametinib resulted in a PR for 1 patient with a co-occurring BRAF V600 mutation[60]. Retrospective analysis of patients with melanoma treated with first-line nivolumab plus ipilimumab showed significantly improved survival for those with BRAF-mutated disease (9.9 months median PFS [mPFS] and median OS [mOS] not reached) relative to those with either NRAS-mutated disease (4.8 months mPFS and 14.2 months mOS) or disease lacking BRAF and NRAS mutations (5.3 months mPFS and 16.1 months mOS)[61].

FREQUENCY & PROGNOSIS

BRAF fusions have been observed in 5% of spitzoid neoplasms[62] and in 1-3% of melanomas[51,63]. A systematic review of 100 BRAF fusion-positive melanocytic tumor cases in the literature described BRAF fusions to be enriched for patients assigned female at birth, for young patients (median age of 33 years), and in tumors with spitzoid histopathologic features[64]; 42 different gene fusion partners were identified, with 55% of the partner genes having known dimerization domains, and AGK and AKAP9 being the most common recurrent partner genes[64]. BRAF rearrangement, leading to loss of the autoinhibitory region, has also been observed in 2 cases of large congenital melanocytic nevi[65]. BRAF mutations have been reported in 37-66% of melanoma cases[66-69], most frequently in cutaneous melanoma (41-51%)[69-70], melanoma of unknown primary (52%)[71] and conjunctival melanoma (14-29%)[72-73]. There are conflicting reports regarding the prognostic significance of BRAF mutation in the context of melanoma[71,74-76]. In one study of non-acral cutaneous melanoma, BRAF non-V600E mutation associated with some, but not other, clinicopathological features but did not impact OS since Stage 4 diagnosis, including OS after initiation of frontline ipilimumab treatment[77].

FINDING SUMMARY

BRAF encodes a member of the RAF family of protein kinases, which includes ARAF, BRAF, and CRAF. These kinases function downstream of RAS as part of the MAPK (RAF-MEK-ERK) signaling cascade that facilitates cell proliferation, survival and transformation[78-79]. BRAF mutations have been reported in up to 20% of all cancers, with the majority of mutations occurring at the V600 position[66,80]. Expression of the BRAF kinase domain without the N-terminal auto-inhibitory domain, whether with or without a fusion partner, is a BRAF class 2 subtype and has been shown to be constitutively active and to drive hyperactivation of the MAPK pathway, exhibiting transforming activity[55,81-92] in a manner sensitive to MEK inhibitors[91,93-97], ERK inhibitors[97], the pan-RAF inhibitor sorafenib[55,92], and second-generation BRAF inhibitors PLX8394 and PLX7904[98-99]. Some patients with BRAF fusions have been reported to benefit from MEK inhibitors[51-52,93,100-102] as well as pan-RAF inhibitor sorafenib[54-55,103-104]. Rearrangements, such as SND1-BRAF fusion and CUL1-BRAF fusion observed here, are predicted to be activating and oncogenic. Rearrangements such as observed here, those that are detected as a reciprocal fusion, are not clearly in frame, or may lack a fusion partner, may be indicative of an activating rearrangement event such as a fusion or an expression of the BRAF kinase domain without the N-terminal auto-inhibitory domain; however, it is unclear whether such rearrangements would lead to an oncogenic BRAF variant. Rearrangements, such as observed here, detected as a deletion of the kinase domain or a duplication of a non-kinase portion of the protein may lead to the production of an oncogenic product such as a fusion or expression of the kinase domain lacking the N-terminal autoinhibitory region; however, it is unclear whether such events would lead to a production of an oncogenic variant.

GENE
CTNNB1

ALTERATION
Y30_D56del

HGVS VARIANT
NM_001904.3:c.88_168del (p.Y30_D56del)

