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 Prostate acinar adenocarcinoma
NAME Wu, Kun-Han
DATE OF BIRTH 04 August 1951
SEX Male
MEDICAL RECORD # 45597873

PHYSICIAN

ORDERING PHYSICIAN Chung, Hsiao-Jen
MEDICAL FACILITY Taipei Veterans General Hospital
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 205872
PATHOLOGIST Not Provided

SPECIMEN

SPECIMEN SITE Liver
SPECIMEN ID S110-24095 A (PF21023)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 19 August 2021
SPECIMEN RECEIVED 01 October 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

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

MYCN amplification
AR amplification
GNAS amplification - equivocal†
IRS2 amplification
RAF1 amplification, E478K
SF3B1 E622D
TP53 splice site 376-1G>C
VHL rearrangement exon 3
ZNF217 amplification

14 Disease relevant genes with no reportable alterations: ***ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***

† See About the Test in appendix for details.

0 Therapies with Clinical Benefit
0 Therapies with Resistance
6 Clinical Trials

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 4 Muts/Mb

GENOMIC FINDINGS

***MYCN* -** amplification

6 Trials *see p. 10*

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
none	none

VARIANTS THAT MAY REPRESENT CLONAL HEMATOPOIESIS (CH)

Genomic findings below may include nontumor somatic alterations, such as CH. The efficacy of targeting such nontumor somatic alterations is unknown. This content should be interpreted based on clinical context. Refer to appendix for additional information on CH.

***SF3B1* -** E622D ..... p. 7

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GENOMIC FINDINGS WITH NO REPORTABLE THERAPEUTIC OR CLINICAL TRIAL OPTIONS

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

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

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

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BIOMARKER

Microsatellite status

RESULT
MS-Stable

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

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

FREQUENCY & PROGNOSIS

MSI has been reported in 3.1-14.6% of prostate cancer samples[6-10]. A study of prostate cancer in hereditary nonpolyposis colorectal cancer (HNPCC) families reported MSI-H in 4-50% of cases[11-13]. For patients with advanced prostate cancer, dMMR/MSI status was associated with shorter median OS compared with patients with proficient MMR (3.8 vs. 7.0 years) by univariate and multivariate analysis (adjusted HR=4.09; P=0.005)[14].

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[15]. 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[15-17]. 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[18-20]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[15,17,19-20].

BIOMARKER

Tumor Mutational Burden

RESULT
4 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[21-23], anti-PD-1 therapies[21-24], and combination nivolumab and ipilimumab[25-30]. In multiple pan-tumor studies, higher TMB has been reported to be associated with increased ORR and OS from treatment with immune checkpoint inhibitors[21-24,31]. Higher TMB was found to be significantly associated with improved OS upon immune checkpoint inhibitor treatment for patients with 9 types of advanced tumors[21]. 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[32] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[22]. However, the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors found significant improvement in ORR for patients with TMB ≥10 Muts/Mb (based on this assay or others) compared to those with TMB <10 Muts/Mb, in a large cohort that included multiple tumor types; similar findings were observed in the KEYNOTE 028 and 012 trials[24,31]. Together, these studies suggest that patients with TMB ≥10 Muts/Mb may derive clinical benefit from PD-1 or PD-L1 inhibitors. The Phase 2 CheckMate 650 trial of nivolumab and ipilimumab treatment for patients with metastatic castration-resistant prostate cancer reported that patients harboring above the median study TMB experienced increased ORR and PSA responses[30].

FREQUENCY & PROGNOSIS

Prostate acinar adenocarcinoma harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 3.4% of cases have high TMB (>20 muts/Mb)[33]. Prostate cancer has been reported to harbor a relatively low TMB among solid tumors[34-35], with approximately 0.5-1.5 (muts/Mb) in localized tumor samples[36-38], and a higher but still low TMB of 2-5 muts/Mb in metastatic, castration-resistant prostate cancer (mCRPC) samples[39-41]. One study reported that 4 of 150 (2.7%) mCRPC cases harbored high TMB (nearly 50 muts/Mb), which was due to defects in mismatch repair genes MLH1 and MSH2 in 3 of the 4 cases[41]. The effects of hypermutation on prognosis and clinical features in prostate cancer have not been extensively investigated (PubMed, Feb 2021).

