FOUNDATIONONE®CDx

PATIENT	TUMOR TYPE	REPORT DATE
Yang, Ssu Hsiu	Kidney carcinoma (NOS)	15 Feb 2023
	COUNTRY CODE	ORDERED TEST #
	TW	ORD-1563049-01

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 Kidney carcinoma (NOS)
NAME Yang, Ssu Hsiu
DATE OF BIRTH 22 September 1955
SEX Female
MEDICAL RECORD # 49243643

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 Kidney
SPECIMEN ID S112-02961F (PF23013)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 30 January 2023
SPECIMEN RECEIVED 08 February 2023

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 6 Muts/Mb

Genomic Findings

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

FGFR1 amplification
MTAP loss exons 2-8
RAD51D K91fs*13
CDKN2A/B CDKN2A loss, CDKN2B loss
MLL2 Q836fs*3, H3037fs*34
MUTYH W142*
NSD3 (WHSC1L1) amplification
TP53 R306*
ZNF703 amplification

Report Highlights

- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants in select cancer susceptibility genes to consider for possible **follow-up germline testing** in the appropriate clinical context: ***MUTYH*** **W142*** (p. 7), ***RAD51D*** **K91fs*13** (p. 5)
- Variants that may represent **clonal hematopoiesis** and may originate from non-tumor sources: ***MLL2*** **H3037fs*34, Q836fs*3** (p. 7)

BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS	
Microsatellite status - MS-Stable	**No therapies or clinical trials.** See Biomarker Findings section	
Tumor Mutational Burden - 6 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)**
***FGFR1* -** amplification	none	none
10 Trials see p. 11		
***MTAP* -** loss exons 2-8	none	none
3 Trials see p. 13		
***RAD51D* -** K91fs*13	none	none
10 Trials see p. 14		

Electronically signed by Erik Williams, M.D. | 15 February 2023
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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

VARIANTS TO CONSIDER FOR FOLLOW-UP GERMLINE TESTING IN SELECT CANCER SUSCEPTIBILITY GENES

Findings below have been previously reported as pathogenic germline in the ClinVar genomic database and were detected at an allele frequency of >10%. See appendix for details.

RAD51D - K91fs*13 p. 5

MUTYH - W142* p. 7

This report does not indicate whether variants listed above are germline or somatic in this patient. In the appropriate clinical context, follow-up germline testing would be needed to determine whether a finding is germline or somatic.

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.

MLL2 - Q836fs*3, H3037fs*34 p. 7

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.

CDKN2A/B - CDKN2A loss, CDKN2B loss p. 6
MLL2 - Q836fs*3, H3037fs*34 p. 7
MUTYH - W142* p. 7
NSD3 (WHSC1L1) - amplification p. 8
TP53 - R306* p. 9
ZNF703 - amplification p. 10

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-high and MSI-low were each reported in 1% of cases in a study of 152 renal cell carcinomas (RCC)[6]. Another study reported that fewer than 1% of RCC cases had MSI-H status[7]. Published data investigating the prognostic implications of MSI in RCC are limited (PubMed, Jan 2023).

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[8]. 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[8-10]. 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[11-13]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[8,10,12-13].

BIOMARKER

Tumor Mutational Burden

RESULT
6 Muts/Mb

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

On the basis of clinical evidence in solid tumors, increased TMB may be associated with greater sensitivity to immunotherapeutic agents, including anti-PD-L1[14-16], anti-PD-1 therapies[14-17], and combination nivolumab and ipilimumab[18-23]. In multiple pan-tumor studies, increased tissue tumor mutational burden (TMB) was associated with sensitivity to immune checkpoint inhibitors[14-17,24-28]. In the KEYNOTE 158 trial of pembrolizumab monotherapy for patients with solid tumors, significant improvement in ORR was observed for patients with TMB ≥10 Muts/Mb (as measured by this assay) compared with those with TMB <10 Muts/Mb in a large cohort that included multiple tumor types[24]; similar findings were observed in the KEYNOTE 028 and 012 trials[17]. At the same TMB cutpoint, retrospective analysis of patients with solid tumors treated with any checkpoint inhibitor identified that tissue TMB scores ≥ 10 Muts/Mb were associated with prolonged time to treatment failure compared with scores <10 muts/Mb (HR=0.68)[28]. For patients with solid tumors treated with nivolumab plus ipilimumab in the CheckMate 848 trial, improved responses were observed in patients with a tissue TMB ≥ 10 Muts/Mb independent of blood TMB at any cutpoint in matched samples[29]. However, support for higher TMB thresholds and efficacy was observed in the prospective Phase 2 MyPathway trial of atezolizumab for patients with pan-solid tumors, where improved ORR and DCR was seen in patients with TMB ≥ 16 Muts/Mb than those with TMB ≥ 10 and <16 Muts/Mb[27]. Similarly, analyses across several solid tumor types reported that patients with higher TMB (defined as ≥16-20 Muts/Mb) achieved greater clinical benefit from PD-1 or PD-L1-targeting monotherapy compared with patients with higher TMB treated with chemotherapy[30] or those with lower TMB treated with PD-1 or PD-L1-targeting agents[15].

FREQUENCY & PROGNOSIS

Kidney carcinoma, including renal clear cell carcinoma, renal papillary carcinoma, and renal sarcomatoid carcinoma subtypes, harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 0-2% of cases have been reported to harbor high TMB (>20 muts/Mb)[31-32]. Renal cell carcinomas harbor an average TMB among solid tumors, with a median of approximately 1-2 non-synonymous somatic mutations per megabase in kidney clear-cell or papillary carcinoma[33-34]. For patients with ccRCC, increased TMB is associated with poor survival outcomes, higher tumor grade, and advanced pathological stage[35].

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[36-37] and cigarette smoke in lung cancer[38-39], treatment with temozolomide-based chemotherapy in glioma[40-41], mutations in the proofreading domains of DNA polymerases encoded by the POLE and POLD1 genes[42-46], and microsatellite instability (MSI)[42,45-46]. 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[15-16,24].