VARIANT CHROMOSOMAL POSITION
chr3:41266089-41266170

VARIANT ALLELE FREQUENCY (% VAF)
24.3%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Mutation or activation of CTNNB1 signaling has been shown to increase mTOR signaling, promote tumorigenesis, and respond to mTOR inhibition in preclinical studies[105-107]. Small studies have reported clinical benefit following treatment of everolimus combined with other targeted agents for patients with CTNNB1-mutated hepatocellular carcinoma[108-109] or endometrial carcinoma[110]. In preclinical studies, CTNNB1 activating mutations have been shown to increase expression of WNT pathway member DKK1, which may promote tumor cell proliferation and immune evasion[111-113]. A Phase 1 trial of DKK1-targeting antibody DKN-01 in combination with paclitaxel in esophageal cancer reported a 50% (2/4) PR rate and 25% (1/4) SD rate in patients with CTNNB1 activating mutations, compared with 24% (10/41) PR and 37% (15/41) SD in unselected patients[114]. Multiple preclinical studies in cancer models harboring CTNNB1 mutation or beta-catenin pathway activation have reported activation of the NOTCH pathway and sensitivity to pharmacologic inhibition of NOTCH signaling by gamma-secretase inhibitors[115-118]. Clinical trials of gamma-secretase inhibitor nirogacestat have shown high response rates in patients with desmoid tumors, which are driven by activating CTNNB1 mutations in the majority of cases[119], suggesting CTNNB1-mutated tumors may be sensitive to gamma-secretase inhibitors. Although WNT pathway inhibitors have been explored preclinically in CTNNB1-mutated cells, clinical data supporting this therapeutic approach are lacking[106,120-122]. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

FREQUENCY & PROGNOSIS

CTNNB1 mutations have been reported in 0-5% of skin melanomas[67-68,123]. Beta-catenin activity has been found to decrease migration of melanoma cells, yet also paradoxically increase melanoma metastasis to the lungs[124-125]. Loss of beta-catenin, along with a panel of other markers, was found to be a negative prognostic factor in early-stage melanoma[126].

FINDING SUMMARY

CTNNB1 encodes beta-catenin, a key downstream component of the WNT signaling pathway. Beta-catenin interacts with cadherin to regulate cell-cell adhesion; as a component of the WNT pathway, it also plays a role in development, cell proliferation, and cell differentiation[127]. CTNNB1 exon 3 mutations are activating in that they lead to increased beta-catenin protein stability and activation of the WNT pathway[128-146]. Although CTNNB1 exon 3 alterations such as seen here have not been fully characterized, they have been associated with sensitivity to targeted therapies or have shown cancer association, which may indicate biological relevance[147-148].

GENE
BCOR

ALTERATION
rearrangement intron 9

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address BCOR alterations.

FREQUENCY & PROGNOSIS

BCOR alteration (mutation or homozygous deletion) has been reported in 5.4% of rhabdomyosarcoma cases, with BCOR alterations occurring more frequently in PAX fusion-negative tumors (7%) than PAX fusion-positive (1.9%) tumors[149]; BCOR mutation has also been reported in 3.2% (3/92) of medulloblastoma cases[150]. In the context of hematologic disease, BCOR mutation has also been reported in 4% of aplastic anemia cases[151], 4.2% of myelodysplastic syndrome (MDS) cases[152], 7.2% of chronic myelomonocytic leukemia cases[152], and 3.8% of normal karyotype acute myeloid leukemia (AML) cases[153]. Published data investigating the prognostic implications of BCOR mutations or inactivating alterations in solid tumors are generally limited (PubMed, Jun 2023).

FINDING SUMMARY

BCOR encodes a transcriptional corepressor that interacts with BCL6 but not with related POZ domain-containing proteins[154]. BCOR activity is required for normal development; de novo germline mutations in BCOR have been linked to syndromic microphthalmia-2 and oculofaciocardiodental syndrome[155]. BCOR inactivation has been reported in various malignancies, whereas BCOR fusions and internal tandem duplications (ITDs) are characteristic of specific tumor types[156-165].

GENE
CDKN2A/B

ALTERATION
p16INK4a loss and p14ARF loss exons 2-3

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as abemaciclib, ribociclib, and palbociclib[166-169]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[170] and palbociclib treatment[171-172]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[173-179]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[180-181], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