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[42-43] and cigarette smoke in lung cancer[44-45], treatment with temozolomide-based chemotherapy in glioma[46-47], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[48-52], and microsatellite instability (MSI)[48,51-52]. This sample harbors a TMB level associated with lower rates of clinical benefit from treatment with PD-1- or PD-L1-targeting immune checkpoint inhibitors compared with patients with tumors harboring higher TMB levels, based on several studies in multiple solid tumor types[22-23,31].

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GENE
MYCN

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of extensive preclinical data across multiple cancer types, tumors with MYCN amplification may be sensitive to CDK2 inhibitors[53-57] or inhibitors of BET bromodomain-containing proteins[58-62]. BET inhibitors are under investigation in clinical trials and have shown clinical activity in patients with acute myeloid leukemia, lymphoma, or NUT midline carcinoma[63-65] . Extensive preclinical evidence in models of neuroblastoma also suggests that MYCN amplification may predict sensitivity to inhibitors of Aurora kinase A[66-72], although it should be noted that a Phase 1 study of the Aurora kinase A and B inhibitor AT9283 reported progressive disease (PD) in a patient with neuroblastoma harboring MYCN amplification and 1 mixed response and 1 PD in 2 patients with non-MYCN-amplified neuroblastoma[73]. Further, another Phase 1 study evaluating the Aurora kinase A inhibitor alisertib in patients with neuroblastoma did not report a significant difference between those that were MYCN-amplified and those that were MYCN-non amplified (35.7% vs 16.7%; p=0.61)[74]. Multiple preclinical experiments in models of neuroblastoma have also shown that MYCN amplification or overexpression, in the absence of concurrent mutations in TP53, is associated with sensitivity to MDM2 inhibitors[75-79]. Newer approaches to target MYCN amplification in cancers, including inhibition of N-MYC expression and indirect targeting of N-MYC, are in preclinical development[80-81].

FREQUENCY & PROGNOSIS

MYCN amplification has been reported in up to 4% of prostate adenocarcinoma cases[38,82-84] and in 15-40% of prostate neuroendocrine adenocarcinoma samples[83-85]. MYCN overexpression has been reported to be significantly more frequent in prostate neuroendocrine carcinoma as compared with prostate carcinoma; overexpression of MYCN in benign or prostate cancer cells induced the expression of various neuroendocrine markers[84]. MYCN amplification has been implicated in disease progression in patients with prostate cancer[83-84].

FINDING SUMMARY

MYCN encodes a MYC family protein; MYC gene products are thought to act as oncoproteins by preventing cell differentiation and promoting cell proliferation, in part by altering transcription of many target genes[86-87]. MYCN has been reported to be amplified in cancer[88], and may be biologically relevant in this context[89-90].

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GENE
AR

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Antiandrogens such as apalutamide, bicalutamide, cyproterone, darolutamide, enobosarm, enzalutamide, flutamide, and nilutamide directly target AR, whereas hormone therapies such as the CYP17A1 inhibitor abiraterone and luteinizing hormone-releasing hormone agonists or antagonists modulate androgen production[91-99]. Resistance to androgen deprivation therapy (ADT) commonly occurs in prostate cancer through mechanisms such as increased AR expression, AR activation by tyrosine kinase-dependent signaling, alterations in AR co-activators, expression of alternatively spliced isoforms of AR mRNAs (AR-Vs), and extragonadal synthesis of androgenic compounds[100-104]. AR signaling may promote radioresistance in prostate cancer by transcriptionally upregulating DNA repair genes[105]. There is preclinical evidence that development of resistance to anti-AR therapies, such as abiraterone and enzalutamide, may engender cross-resistance to the taxanes docetaxel and cabazitaxel[106]; however, certain AR-Vs may remain sensitive to taxanes[107-108]. Approaches currently in clinical and preclinical development for prostate cancer include therapies that target AR nuclear translocation and degradation pathways[109-115], combination approaches to suppress androgen biosynthesis[116], and the use of bromodomain and extraterminal (BET) inhibitors that disrupt the interaction between AR and BRD4[117-119]; the latter approach has potential to target AR-Vs[118-120]. The BET inhibitor mivebresib led to an SD rate of 60% (6/10) for patients with genomically unselected prostate cancer who had progressed on multiple standard of care therapies[121]. Galeterone, a multifunctional AR inhibitor, has been evaluated in several Phase 1 and 2 studies and has been found to reduce prostate-specific antigen levels for 49-73% of patients, although clinical trials of this reagent are not recruiting patients[122].