GENE
FGFR1

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Alterations that activate FGFR1 may predict sensitivity to selective FGFR inhibitors including erdafitinib[47-49], pemigatinib[50], infigratinib[51-52], futibatinib[53-55], rogaratinib[56], Debio 1347[57-58], and derazantinib[59] or to multikinase inhibitors such as pazopanib[60] and ponatinib[61-63]. The activity and efficacy of selective FGFR inhibitors for FGFR1-amplified tumors has been modest, with limited responses reported in FGFR1-amplified lung squamous cell carcinoma (SCC) treated with infigratinib[64] or AZD4547[65], in FGFR1-amplifed uterine cancer treated with pemigatinib[50], and no responses reported among patients with FGFR1-amplified breast cancer treated with infigratinib[64] or pemigatinib[50]. Two case studies reported PRs in patients with FGFR1-amplified breast cancer treated with pazopanib[60].

FREQUENCY & PROGNOSIS

In the TCGA datasets, FGFR1 amplification and mutation have each been reported in 0-1% of renal cell carcinomas across clear cell, papillary, and chromophobe subtypes (cBioPortal, Feb 2022)[66-67]. Intense expression of FGFR1 protein was associated with shorter PFS by univariate and multivariate analysis among patients with metastatic renal cell carcinoma treated with sorafenib in 1 study[68].

FINDING SUMMARY

FGFR1 encodes the protein fibroblast growth factor receptor 1, which plays key roles in regulation of the cell cycle and angiogenesis and is an upstream regulator of the RAS, MAPK, and AKT signaling pathways[69]. Amplification of FGFR1 has been correlated with protein expression[70-71] and may predict pathway activation and sensitivity to therapies targeting this pathway[72-73].

GENE
MTAP

ALTERATION
loss exons 2-8

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

MTAP inactivation produces specific metabolic vulnerabilities that may be sensitive to MAT2A[74-75] or PRMT5 inhibition[75-77]. A Phase 1 trial of MAT2A inhibitor AG-270 reported 1 PR and 2 SDs lasting longer than 6 months for patients with advanced solid tumors displaying MTAP loss[78]. Preclinical data suggest that MTAP loss sensitizes cells to S-adenosyl-L-methionine (SAM)-competitive PRMT5 inhibitors[79], dual PRMT1 and PRMT5 inhibitors[80-82], and PRMT5 inhibitors that selectively bind the PRMT5 when complexed with S-methyl-5'-thioadenosine (MTA), such as MRTX1719, TNG908, and AMG193[83]. In preclinical models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA[84-94]. A Phase 2 study of L-alanosine, an inhibitor of adenine synthesis, as a monotherapy for 65 patients with MTAP-deficient cancers reported no responses and SD for 24% (13/55) of patients[95]. Preclinical and limited clinical evidence suggest MTAP deficiency may confer sensitivity to pemetrexed[96].

FREQUENCY & PROGNOSIS

MTAP loss/homozygous deletion as well as loss of expression has been reported in a wide variety of solid tumors and hematologic cancers[97-98]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[99], gastrointestinal stromal tumors[100], mantle cell lymphoma (MCL)[101], melanoma[102-103], gastric cancer[104], myxofibrosarcoma[105], nasopharyngeal carcinoma[106], ovarian carcinoma[97] and non-small cell lung cancer[107]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[108] or in astrocytoma[109]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[110], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[111]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[112-113], esophageal cancer[114-115], osteosarcoma[116], and CRC[117].

FINDING SUMMARY

MTAP encodes S-methyl-5'-thioadenosine (MTA) phosphorylase, a tumor suppressor involved in polyamine metabolism and methionine synthesis, although its enzymatic function is dispensable for its tumor suppressor activity[118-119]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[99,120-121], thereby reducing intracellular arginine methylation[75-77] and altering cell signaling[121-122]. MTAP is located at 9p21, adjacent to CDKN2A and CDKN2B, with which it is frequently co-deleted in various cancers. Other alterations in MTAP are rare and have not been extensively characterized.

GENE
RAD51D

ALTERATION
K91fs*13

TRANSCRIPT ID
NM_002878.3

CODING SEQUENCE EFFECT
271_272insTA

VARIANT CHROMOSOMAL POSITION
chr17:33434458

VARIANT ALLELE FREQUENCY (% VAF)
48.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Limited preclinical data[123-124] and clinical evidence in ovarian cancer[125-126] indicate that loss or inactivation of RAD51D may confer sensitivity to PARP inhibitors. Loss of functional RAD51D may also predict sensitivity to DNA-damaging drugs such as mitomycin C and cisplatin[123,127-129].

FREQUENCY & PROGNOSIS

RAD51D mutation has been reported in <0.5% of analyzed kidney tumors (COSMIC, cBioPortal, Mar 2021)[66-67,130]. Published data investigating the prognostic implications of RAD51D alterations in kidney cancer are limited (PubMed, Mar 2021).

FINDING SUMMARY

RAD51D, also known as RAD51L3, is involved in homologous recombination-mediated DNA repair and telomere maintenance[131-134]. Germline mutations in RAD51D have been associated with hereditary breast and ovarian cancer[124,135-138], and RAD51D mutation carriers have an increased lifetime risk of ovarian cancer, estimated to be 10-12%[124,139]. Alterations such as seen here may disrupt RAD51D function or expression[123,127-128,140-143].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the RAD51D variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with hereditary breast and ovarian cancer syndrome (ClinVar, Sep 2022)[144]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Inactivating germline mutations in RAD51D are associated with hereditary breast and ovarian cancer (HBOC) syndrome, an autosomal dominant disorder that predisposes patients to breast and ovarian malignancies[145-146]. The risk of ovarian cancer in RAD51D mutation carriers has been estimated to be 10 to 12%[124,139]. Germline RAD51D mutation has been reported at frequencies of up to 1% in breast and ovarian familial cancer populations without BRCA1/2 mutation[138,147-148]. In the appropriate clinical context, germline testing of RAD51D is recommended.