Homozygous deletion of CDKN2A and/or CDKN2B has been reported in 14-29% of melanoma cases (cBioPortal, Oct 2022)[182-186]. Concomitant loss of p16INK4a and p14ARF in melanoma is common, although loss of activity of either may also occur as a result of transcript-specific mutations or hypermethylation[187-193]. Various correlations between CDKN2A alterations and tumor histology or patient prognosis in melanoma have been reported in the literature, with some studies reporting CDKN2A deletion to be associated with adverse prognosis and other studies reporting no association between CDKN2A deletion and prognosis[184-185,194-195]. Studies suggest that deletion of CDKN2A is an early event in melanoma tumorigenesis, and loss of p16INK4a has been associated with increased DNA damage in human benign melanocytic tumors and has been suggested to contribute to tumorigenesis by promoting the proliferation of cells with genetic damage[196-197]. CDKN2A alterations affecting p16INK4a, p14ARF, or both have been strongly associated (up to a 76% risk) with familial melanoma[198-208].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[209-210]. Both p15INK4b and p16INK4a bind to and inhibit CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor; loss or inactivation of either p15INK4b or p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control[211-212]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[213-214]. One or more alterations observed here are predicted to result in p16INK4a loss of function[215-236]. One or more alterations seen here are predicted to result in p14ARF loss of function[219,236-239].

POTENTIAL GERMLINE IMPLICATIONS

Germline CDKN2A mutation is associated with melanoma-pancreatic cancer syndrome, a condition marked by increased risk of developing malignant melanoma and/or pancreatic cancer[240]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[241-242]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[243-245]. CDKN2A alteration has also been implicated in familial melanoma-astrocytoma syndrome, an extremely rare tumor association characterized by dual predisposition to melanoma and nervous system tumors[246-248]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

Trametinib

Assay findings association

BRAF
BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion

AREAS OF THERAPEUTIC USE

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

GENE ASSOCIATION

Activating BRAF fusions may predict sensitivity to MEK inhibitors such as trametinib. Clinical responses to trametinib have been achieved by patients with BRAF-fusion-positive melanoma[51-53,249] , low-grade glioma[250-252] , histiocytosis[253-254] , and prostate cancer[255].

SUPPORTING DATA

Individual patients with BRAF-fusion-positive melanoma have experienced either a PR or clinical benefit from single-agent trametinib[51-53,249] . As a monotherapy for patients with BRAF V600E/K-mutated metastatic melanoma, trametinib improved PFS (4.9 vs. 1.5 months, HR=0.54) and median OS (15.6 vs. 11.3 months, HR=0.84) compared with patients treated with chemotherapy[256]. In a Phase 1 study, 10% (4/40) of patients with BRAF-wildtype metastatic melanoma achieved a PR[257]. Whereas frequent adverse events precluded a recommended Phase 2 dose and schedule for the combination of trametinib and everolimus in a Phase 1b trial for solid tumors[258], a retrospective study for heavily pretreated patients with solid tumors reported tolerable regimens of the combination for 23/31 patients, with 16 patients treated >3 months and evaluable patients achieving a median PFS of 6.5 months[259].

Cobimetinib

Assay findings association

BRAF
BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion

AREAS OF THERAPEUTIC USE

Cobimetinib is a MEK inhibitor that is FDA approved to treat patients with histiocytic neoplasms. Please see the drug label for full prescribing information.

GENE ASSOCIATION

On the basis of clinical evidence, BRAF activating mutations may predict sensitivity to MEK inhibitors such as cobimetinib[260-263] .

SUPPORTING DATA

A Phase 1 study of cobimetinib monotherapy in solid tumors reported 1% (1/97) CR and 6% (6/97) PR, all of which were achieved by patients with melanoma (6 with BRAF V600E)[264]. Patients with metastatic melanoma treated with cobimetinib combined with the RAF inhibitor belvarafenib experienced PRs for those with BRAF V600 mutations (33% [3/9]) and non-V600 mutations (50% [3/6])[265]. In the Phase 3 IMspire170 study, the combination of atezolizumab and cobimetinib did not improve median PFS (5.5 vs. 5.7 months), ORR (26% vs. 32%) or 6-month OS (88% vs. 87%) compared with pembrolizumab for patients with previously untreated BRAF V600 wildtype melanoma[266]. Similarly, the Phase 2 TRICOTEL trial for patients with BRAF wildtype melanoma with central nervous system metastases reported an intracranial ORR of 27% following combination treatment of atezolizumab and cobimetinib[267]. A Phase 1b study evaluating the combination of atezolizumab and cobimetinib for the treatment of patients with solid tumors reported an ORR of 41% (9/22) in patients with melanoma, regardless of BRAF status; the 12-month PFS and OS rates were 50% and 85%, respectively[268].