— Potential Resistance —

Extensive clinical data have demonstrated that AR amplification may confer resistance to androgen deprivation therapy[104,123-125] or androgen receptor signaling inhibitors (ARSIs) such as abiraterone and enzalutamide[126-129], although a few studies suggested that AR amplification confers resistance only to enzalutamide but not to abiraterone[130], or its presence does not preclude response to ARSIs[131].

FREQUENCY & PROGNOSIS

Aberrant activation of AR through mutation and amplification of AR has been shown to be fundamental to prostate cancer progression; AR amplification is rare in hormone-naive prostate cancer[123-124,132-134], but has been reported for 13-49% of patients with castration-resistant prostate cancer (CRPC) following progression on androgen-deprivation therapy or AR pathway inhibitors, such as abiraterone or enzalutamide[39,82,123-125,133,135-142]. Some studies have shown that AR amplification was significantly more common for patients who progressed on enzalutamide than for those who progressed on abiraterone or other agents[139,143]. AR copy number gain is associated with increased Gleason score, increased baseline prostate-specific antigen (PSA), more advanced clinical stage, and disease progression[125,128,132], and is significantly associated with worse OS in castration-resistant prostate cancer (CRPC)[128,144-147]. For patients with CRPC treated with enzalutamide or abiraterone, AR copy number gain or amplification has been associated with worse outcomes[139,148-152]; however, AR amplification does not always correlate with poor outcomes on these treatments[131,140]. In the context of chemotherapy, patients with AR-amplified castration-resistant prostate cancer (CRPC) experienced longer OS on docetaxel compared with enzalutamide or abiraterone[147]. In a meta-analysis study, AR gain did not affect OS and PFS for patients treated with first-line docetaxel or second-line or third-line cabazitaxel, but was associated with reduced response in later lines of docetaxel[153]. For patients with poor-prognosis CRPC treated with either cabazitaxel followed by androgen receptor pathway inhibitors (ARPIs) or ARPIs followed by cabazitaxel, AR amplification was significantly associated with shorter time to progression for both ARPIs and cabazitaxel, without significant difference observed between the 2 methods of treatment[144]. AR amplification has also been associated with poor outcomes for patients with metastatic CPRC treated with radioligand therapy 177Lu-PSMA-617[154].

FINDING SUMMARY

AR encodes the androgen receptor, a nuclear receptor that binds to testosterone and dihydroxytestosterone. AR is frequently amplified and overexpressed in castration-resistant prostate cancer (CRPC), also called hormone-refractory prostate cancer[155].

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GENE
GNAS

ALTERATION
amplification - equivocal

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies targeted to GNAS mutation in cancer. However, there is limited data indicating that a patient with appendiceal adenocarcinoma and a GNAS mutation (R201H) benefited from trametinib for 4 months[156]. Additionally, a patient with GNAS-mutated Erdheim-Chester disease exhibited a PR following treatment with single-agent trametinib[157].

FREQUENCY & PROGNOSIS

The highest incidences of GNAS mutations have been reported in intraductal papillary mucinous neoplasms (40-66%)[158-159] and appendiceal mucinous neoplasms (50-72%)[160-161] as well as in tumors affecting the peritoneum (22%), pituitary gland (20%), bone (15%), pancreas (12%), and small intestine (12%)(COSMIC, 2021)[162]. Amplification of GNAS has been reported in ovarian epithelial carcinomas (12-30%)[163-165], colorectal adenocarcinoma (9%)[51], stomach adenocarcinoma (7%)[166], lung adenocarcinoma (6.5%)[167], breast invasive carcinoma (6.5%)[168], pancreatic adenocarcinoma (6%)[169], and sarcomas (5.8%)[170]. GNAS mutations are rare in hematological malignancies generally (COSMIC, 2021)[162,171-172]. Activating GNAS mutations have been identified in gastrointestinal polyps in 75% (3/4) of patients with McCune-Albright syndrome[173]. Amplification of GNAS has been associated with shorter progression-free survival in patients with ovarian cancer[164-165], while activating GNAS mutations have been correlated with tumor progression and poor prognosis in patients with gastric cancer[174].