GENE
CDKN2A/B

ALTERATION
CDKN2A loss, CDKN2B loss

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[149-152]. Clinical data in mesothelioma, breast cancer, and uterine leiomyosarcoma indicate that CDKN2A loss may predict sensitivity to abemaciclib[153] and palbociclib treatment[154-155]. However, multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[156-162]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. The p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, and although concomitant loss of CDKN2A and CDKN2B may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[159-160,163-164], direct supporting data for CDKN2B alteration as a predictive biomarker for these therapies are limited[165-166]. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[167-168], the clinical relevance of p14ARF as a predictive biomarker is not clear.

FREQUENCY & PROGNOSIS

In the Kidney Renal Clear Cell Carcinoma (ccRCC) and Kidney Renal Papillary Cell Carcinoma TCGA datasets, putative homozygous deletion of both the CDKN2A and CDKN2B genes has been reported in 4.5% and 3% of cases, respectively (cBioPortal, Jul 2022)[66-67]. CDKN2A/B deletion has been reported to be one of the most significant copy number alterations in ccRCC[169]. In a study of sarcomatoid renal cell carcinoma (RCC), CDKN2A alterations were reported in 27% (7/26) of cases, with CDKN2B also altered in 15% (4/26) of these samples[170]. One study has reported loss of heterozygosity (LOH) on 9p21, which includes the region that encodes CDKN2A and CDKN2B, in 25% of papillary renal cell carcinoma tumors[171]. Loss due to deletion or hypermethylation of chromosome 9p, which includes the CDKN2A and CDKN2B loci, has been reported at frequencies ranging from 13% to 80% of renal cell carcinoma samples, including ccRCC and papillary subtypes, and has been associated with poor prognosis[172-176]. In addition, loss of chromosome 9p has been associated with advanced tumor grade, disease progression, and overall poor prognosis in both ccRCC and papillary renal cell carcinoma[173-174,177].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[178-179]. 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[180-181]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[182-183]. One or more alterations observed here are predicted to result in p16INK4a loss of function[184-205]. One or more alterations seen here are predicted to result in p14ARF loss of function[188,205-208]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[209].

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[210]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[211-212]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[213-215]. 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[216-218]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

GENE
MLL2

ALTERATION
Q836fs*3, H3037fs*34

TRANSCRIPT ID
NM_003482.4, NM_003482.4

CODING SEQUENCE EFFECT
2506_2507insC, 9109delC

VARIANT CHROMOSOMAL POSITION
chr12:49444959, chr12:49432029-49432030

VARIANT ALLELE FREQUENCY (% VAF)
17.9%, 27.6%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in MLL2.

FREQUENCY & PROGNOSIS

MLL2 alterations are observed in a number of solid tumor contexts[219], and are especially prevalent in lung squamous cell carcinoma (SCC)[220] and small cell lung carcinoma (SCLC)[221]. MLL2 mutation was found to be an independent prognostic factor of poor PFS and OS in non-small cell lung cancer, but not in SCLC[222]. One study reported that MLL2 truncating mutations were more common in recurrent ovary granulosa cell tumors (GCT) compared with primary GCTs (24% [10/42] vs. 3.0% [1/32])[223]. In a study of esophageal SCC, high MLL2 expression positively correlated with tumor stage, differentiation, and size, and negatively correlated with OS[224].

FINDING SUMMARY

MLL2 encodes an H3K4-specific histone methyltransferase that is involved in the transcriptional response to progesterone signaling[225]. Germline de novo mutations of MLL2 are responsible for the majority of cases of Kabuki syndrome, a complex and phenotypically distinctive developmental disorder[226]. A significant number of inactivating MLL2 alterations have been observed in multiple tumor types, suggesting a tumor suppressor role[227].

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[228-233]. Comprehensive genomic profiling of solid tumors may detect nontumor alterations that are due to CH[232,234-235]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
MUTYH

ALTERATION
W142*

TRANSCRIPT ID
NM_001048171.1

CODING SEQUENCE EFFECT
425G>A

VARIANT CHROMOSOMAL POSITION
chr1:45798627

VARIANT ALLELE FREQUENCY (% VAF)
47.5%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapies or clinical trials available to address MUTYH alterations in cancer.

FREQUENCY & PROGNOSIS

In general, somatic MUTYH mutations are infrequently reported across cancer types (COSMIC, 2023)[130]. Monoallelic MUTYH mutation occurs in 1-2% of the general population[236-237]. There are conflicting data regarding the impact of monoallelic mutations on the risk of developing colorectal cancer (CRC)[238-240]. Patients with MUTYH-mutated CRC were reported to have significantly improved OS compared with patients without MUTYH mutation[241].

FINDING SUMMARY

MUTYH (also known as MYH) encodes an enzyme involved in DNA base excision repair, and loss of function mutations in MUTYH result in increased rates of mutagenesis and promotion of tumorigenesis[242]. The two most frequently reported MUTYH loss of function mutations are G382D (also referred to as G396D) and Y165C (also referred to as Y179C)[236-237,243-245]. Numerous other MUTYH mutations have also been shown to result in loss of function[243-246].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the MUTYH variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with MUTYH-associated polyposis (ClinVar, Sep 2022)[144]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline biallelic MUTYH mutation causes MUTYH-associated polyposis (also known as MYH-associated polyposis or MAP), an autosomal recessive condition characterized by multiple colorectal adenomas and increased lifetime risk of colorectal cancer (CRC)[236,247-249]. MAP accounts for approximately 0.7% of all CRC cases and 2% of early-onset CRC cases[236]. In contrast to CRC, the role of MUTYH mutation in the context of other cancer types is not well established[250-254]. Estimates for the prevalence of MAP in the general population range from 1:5,000-1:10,000[237]. Therefore, in the appropriate clinical context, germline testing of MUTYH is recommended.

GENE
NSD3 (WHSC1L1)

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no targeted therapies available to address genomic alterations in NSD3.