Selumetinib

Assay findings association

BRAF
BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion

AREAS OF THERAPEUTIC USE

Selumetinib is a MEK inhibitor that is FDA approved to treat pediatric patients with neurofibromatosis type 1 (NF1)-associated plexiform neurofibromas (PNs). Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activating BRAF fusions may predict sensitivity to MEK inhibitors such as selumetinib. Clinical responses to selumetinib have been achieved by patients with BRAF-fusion-positive low-grade glioma[100,102] .

SUPPORTING DATA

In a Phase 2 study for patients with metastatic melanoma, selumetinib monotherapy achieved an ORR of 5.8%; among patients with BRAF mutations, the ORR was 11% (5/45)[269]. In a Phase 2 trial of first-line treatment of BRAF-mutated metastatic melanoma, the addition of selumetinib to dacarbazine increased PFS compared to dacarbazine plus placebo (5.6 vs 3.0 months, HR=0.63) but did not significantly improve OS (13.9 vs 10.5 months, HR 0.93, p=0.39)[270]. In a Phase 2 trial for patients with BRAF wildtype advanced melanoma, the addition of selumetinib to docetaxel did not improve median PFS compared to docetaxel plus placebo (4.2 vs 3.9 months) and was associated with lower OS (9.5 months vs 11.4 months); NRAS mutation was associated with inferior OS (HR=0.78)[271].

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

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

BRAF

ALTERATION

BRAF-DPP6 rearrangement, PRSS37-BRAF fusion, rearrangement intron 8, TRIO-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, PRSS37-BRAF rearrangement, rearrangement intron 8, rearrangement intron 8, rearrangement intron 8, SND1-BRAF fusion, CUL1-BRAF fusion

RATIONALE

BRAF activating alterations may predict sensitivity to inhibitors of BRAF, MEK, or ERK.

NCT04589845

PHASE 2

Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study

TARGETS

TRKB, ALK, TRKC, ROS1, TRKA, RET, PD-L1, AKTs, ERBB2, MDM2, PI3K-alpha, RAFs, NRAS

LOCATIONS: Taipei City (Taiwan), Taoyuan County (Taiwan), Shanghai City (China), Shanghai (China), Shatin (Hong Kong), Hong Kong (Hong Kong), Seoul (Korea, Republic of), Xi'an (China), Tianjin (China), Beijing City (China)

NCT04913285

PHASE 1

A Study to Evaluate KIN-2787 in Subjects With BRAF Mutation Positive Solid Tumors

TARGETS

BRAF, MEK

LOCATIONS: Taipei (Taiwan), Shanghai (China), Bengbu (China), Wuhan (China), Linyi (China), Gyeonggi-do (Korea, Republic of), Cheongju-si (Korea, Republic of), Incheon (Korea, Republic of), Seoul (Korea, Republic of), Beijing (China)

NCT04803318

PHASE 2

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

TARGETS

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

LOCATIONS: Guangzhou (China)

NCT04985604

PHASE 1/2

DAY101 Monotherapy or in Combination With Other Therapies for Patients With Solid Tumors

TARGETS BRAF, MEK

LOCATIONS: Busan (Korea, Republic of), Seoul (Korea, Republic of), Clayton (Australia), Edegem (Belgium), Oregon, Barcelona (Spain), Madrid (Spain), California, Colorado

NCT03284502

PHASE 1

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

TARGETS MEK, RAFs, NRAS

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

NCT05580770

PHASE 1/2

Mirdametinib + BGB-3245 in Advanced Solid Tumors

TARGETS BRAF, MEK

LOCATIONS: Waratah (Australia), Melbourne (Australia), California, Ohio, Massachusetts, Texas, Connecticut, Florida

NCT04551521

PHASE 2

CRAFT: The NCT-PMO-1602 Phase II Trial

TARGETS PD-L1, AKTs, MEK, BRAF, ALK, RET, ERBB2

LOCATIONS: Lübeck (Germany), Würzburg (Germany), Mainz (Germany), Heidelberg (Germany), Tübingen (Germany)

NCT04720976

PHASE 1/2

JAB-3312 Activity in Adult Patients With Advanced Solid Tumors

TARGETS MEK, SHP2, PD-1, EGFR, KRAS

LOCATIONS: Utah, California, Arizona, Minnesota, Illinois, Michigan, Oklahoma, Missouri, Indiana, Connecticut