FINDING SUMMARY

GNAS encodes the alpha subunit of the stimulatory G protein (Gs-alpha)[175]. Gs-alpha is a guanine-nucleotide binding protein (G protein) that is involved in hormonal regulation of adenylate cyclase[175]. GNAS has been reported to be amplified in cancer[88] and may be biologically relevant in this context[89-90]. GNAS alterations that have been shown to result in constitutive activation of adenylyl cyclase and an increase in cellular cAMP concentration[176-181] are predicted to be activating. Mutations at R201 specifically are commonly associated with McCune-Albright syndrome, a disease that can co-occur with various cancers in patients with GNAS activating mutations[182-184].

GENE
IRS2

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies to directly target IRS2 amplification. However, preclinical studies using breast and CRC cell lines suggest that copy number gain and/or high levels of IRS2 may confer sensitivity to IGF1R inhibitors[185-186]. Clinical trials of IGF1R inhibitors are in progress in multiple tumor types.

FREQUENCY & PROGNOSIS

IRS2 copy number gain has been reported most commonly in colorectal cancer (CRC), with a frequency of 8-26% across several datasets[41,186-188]. IRS2 amplification has been observed less frequently in bladder urothelial carcinomas (4.7%)[189], sarcomas (3.9%)[170], stomach adenocarcinomas (3.8%)[166], and hepatocellular carcinomas (1.3%)[190]. Increased IRS2 protein expression has been reported in some tumor types, including 88% (46/53) of malignant peripheral nerve sheath tumors[191]. Several preclinical studies in breast cancer have shown that IRS2 expression is associated with metastatic behavior[192-195]; another study demonstrated that IRS2 protein levels were low in a panel of ductal carcinoma in situ but increased significantly in relation to tumor invasiveness[196]. In CRC, however, no difference was found in the prevalence of IRS2 amplification between primary and metastatic colorectal tumors[186]. Despite this finding, elevated IRS2 has been shown to correlate with CRC disease progression[188].

FINDING SUMMARY

IRS2 encodes the protein insulin receptor substrate 2, which is a cytoplasmic signaling molecule that links insulin receptor activation to downstream effectors, including the PI3K-mTOR pathway[197]. IRS2 amplification has been shown to correlate with increased mRNA expression levels[186,188].

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GENE
RAF1

ALTERATION
amplification, E478K

TRANSCRIPT ID
NM_002880

CODING SEQUENCE EFFECT
1432G>A

VARIANT ALLELE FREQUENCY (% VAF)
15.7%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

RAF1 activating mutations may predict sensitivity to MEK inhibitors. A patient with mixed histiocytosis harboring an activating RAF1 mutation exhibited a CR by PET response criteria to the MEK inhibitor cobimetinib[198]. RAF1 amplification may predict sensitivity to pan-RAF inhibitors. The addition of sorafenib to chemotherapy improved PFS for patients with melanoma and RAF1 copy number gains (HR=0.37, p=0.025) in a retrospective analysis[199]. A retrospective study reported RAF1 expression as a predictor of improved OS (HR=1.84) and tumor-free survival (HR=1.32) for patients with hepatocellular carcinoma treated with adjuvant sorafenib in multivariate analyses[200].

FREQUENCY & PROGNOSIS

RAF1 amplification has been reported in 0.7% of prostate adenocarcinomas analyzed in cBioPortal (Aug 2021)[88,201]. In one study, RAF1 copy number gain was reported in 15% of prostate carcinomas[202]. RAF1 mutations have been reported in 2.0% of prostate carcinoma samples analyzed in COSMIC (Aug 2021)[162]. Polymorphisms in RAF1 have been associated with prostate cancer development[203]. Published data investigating the prognostic implications of RAF1 alterations in prostate cancer are generally limited (PubMed, Mar 2021). One study reported an association between increased RAF1 expression and earlier relapse in androgen-insensitive prostate cancer[204]. In another study, RAF1 fusions were associated with castration-resistance and features of aggressiveness, including high Gleason score[205].

FINDING SUMMARY

RAF1 encodes c-RAF, a member of the RAF family of signaling kinases[206]. These kinases are downstream of RAS and activate the MEK-ERK signaling pathway that promotes cell proliferation and survival[207]. RAF1 has been reported to be amplified in cancer[88] and may be biologically relevant in this context[89-90]. RAF1 alterations that have been characterized as activating, as observed here, are predicted to be oncogenic[208-223].