FREQUENCY & PROGNOSIS

In TCGA datasets, NSD3 amplification has been most frequently observed in lung squamous cell carcinoma (17%)[220], breast invasive carcinoma (13%)[255], bladder urothelial carcinoma (9%)[256], and head and neck squamous cell carcinoma (9%)[257] samples[66-67]. Amplification of at least 1 member of the NSD3-CHD8-BRD4 pathway has been associated with worse OS in ovarian high-grade serous carcinoma and endometrial cancer[258]. In endometrial cancers, amplification of this pathway was more frequent in endometrial serous and endometrioid serious-like carcinomas compared to low-grade endometrioid endometrial adenocarcinomas[258].

FINDING SUMMARY

NSD3, also known as WHSC1L1, encodes an enzyme that mediates histone methylation[259]. NSD3 has been shown to be amplified in various cancers[260-262].

GENE
TP53

ALTERATION
R306*

TRANSCRIPT ID
NM_000546.4

CODING SEQUENCE EFFECT
916C>T

VARIANT CHROMOSOMAL POSITION
chr17:7577022

VARIANT ALLELE FREQUENCY (% VAF)
31.5%

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[263-266] or p53 gene therapy such as SGT53[267-271]. In a Phase 1 study, adavosertib in combination with gemcitabine, cisplatin, or carboplatin elicited PRs in 9.7% and SDs in 53% of patients with solid tumors; the response rate was 21% (4/19) for patients with TP53 mutations versus 12% (4/33) for patients who were TP53 wildtype[272]. A Phase 2 trial of adavosertib in combination with chemotherapy (gemcitabine, carboplatin, paclitaxel, or doxorubicin) reported a 32% (30/94, 3 CR) ORR and a 73% (69/94) DCR for patients with platinum-refractory TP53-mutated ovarian, Fallopian tube, or peritoneal cancer[273]. A smaller Phase 2 trial of adavosertib in combination with carboplatin achieved a 43% (9/21, 1 CR) ORR and a 76% (16/21) DCR for patients with platinum-refractory TP53-mutated ovarian cancer[274]. 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[275]. In the Phase 2 VIKTORY trial, patients with TP53-mutated metastatic and/or recurrent gastric cancer experienced a 24% (6/25) ORR with adavosertib combined with paclitaxel[276]. A Phase 1 trial of neoadjuvant adavosertib in combination with cisplatin and docetaxel for head and neck squamous cell carcinoma (HNSCC) elicited a 71% (5/7) response rate for patients with TP53 alterations[277]. The Phase 2 FOCUS4-C trial for patients with TP53- and RAS-mutated colorectal cancer reported improvement in PFS (3.61 vs. 1.87 months, HR=0.35, p=0.0022), but not OS (14.0 vs 12.8 months, p=0.93), following adavosertib treatment compared with active monitoring[278]. In a Phase 1b clinical trial of SGT-53 in combination with docetaxel for patients with solid tumors, 75% (9/12) of evaluable patients experienced clinical benefit, including 2 confirmed and 1 unconfirmed PRs and 2 instances of SD with significant tumor shrinkage[271]. Missense mutations leading to TP53 inactivation may be sensitive to therapies that reactivate mutated p53 such as eprenetapopt. In a Phase 1b trial for patients with p53-positive high-grade serous ovarian cancer, eprenetapopt combined with carboplatin and pegylated liposomal doxorubicin achieved a 52% (11/21) response rate and 100% DCR[279]. A Phase 1 trial of eprenetapopt with pembrolizumab for patients with solid tumors reported an ORR of 10% (3/29)[280].

FREQUENCY & PROGNOSIS

TP53 mutations have been reported in 2.2-6.4% of clear cell renal cell carcinomas (RCCs)[281-284], 2.5% of papillary RCCs (cBioPortal, Feb 2023)[66-67], and 31% of chromophobe RCCs[285]. In the literature, TP53 mutations have been reported in 4-5% of clear cell RCCs and at a higher incidence of 11% in non-clear cell RCCs, with incidences of 11% and 24% in papillary and chromophobe RCCs, respectively[286-287]. TP53 mutations have been reported as more common in ccRCC metastases compared to primary tumors[288]. Coexpression of p53, which has been found to mostly be wild-type, and MDM2 has been associated with poor prognosis in RCC, suggesting that targeting the p53-MDM2 pathway may be a potential therapeutic strategy for a subset of patients with RCC[289].

FINDING SUMMARY

Functional loss of the tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers[290]. Alterations such as seen here may disrupt TP53 function or expression[291-295].

POTENTIAL GERMLINE IMPLICATIONS

One or more of the TP53 variants observed here has been described in the ClinVar database as a likely pathogenic or pathogenic germline mutation (by an expert panel or multiple submitters) associated with Li-Fraumeni syndrome (ClinVar, Sep 2022)[144]. Follow-up germline testing would be needed to distinguish whether the finding in this patient is somatic or germline. Germline mutations in TP53 are associated with the very rare autosomal dominant disorder Li-Fraumeni syndrome and the early onset of many cancers[296-298], including sarcomas[299-300]. Estimates for the prevalence of germline TP53 mutations in the general population range from 1:5,000[301] to 1:20,000[300]. 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[302]. 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[228-233]. 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[228-229]. Clinical management of patients with CH in this gene may include monitoring for hematologic changes and reduction of controllable risk factors for cardiovascular disease[303]. Comprehensive genomic profiling of solid tumors detects nontumor alterations that are due to CH[232,234-235]. Patient-matched peripheral blood mononuclear cell sequencing is required to conclusively determine if this alteration is present in tumor or is secondary to CH.

GENE
ZNF703

ALTERATION
amplification

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no available targeted therapies to directly address ZNF703 alterations in cancer. One preclinical study suggested that ZNF703 expression in breast cancer cell lines is associated with reduced sensitivity to tamoxifen through AKT-mTOR activation[304], although these findings have not been verified in the clinical setting.

FREQUENCY & PROGNOSIS

Amplification and high expression of ZNF703 has been observed in luminal B breast tumors, a subtype associated with aggressive disease progression and poor patient outcomes[305-307]. ZNF703 expression has also been linked with aggressive tumor characteristics in patients with gastric and colorectal cancers[308-309]. Putative high-level amplification of ZNF703 has been reported with the highest frequency in breast carcinoma, bladder urothelial carcinoma, uterine carcinosarcoma, lung squamous cell carcinoma (SCC), esophageal carcinoma and head and neck SCC (5-13% of samples)(cBioPortal, 2023)[66-67].