NCT04375527

PHASE 2

Binimetinib and Nivolumab for the Treatment of Locally Advanced Unresectable or Metastatic BRAF V600 Wildtype Melanoma

TARGETS MEK, PD-1

LOCATIONS: California

NCT02382549

PHASE 1/2

A Clinical Trial to Evaluate a Melanoma Helper Peptide Vaccine Plus Dabrafenib and Trametinib

TARGETS BRAF, MEK

LOCATIONS: Virginia

GENE
CTNNB1

ALTERATION
Y30_D56del

RATIONALE
Based on clinical and preclinical evidence, tumors with activating CTNNB1 alterations may be sensitive to mTOR inhibitors. It is not known whether these therapeutic approaches would be relevant in the context of alterations that have not been fully characterized, as seen here.

NCT04803318

PHASE 2

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

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

LOCATIONS: Guangzhou (China)

NCT05036226

PHASE 1/2

COAST Therapy in Advanced Solid Tumors and Prostate Cancer

TARGETS
DDR2, ABL, SRC, KIT, mTOR

LOCATIONS: South Carolina

NCT03203525

PHASE 1

Combination Chemotherapy and Bevacizumab With the NovoTTF-100L(P) System in Treating Participants With Advanced, Recurrent, or Refractory Hepatic Metastatic Cancer

TARGETS
VEGFA, mTOR

LOCATIONS: Texas

NCT01582191

PHASE 1

A Phase 1 Trial of Vandetanib (a Multi-kinase Inhibitor of EGFR, VEGFR and RET Inhibitor) in Combination With Everolimus (an mTOR Inhibitor) in Advanced Cancer

TARGETS
mTOR, EGFR, SRC, RET, VEGFRs

LOCATIONS: 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.

EZH2
amplification

FANCC
NM_000136.2: c.436_438del
(p.Y146del)
chr9:97934336-97934339

FGFR4
NM_213647.3: c.376G>A
(p.D126N)
chr5:176517766

KMT2D (MLL2)
NM_003482.4: c.7046C>T
(p.P2349L)
chr12:49434507

MSH3
NM_002439.3: c.162_170del
(p.A60_A62del)
chr5:79950696-79950705

MSH6
NM_000179.2: c.3762A>T
(p.E1254D)
chr2:48033458

POLE
NM_006231.2: c.2450G>A
(p.G817D)
chr12:133241906

PRDM1
NM_001198.3: c.239A>T
(p.E80V)
chr6:106536272

RET
NM_020975.4: c.1045G>T
(p.A349S)
chr10:43602001 and
NM_020975.4: c.874G>A
(p.V292M)
chr10:43601830

SDHA
amplification

SMO
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 BIOMARKERS

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

Biomarker and genomic findings detected may be associated with certain entries within the NCCN Drugs & Biologics Compendium® (NCCN Compendium®) (www.nccn.org). The NCCN Categories of Evidence and Consensus indicated reflect the highest possible category for a given therapy in association with each biomarker or genomic finding. Please note, however, that the accuracy and applicability of these NCCN categories within a report may be impacted by the patient's clinical history, additional biomarker information, age, and/or co-occurring alterations. For additional information on the NCCN categories, please refer to the NCCN Compendium®. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 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 of 10 samples) were negative by the FISH test with an average ratio of 2.3. The frequency of *ERBB2* copy number 4 in breast cancer is estimated to be approximately 2%. Multiple references listed in https://www.mycancergenome.org/content/disease/breast-cancer/ERBB2/238/ report the frequency of HER2 overexpression as 20% in breast cancer. Based on the F1CDx HER2 CDx concordance study, approximately 10% of HER2 amplified samples had copy number 4. Thus, total frequency is conservatively estimated to be approximately 2%.

REPORT HIGHLIGHTS

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

tumor sequencing is germline or somatic. Interpretation should be based on clinical context.

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS

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

LEVEL OF EVIDENCE NOT PROVIDED

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

NO GUARANTEE OF CLINICAL BENEFIT

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

NO GUARANTEE OF REIMBURSEMENT

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

TREATMENT DECISIONS ARE RESPONSIBILITY OF PHYSICIAN

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

SELECT ABBREVIATIONS

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

REFERENCE SEQUENCE INFORMATION

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

MR Suite Version (RG) 7.9.0

The median exon coverage for this sample is 760x

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