GENE
SF3B1

ALTERATION
E622D

TRANSCRIPT ID
NM_012433

CODING SEQUENCE EFFECT
1866G>T

VARIANT ALLELE FREQUENCY (% VAF)
15.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical studies suggest that mutations in genes encoding spliceosome components, including SF3B1, may confer sensitivity to spliceosome inhibitors[224-228]. In preclinical models, SF3B1 mutation leads to DNA damage and ATR-CHK1 pathway activation, increasing sensitivity to ATR and CHK1 inhibitors[228]. However, clinical data supporting SF3B1 as biomarkers for the efficacy of these approaches is lacking.

FREQUENCY & PROGNOSIS

In the context of solid tumors, SF3B1 mutation has been reported in adenoid cystic carcinomas of the salivary gland (4%, 1/24)[229] and breast[230] as well as in pancreatic carcinoma[231], glioblastoma, and renal clear cell carcinoma[232]. Mutation of SF3B1 was found to be recurrent in several breast carcinoma subtypes[168,233-234], and in unselected breast cancers, it correlated with ER-positivity and frequent co-occurrence with AKT1 and PIK3CA mutations[234-235]. The hot spot mutation K700E was found in 16% (3/19) of papillary and 6% of breast mucinous carcinomas[235]. In solid tumors, the prognostic implications of SF3B1 alterations are dependent on disease context. In a study of 3282 breast cancer cases, SF3B1 mutation was significantly associated with a poor prognosis for patients with luminal B and progesterone receptor (PR)-negative subtypes of disease[236]. For patients with hepatocellular carcinoma, one study showed that SF3B1 mutation was associated with an advanced stage of disease[237]. However, in one study of primary uveal melanoma, SF3B1 mutation was correlated with improved PFS[238].

FINDING SUMMARY

SF3B1 encodes a subunit of the spliceosome, the complex that is responsible for the splicing of pre-mRNA molecules to create mature messenger RNA[239-242]. SF3B1 mutations predominantly occur in HEAT domains 5-7 at codons 625, 662, 666, and 700[235,243-247], which result in neomorphic activity that upregulates aberrant mRNA splicing[248-251]. The consequences of SF3B1 alterations outside of these sites have not been extensively characterized.

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[232,252-256]. 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[252-253]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[257]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[255,258-259]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
TP53

ALTERATION
splice site 376-1G>C

TRANSCRIPT ID
NM_000546

CODING SEQUENCE EFFECT
376-1G>C

VARIANT ALLELE FREQUENCY (% VAF)
61.6%

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[260-263], or p53 gene therapy and immunotherapeutics such as SGT-53[264-268] and ALT-801[269]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% (17/176) and SDs in 53.4% (94/176) of patients with solid tumors; the response rate was 21.1% (4/19) for patients with TP53 mutations versus 12.1% (4/33) for patients who were TP53 wild-type[270]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 31.9% (30/94, 3 CR) ORR and a 73.4% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[271]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 42.9% (9/21, 1 CR) ORR and a 76.2% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[272]. The combination of adavosertib with paclitaxel and carboplatin for patients with TP53-mutated ovarian cancer also significantly increased PFS compared with paclitaxel and carboplatin alone[273]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24.0% (6/25) ORR with adavosertib combined with paclitaxel[274]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71.4% (5/7) response rate for patients with TP53 alterations[275]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75.0% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[268]. Additionally, the combination of a CHK1 inhibitor and irinotecan reportedly reduced tumor growth and prolonged survival in a TP53-mutated, but not TP53-wild-type, breast cancer xenotransplant mouse model[276]. ATR inhibitor treatment of chronic lymphocytic leukemia (CLL) cells with biallelic inactivation of TP53 suppressed cell viability, promoted DNA damage, and attenuated xenograft growth in preclinical studies[277-278]; however, ATR inhibitors as monotherapy had little effect on these parameters in solid tumor models in other preclinical studies[279-280]. Therefore, it is unclear whether TP53 inactivation predicts sensitivity to ATR inhibition.

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 18-40% of prostate cancers[281-282]. Overexpression of p53, which is indicative of TP53 dysregulation, has been reported to be significantly more common in late-stage and hormone-refractory prostate cancers and has been found to be associated with prostate-specific antigen (PSA) recurrence in low- and intermediate-grade prostate cancer[283]. TP53 loss has been found to be associated with prostate cancer-specific mortality in univariate analysis[284].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[285]. Alterations such as seen here may disrupt TP53 function or expression[286-290].