FINDING SUMMARY

ZNF703 encodes a transcriptional repressor that plays roles in stem cell proliferation, cell cycle progression, and other key cellular functions[306,310]. Amplification of ZNF703 has been correlated with protein expression[305-306]. ZNF703 was established as a breast cancer oncoprotein by studies showing that ZNF703 expression resulted in transformation and increased proliferation of cultured cells[305-306,311], as well as increased lung metastases in a breast cancer xenograft model[311].

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
FGFR1

RATIONALE
FGFR inhibitors may be relevant in tumors with alterations that activate FGFR1.

ALTERATION
amplification

NCT04736706

PHASE 3

A Study of Pembrolizumab (MK-3475) in Combination With Belzutifan (MK-6482) and Lenvatinib (MK-7902), or Pembrolizumab/Quavonlimab (MK-1308A) in Combination With Lenvatinib, Versus Pembrolizumab and Lenvatinib, for Treatment of Advanced Clear Cell Renal Cell Carcinoma (MK-6482-012)

TARGETS
FGFRs, RET, PDGFRA, VEGFRs, KIT, CTLA-4, HIF2a, PD-1

LOCATIONS: Taipei (Taiwan), Taoyuan (Taiwan), Taichung (Taiwan), Tainan (Taiwan), Kaohsiung (Taiwan), Wenzhou (China), Xiamen (China), Ningbo (China), Hangzhou (China), Jiaxing (China)

NCT05024214

PHASE 1/2

Phase Ib/II Trial of Envafolimab Plus Lenvatinib for Subjects With Solid Tumors

TARGETS
PD-L1, FGFRs, RET, PDGFRA, VEGFRs, KIT, FLT3, CSF1R

LOCATIONS: Hangzhou (China), Shanghai (China), Dongguan (China), Guangzhou (China), Zhuhai (China), Benbu (China), Zhengzhou (China), Jinan (China), Dalian (China), Tianjin (China)

NCT05014828

PHASE 2

To Evaluate the Efficacy and Safety of Tislelizumab in Combination With Lenvatinib in Patients With Selected Solid Tumors

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

LOCATIONS: Hangzhou (China), Nanchang (China), Nanjing (China), Hefei (China), Changsha (China), Wuhan (China), Nanning (China), Chongqing (China), Beijing (China), Harbin (China)

NCT04169672

PHASE 2

Study of Surufatinib Combined With Toripalimab in Patients With Advanced Solid Tumors

TARGETS
FGFR1, CSF1R, VEGFRs, PD-1

LOCATIONS: Shanghai (China), Beijing (China)

NCT05098847

PHASE 2

Cryoablation Combined With Sintilimab Plus Lenvatinib In Previously Treated Unresectable Liver Metastasis From Solid Tumors

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

LOCATIONS: Shanghai (China)

NCT03564691

PHASE 1

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

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

LOCATIONS: Shanghai (China), Seoul (Korea, Republic of), Brisbane (Australia), Liverpool (Australia), Petah Tikva (Israel), Ramat Gan (Israel), Tel Aviv (Israel), Haifa (Israel), Warszawa (Poland), Gdansk (Poland)

NCT04586231

PHASE 3

A Study of MK-6482 in Combination With Lenvatinib Versus Cabozantinib for Treatment of Renal Cell Carcinoma (MK-6482-011)

TARGETS
HIF2a, MET, ROS1, RET, VEGFRs, FGFRs, PDGFRA, KIT

LOCATIONS: Hwasun (Korea, Republic of), Fukuoka (Japan), Seoul (Korea, Republic of), Osakasayama (Japan), Suita (Japan), Kashihara (Japan), Toyoake (Japan), Hamamatsu (Japan), Yokohama (Japan), Tokyo (Japan)

NCT04977453

PHASE 1/2

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

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

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

NCT04626479

PHASE 1/2

Substudy 03A: A Study of Immune and Targeted Combination Therapies in Participants With First Line (1L) Renal Cell Carcinoma (MK-3475-03A)

TARGETS
PD-1, HIF2a, LAG-3, FGFRs, RET, PDGFRA, VEGFRs, KIT

LOCATIONS: Songpagu (Korea, Republic of), Seoul (Korea, Republic of), Herston (Australia), Blacktown (Australia), Kogarah (Australia), Heidelberg (Australia), Haifa (Israel), Jerusalem (Israel), Petah Tiqwa (Israel), Ramat Gan (Israel)

NCT04626518

PHASE 1/2

Substudy 03B: A Study of Immune and Targeted Combination Therapies in Participants With Second Line Plus (2L+) Renal Cell Carcinoma (MK-3475-03B)

TARGETS
HIF2a, CTLA-4, FGFRs, RET, PDGFRA, VEGFRs, KIT, ITL4, LAG-3, PD-1

LOCATIONS: Seoul (Korea, Republic of), Songpagu (Korea, Republic of), Herston (Australia), Blacktown (Australia), Kogarah (Australia), Melbourne (Australia), Jerusalem (Israel), Petah Tiqwa (Israel), Ramat Gan (Israel), Tel Aviv (Israel)

GENE
MTAP

ALTERATION
loss exons 2-8

RATIONALE
MTAP loss may predict sensitivity to MAT2A inhibitors, or to inhibitors that target PRMT5 when in complex with MTA.