POTENTIAL GERMLINE IMPLICATIONS

Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[291-293], including sarcomas[294-295]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[296] to 1:20,000[295]. 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[297]. 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[232,252-256]. 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[252-253]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[257]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[255,258-259]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

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GENE
VHL

ALTERATION
rearrangement exon 3

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Various strategies are under clinical investigation to block pathways downstream of inactivated VHL, including HIF, VEGF, and mTOR. The multikinase inhibitor sunitinib, which has activity against VEGFRs and other targets, is approved to treat several tumor types and has shown strong efficacy in patients with VHL disease[298-302]. Several clinical trials found response rates up to 64% and disease control rates up to 90%[303-304]. However, multiple clinical studies of sunitinib in patients with renal cell carcinoma reported that mutation or inactivation of the VHL gene is not significantly associated with therapeutic response or survival[305-307]. Other agents that inhibit VEGFRs, including the multikinase inhibitors sorafenib, axitinib, pazopanib, regorafenib, cabozantinib, and vandetanib; the anti-VEGFR2 antibody ramucirumab; and the mTOR inhibitors everolimus and temsirolimus, are also approved in multiple tumor types. However, studies have similarly shown that VHL mutation or inactivation does not correlate with responses to these agents[306,308-309]. Therefore, it is unclear whether these therapeutic strategies would be beneficial in this case. The HIF2a inhibitor belzutifan achieved an ORR of 36% in a clinical trial for VHL disease-associated clear cell renal cell carcinoma[310]. Responses were also seen in other VHL mutation-associated tumor types, including CNS hemangioblastomas and pancreatic neuroendocrine tumors; however, it was not determined whether VHL inactivation was significantly associated with these responses[310].

FREQUENCY & PROGNOSIS

VHL is frequently mutated in renal cell carcinomas, but VHL mutation has been detected in fewer than 1% of prostate adenocarcinoma cases[36-38]. Published data investigating the prognostic implications of VHL alteration in prostate carcinomas are limited (PubMed, Feb 2021).

FINDING SUMMARY

VHL encodes the protein pVHL (von Hippel-Lindau tumor suppressor), which is frequently inactivated, either via mutation or hypermethylation, in clear cell renal cell carcinoma (ccRCC) and plays an important role in its pathogenesis[311]. Inactivating mutations in VHL lead to dysregulation of critical downstream growth regulators, especially members of the HIF family and VEGF[312-313]. Alterations such as seen here may disrupt VHL function or expression[314-352].

POTENTIAL GERMLINE IMPLICATIONS

Inactivating germline mutations in VHL underlie von Hippel-Lindau syndrome, a rare but highly penetrant autosomal dominant syndrome occurring in 1/36,000 live births that predisposes to the development of several types of cancer, including clear cell renal cell carcinomas and pancreatic neuroendocrine tumors, as well as retinal and central nervous system hemangioblastomas[353-355]. In the appropriate clinical context, germline testing of VHL is recommended.

GENE
ZNF217

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to address genomic alterations in ZNF217. Expression of ZNF217 may predict relapse of estrogen receptor (ER)-positive breast cancer under hormone therapy through its direct interaction with ER-alpha[356-357]. ZNF217 overexpression has also been associated with resistance to paclitaxel[358] and doxorubicin[359] in breast cancer cell lines. ZNF217 has been suggested as a potential biomarker for treatment with the DNA synthesis inhibitor and AKT inhibitor triciribine in breast cancer based on preclinical findings in cultured cells and xenografts expressing high levels of ZNF217; triciribine treatment also restored sensitivity to doxorubicin in these cells[360].

FREQUENCY & PROGNOSIS

Amplification and/or overexpression of ZNF217 has been reported in breast[361], ovarian[362-363], gastric[364-365], colon[366], prostate[367], esophageal[368], and urothelial carcinomas[369], glioblastoma[370], and ovarian carcinosarcomas[371]. Overexpression in these tumors has generally been linked with aggressive tumor behavior and poor clinical prognosis. High levels of ZNF217 expression result in dysregulation of a broad range of genes that may contribute to tumorigenesis[372-374], and increased expression or activation of ERBB3[361,375], FAK[361], Aurora kinase A[358], AKT[359], and TGF-beta/SMAD signaling[361] has been demonstrated in ZNF217-expressing tumors or cells.