NCT05094336

PHASE 1/2

AMG 193, Methylthioadenosine (MTA) Cooperative Protein Arginine Methyltransferase 5 (PRMT5) Inhibitor, Alone and in Combination With Docetaxel in Advanced Methylthioadenosine Phosphorylase (MTAP)-Null Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Tainan (Taiwan), Hong Kong (Hong Kong), Nagoya-shi (Japan), Chuo-ku (Japan), Kashiwa-shi (Japan), Camperdown (Australia), Halle (Saale) (Germany), Salzburg (Austria), Wuerzburg (Germany), Ulm (Germany)

NCT05275478

PHASE 1/2

Safety and Tolerability of TNG908 in Patients With MTAP-deleted Solid Tumors

TARGETS
PRMT5-MTA

LOCATIONS: Lyon (France), Villejuif (France), Missouri, Massachusetts, Tennessee, Texas, Virginia

NCT05245500

PHASE 1/2

Phase 1/2 Study of MRTX1719 in Solid Tumors With MTAP Deletion

TARGETS
PRMT5-MTA

LOCATIONS: Colorado, Massachusetts, New York, Tennessee, Texas

GENE
RAD51D

RATIONALE
Inactivation of RAD51D may predict sensitivity to PARP inhibitors.

ALTERATION
K91fs*13

NCT04644068

PHASE 1/2

Study of AZD5305 as Monotherapy and in Combination With Anti-cancer Agents in Patients With Advanced Solid Malignancies

TARGETS
ERBB2, TROP2, PARP

LOCATIONS: Shanghai (China), Guangzhou (China), Seoul (Korea, Republic of), Chongqing (China), Chengdu (China), Chuo-ku (Japan), Koto-ku (Japan), Melbourne (Australia), Lublin (Poland), Warszawa (Poland)

NCT04123366

PHASE 2

Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)

TARGETS
PARP, PD-1

LOCATIONS: Fukuoka (Japan), Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Okayama (Japan), Nagoya (Japan), Tokyo (Japan), Kashiwa (Japan), Sapporo (Japan), Nedlands (Australia), Southport (Australia)

NCT03742895

PHASE 2

Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)

TARGETS
PARP

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Darlinghurst (Australia), Adana (Turkey), Jerusalem (Israel), Konya (Turkey), Ramat Gan (Israel), Istanbul (Turkey), Antalya (Turkey), Brasov (Romania)

NCT02264678

PHASE 1/2

Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

TARGETS
ATR, PARP, PD-L1

LOCATIONS: Seongnam-si (Korea, Republic of), Seoul (Korea, Republic of), Goyang-si (Korea, Republic of), Cambridge (United Kingdom), Withington (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Coventry (United Kingdom), Sutton (United Kingdom), Oxford (United Kingdom)

NCT05035745

PHASE 1/2

Selinexor & Talazoparib in Advanced Refractory Solid Tumors; Advanced/Metastatic Triple Negative Breast Cancer (START)

TARGETS
XPO1, PARP

LOCATIONS: Singapore (Singapore)

NCT03772561

PHASE 1

Phase I Study of AZD5363 + Olaparib + Durvalumab in Patients With Advanced or Metastatic Solid Tumor Malignancies

TARGETS
PARP, AKTs, PD-L1

LOCATIONS: Singapore (Singapore)

NCT04801966

PHASE NULL

Safety and Oversight of the Individually Tailored Treatment Approach: A Novel Pilot Study

TARGETS
CDK4, CDK6, PI3K-alpha, PD-L1, MEK, PARP, PD-1, BRAF

LOCATIONS: Melbourne (Australia)

NCT04497116

PHASE 1/2

Study of RP-3500 in Advanced Solid Tumors

TARGETS
ATR, PARP

LOCATIONS: Copenhagen (Denmark), Newcastle Upon Tyne (United Kingdom), Manchester (United Kingdom), London (United Kingdom), Illinois, Toronto (Canada), Massachusetts, Rhode Island, New York, Tennessee

NCT03297606

PHASE 2

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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

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

NCT04991480

PHASE 1/2

A Study of ART4215 for the Treatment of Advanced or Metastatic Solid Tumors

TARGETS
PARP, Pol theta

LOCATIONS: London (United Kingdom), Oklahoma, Connecticut, New York, Pennsylvania, Tennessee, Texas, Florida

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.