FINDING SUMMARY

ZNF217 encodes a candidate oncogene that has likely roles in histone modification and transcriptional repression[359,376]. ZNF217 amplification has been correlated with protein overexpression in breast carcinoma tumors and cell lines[377]. The role of ZNF217 in promoting tumorigenesis was established in preclinical studies demonstrating that expression of ZNF217 results in the immortalization of both human mammary epithelial cells and ovarian surface epithelial cells in culture[378-379].

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

GENE

MYCN

ALTERATION

amplification

RATIONALE

MYCN amplification may predict sensitivity to inhibition of CDKs, especially CDK1 and CDK2, of Aurora kinases, particularly Aurora kinases A and B, of MDM2, and of BET bromodomain-containing proteins.

NCT03220347

PHASE 1

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of CC-90010 in Subjects With Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin's Lymphomas

TARGETS
BRD2, BRD3, BRD4, BRDT

LOCATIONS: Kashiwa (Japan), Meldola (Italy), Napoli, Campania (Italy), Rozzano (MI) (Italy), Villejuif (France), Bordeaux (France), Barcelona (Spain), Madrid (Spain)

NCT04556617

PHASE 1/2

PLX2853 in Combination With Abiraterone Acetate and Prednisone and in Combination With Olaparib in Subjects With Metastatic Castration-Resistant Prostate Cancer (mCRPC)

TARGETS
BRD4, CYP17, PARP

LOCATIONS: London (United Kingdom), Wisconsin, Illinois, Michigan, New York, Tennessee, Virginia, South Carolina

NCT03297424

PHASE 1/2

A Study of PLX2853 in Advanced Malignancies.

TARGETS
BRD4

LOCATIONS: Arizona, New York, Texas, Virginia, Florida

NCT03611868

PHASE 1/2

A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors

TARGETS
MDM2, PD-1

LOCATIONS: Brisbane (Australia), California, Arizona, Missouri, Arkansas, Pennsylvania, New York, Tennessee, Texas

NCT04555837

PHASE 1/2

Alisertib and Pembrolizumab for the Treatment of Patients With Rb-deficient Head and Neck Squamous Cell Cancer

TARGETS
Aurora kinase A, PD-1

LOCATIONS: Texas

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ORDERED TEST # ORD-1201785-01

CLINICAL TRIALS

NCT01434316

PHASE 1

Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors

TARGETS
PARP, CDK1, CDK2, CDK5, CDK9

LOCATIONS: Massachusetts

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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.

AXL
V150A

CCND2
V240M

FBXW7
amplification

KDM5A
T741S

KMT2A (MLL)
Y2473C

MLH1
amplification

MYD88
amplification

NBN
amplification

NKX2-1
A63S

PPARG
amplification

RAF1
splice site 1418-1G>A

REL
N551S

SETD2
amplification

TGFBR2
amplification

VHL
amplification

ZNF217
rearrangement

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

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

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

DNA GENE LIST: FOR THE DETECTION OF SELECT REARRANGEMENTS

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

*TERC is an NCRNA

**Promoter region of TERT is interrogated

ADDITIONAL ASSAYS: FOR THE DETECTION OF SELECT CANCER BIOMARKERS

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

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

ABOUT FOUNDATIONONE CDX

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

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

INTENDED USE

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

TEST PRINCIPLES

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

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

THE REPORT

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

Diagnostic Significance

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

Qualified Alteration Calls (Equivocal and Subclonal)

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

Ranking of Therapies and Clinical Trials

Ranking of Therapies in Summary Table

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

Ranking of Clinical Trials

Pediatric trial qualification → Geographical proximity → Later trial phase.

NATIONAL COMPREHENSIVE CANCER NETWORK® (NCCN®) CATEGORIZATION

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

Limitations

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

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

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

VARIANT ALLELE FREQUENCY

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

Precision of VAF for base substitutions and indels

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

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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING

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

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

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physician. Indeed, the information in this Report must be considered in conjunction with all other relevant information regarding a particular patient, before the patient's treating physician recommends a course of treatment. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test, such as this Test, or the information contained in this Report. Certain sample or variant characteristics may result in reduced sensitivity. FoundationOne CDx is performed using DNA derived from tumor, and as such germline events may not be reported.

SELECT ABBREVIATIONS

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

MR Suite Version 5.0.0

The median exon coverage for this sample is 477x

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