BCL6
D17N

BRCA2
H523R

EP300
P1875S

FLT3
V491fs*11

KDR
E732K

LTK
R606Q

MSH2
E809K

MST1R
V366F

NOTCH2
L823R

PARP1
V979M

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) 7.5.0

The median exon coverage for this sample is 831x

1. Gatalica Z, et al. Cancer Epidemiol. Biomarkers Prev. (2014) pmid: 25392179
2. Kroemer G, et al. Oncoimmunology (2015) pmid: 26140250
3. Lal N, et al. Oncoimmunology (2015) pmid: 25949894
4. Le DT, et al. N. Engl. J. Med. (2015) pmid: 26028255
5. Ayers et al., 2016; ASCO-SITC Abstract P60
6. Stoehr C, et al. Pathobiology (2012) pmid: 22378480
7. Bratslavsky G, et al. Urol Oncol (2021) pmid: 33775530
8. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
9. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
10. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
11. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
12. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
13. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
14. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
15. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
16. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
17. Cristescu R, et al. Science (2018) pmid: 30309915
18. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
19. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
20. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
21. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
22. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
23. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
24. Marabelle A, et al. Lancet Oncol. (2020) pmid: 32919526
25. Ott PA, et al. J. Clin. Oncol. (2019) pmid: 30557521
26. Cristescu R, et al. J Immunother Cancer (2022) pmid: 35101941
27. Friedman CF, et al. Cancer Discov (2022) pmid: 34876409
28. Sturgill EG, et al. Oncologist (2022) pmid: 35274716
29. Schenker at al., 2022; AACR Abstract 7845
30. Legrand et al., 2018; ASCO Abstract 12000
31. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
32. Pal SK, et al. Eur. Urol. (2018) pmid: 28592388
33. Lawrence MS, et al. Nature (2013) pmid: 23770567
34. Alexandrov LB, et al. Nature (2013) pmid: 23945592
35. Zhang C, et al. Ann Transl Med (2019) pmid: 31930049
36. Pfeifer GP, et al. Mutat. Res. (2005) pmid: 15748635
37. Hill VK, et al. Annu Rev Genomics Hum Genet (2013) pmid: 23875803
38. Pfeifer GP, et al. Oncogene (2002) pmid: 12379884
39. Rizvi NA, et al. Science (2015) pmid: 25765070
40. Johnson BE, et al. Science (2014) pmid: 24336570
41. Choi S, et al. Neuro-oncology (2018) pmid: 29452419
42. Cancer Genome Atlas Research Network, et al. Nature (2013) pmid: 23636398
43. Briggs S, et al. J. Pathol. (2013) pmid: 23447401
44. Heitzer E, et al. Curr. Opin. Genet. Dev. (2014) pmid: 24583393
45. Nature (2012) pmid: 22810696
46. Roberts SA, et al. Nat. Rev. Cancer (2014) pmid: 25568919
47. Loriot Y, et al. N. Engl. J. Med. (2019) pmid: 31340094
48. Tabernero J, et al. J. Clin. Oncol. (2015) pmid: 26324363
49. Karkera JD, et al. Mol. Cancer Ther. (2017) pmid: 28416604
50. Subbiah V, et al. Ann Oncol (2022) pmid: 35176457
51. Pal SK, et al. Cancer Discov (2018) pmid: 29848605
52. Pal SK, et al. Cancer (2020) pmid: 32208524
53. Bahleda R, et al. Ann Oncol (2020) pmid: 32622884
54. Meric-Bernstam F, et al. Cancer Discov (2022) pmid: 34551969
55. Kasbekar M, et al. Blood Adv (2020) pmid: 32649766
56. Schuler M, et al. Lancet Oncol. (2019) pmid: 31405822
57. Farouk Sait S, et al. JCO Precis Oncol (2021) pmid: 34250399
58. Voss MH, et al. Clin. Cancer Res. (2019) pmid: 30745300
59. Papadopoulos KP, et al. Br. J. Cancer (2017) pmid: 28972963
60. Cheng FT, et al. J Natl Compr Canc Netw (2017) pmid: 29223982
61. Khodadoust MS, et al. Leukemia (2016) pmid: 26055304
62. Tanasi I, et al. Blood (2019) pmid: 31434701
63. Strati P, et al. Leuk. Lymphoma (2018) pmid: 29119847
64. Nogova L, et al. J. Clin. Oncol. (2017) pmid: 27870574
65. Aggarwal C, et al. J Thorac Oncol (2019) pmid: 31195180
66. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
67. Gao J, et al. Sci Signal (2013) pmid: 23550210
68. Ho TH, et al. BMC Cancer (2015) pmid: 25900027
69. Turner N, et al. Nat. Rev. Cancer (2010) pmid: 20094046
70. Kohler LH, et al. Virchows Arch. (2012) pmid: 22648708
71. Kim HR, et al. J. Clin. Oncol. (2013) pmid: 23182986
72. André F, et al. Lancet Oncol. (2014) pmid: 24508104
73. Dienstmann R, et al. Ann. Oncol. (2014) pmid: 24265351
74. Kalev P, et al. Cancer Cell (2021) pmid: 33450196
75. Marjon K, et al. Cell Rep (2016) pmid: 27068473
76. Mavrakis KJ, et al. Science (2016) pmid: 26912361
77. Kryukov GV, et al. Science (2016) pmid: 26912360
78. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
79. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
80. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
81. Srour N, et al. Cancer Cell (2019) pmid: 31287990
82. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
83. Smith CR, et al. J Med Chem (2022) pmid: 35041419
84. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
85. Tang B, et al. Cancer Res. (2018) pmid: 29844120
86. Munshi PN, et al. Oncologist (2014) pmid: 24928612
87. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
88. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
89. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
90. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
91. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
92. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
93. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
94. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
95. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
96. Alhalabi O, et al. Nat Commun (2022) pmid: 35379845
97. Wei R, et al. Sci Rep (2016) pmid: 27929028
98. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
99. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
100. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
101. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
102. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
103. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
104. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
105. Li CF, et al. Oncotarget (2014) pmid: 25426549
106. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
107. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
108. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
109. Becker AP, et al. Pathobiology (2015) pmid: 26088413
110. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
111. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
112. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
113. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
114. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
115. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
116. Zhi L, et al. J Cancer (2016) pmid: 27994653
117. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
118. Limm K, et al. PLoS ONE (2016) pmid: 27479139
119. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
120. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
121. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
122. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
123. Rivera B, et al. Cancer Res. (2017) pmid: 28646019
124. Loveday C, et al. Nat. Genet. (2011) pmid: 21822267
125. Swisher EM, et al. Lancet Oncol. (2017) pmid: 27908594
126. Kondrashova O, et al. Cancer Discov (2017) pmid: 28588062
127. Hinz JM, et al. Nucleic Acids Res. (2006) pmid: 16522646
128. Wiese C, et al. Nucleic Acids Res. (2006) pmid: 16717288
129. Wickramanayake A, et al. Gynecol. Oncol. (2012) pmid: 22986143
130. Tate JG, et al. Nucleic Acids Res. (2019) pmid: 30371878
131. Tarsounas M, et al. Cell (2004) pmid: 15109494
132. Suwaki N, et al. Semin. Cell Dev. Biol. (2011) pmid: 21821141
133. Sasaki MS, et al. Cytogenet. Genome Res. (2004) pmid: 15162012
134. Smiraldo PG, et al. Cancer Res. (2005) pmid: 15781618
135. Graffeo R, et al. Breast Cancer Res. Treat. (2016) pmid: 27734215
136. Osher DJ, et al. Br. J. Cancer (2012) pmid: 22415235
137. Pelttari LM, et al. J. Med. Genet. (2012) pmid: 22652533
138. Gutiérrez-Enríquez S, et al. Int. J. Cancer (2014) pmid: 24130102
139. Song H, et al. J. Clin. Oncol. (2015) pmid: 26261251
140. Miller KA, et al. Nucleic Acids Res. (2004) pmid: 14704354
141. Gruver AM, et al. Mutagenesis (2005) pmid: 16236763
142. Gruver AM, et al. BMC Mol. Biol. (2009) pmid: 19327148
143. Fernandes VC, et al. J Biol Chem (2019) pmid: 30765603
144. Landrum MJ, et al. Nucleic Acids Res. (2018) pmid: 29165669
145. Janatova M, et al. PLoS ONE (2015) pmid: 26057125
146. Stafford JL, et al. PLoS ONE (2017) pmid: 28591191
147. Konstanta I, et al. J. Hum. Genet. (2018) pmid: 30111881
148. Chen X, et al. Ann. Oncol. (2018) pmid: 30165555
149. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
150. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
151. Cen L, et al. Neuro-oncology (2012) pmid: 22711607

152. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
153. Fennell DA, et al. Lancet Oncol (2022) pmid: 35157829
154. Elvin JA, et al. Oncologist (2017) pmid: 28283584
155. Gao J, et al. Curr Oncol (2015) pmid: 26715889
156. Gopalan et al., 2014; ASCO Abstract 8077
157. Peguero et al., 2016; ASCO Abstract 2528
158. Konecny et al., 2016; ASCO Abstract 5557
159. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
160. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
161. Infante JR, et al. Clin. Cancer Res. (2016) pmid: 27542767
162. Johnson DB, et al. Oncologist (2014) pmid: 24797823
163. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
164. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
165. Su D, et al. Nat Commun (2019) pmid: 31700061
166. Tramontana TF, et al. JCO Precis Oncol (2020) pmid: 32923894
167. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
168. Gamble LD, et al. Oncogene (2012) pmid: 21725357
169. Girgis AH, et al. Cancer Res. (2012) pmid: 22926558
170. Malouf GG, et al. Eur. Urol. (2016) pmid: 26895810
171. Maestro de las Casas ML, et al. Arch. Esp. Urol. (2000) pmid: 11037653
172. Toma MI, et al. Neoplasia (2008) pmid: 18592004
173. Klatte T, et al. J. Clin. Oncol. (2009) pmid: 19124809
174. Gunawan B, et al. Cancer Res. (2003) pmid: 14559804
175. Onay H, et al. Urol. Int. (2009) pmid: 19641369
176. Sanz-Casla MT, et al. Urol. Res. (2003) pmid: 12883879
177. Grady B, et al. J. Urol. (2001) pmid: 11490304
178. Quelle DE, et al. Cell (1995) pmid: 8521522
179. Mutat. Res. (2005) pmid: 15878778
180. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
181. Oncogene (1999) pmid: 10498883
182. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
183. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
184. Ruas M, et al. Oncogene (1999) pmid: 10498896
185. Jones R, et al. Cancer Res. (2007) pmid: 17909018
186. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
187. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
188. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
189. Gombart AF, et al. Leukemia (1997) pmid: 9324288
190. Yang R, et al. Cancer Res. (1995) pmid: 7780957
191. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
192. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
193. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
194. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
195. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
196. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
197. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
198. Koh J, et al. Nature (1995) pmid: 7777061
199. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
200. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
201. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
202. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
203. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
204. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
205. Rutter JL, et al. Oncogene (2003) pmid: 12853981
206. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
207. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
208. Zhang Y, et al. Cell (1998) pmid: 9529249
209. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
210. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
211. Adv Exp Med Biol (2010) pmid: 20687502
212. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
213. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
214. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
215. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
216. Kaufman DK, et al. Neurology (1993) pmid: 8414022
217. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
218. Chan AK, et al. Clin Neuropathol () pmid: 28699883
219. Zehir A, et al. Nat. Med. (2017) pmid: 28481359
220. Nature (2012) pmid: 22960745
221. Augert A, et al. J Thorac Oncol (2017) pmid: 28007623
222. Ardeshir-Larijani F, et al. Clin Lung Cancer (2018) pmid: 29627316
223. Hillman RT, et al. Nat Commun (2018) pmid: 29950560
224. Abudureheman A, et al. J. Cancer Res. Clin. Oncol. (2018) pmid: 29532228
225. Vicent GP, et al. Genes Dev. (2011) pmid: 21447625
226. Hannibal MC, et al. Am. J. Med. Genet. A (2011) pmid: 21671394
227. Fagan RJ, et al. Cancer Lett. (2019) pmid: 31128216
228. Jaiswal S, et al. N. Engl. J. Med. (2014) pmid: 25426837
229. Genovese G, et al. N. Engl. J. Med. (2014) pmid: 25426838
230. Xie M, et al. Nat. Med. (2014) pmid: 25326804
231. Acuna-Hidalgo R, et al. Am. J. Hum. Genet. (2017) pmid: 28669404
232. Severson EA, et al. Blood (2018) pmid: 29678827
233. Fuster JJ, et al. Circ. Res. (2018) pmid: 29420212
234. Chabon JJ, et al. Nature (2020) pmid: 32269342
235. Razavi P, et al. Nat. Med. (2019) pmid: 31768066
236. Hegde M, et al. Genet. Med. (2014) pmid: 24310308
237. Aretz S, et al. Eur. J. Hum. Genet. (2013) pmid: 22872101
238. Win AK, et al. Gastroenterology (2014) pmid: 24444654
239. Lubbe SJ, et al. J. Clin. Oncol. (2009) pmid: 19620482
240. Jones N, et al. Gastroenterology (2009) pmid: 19394335
241. Nielsen M, et al. J. Natl. Cancer Inst. (2010) pmid: 21044966
242. David SS, et al. Nature (2007) pmid: 17581577
243. Molatore S, et al. Hum. Mutat. (2010) pmid: 19953527
244. Kundu S, et al. DNA Repair (Amst.) (2009) pmid: 19836313
245. D'Agostino VG, et al. DNA Repair (Amst.) (2010) pmid: 20418187
246. Ali M, et al. Gastroenterology (2008) pmid: 18534194
247. Sampson JR, et al. Lancet (2003) pmid: 12853198
248. Sieber OM, et al. N. Engl. J. Med. (2003) pmid: 12606733
249. Al-Tassan N, et al. Nat. Genet. (2002) pmid: 11818965
250. Rennert G, et al. Cancer (2012) pmid: 21952991
251. Zhang Y, et al. Cancer Epidemiol. Biomarkers Prev. (2006) pmid: 16492928
252. von der Thüsen JH, et al. J. Clin. Oncol. (2011) pmid: 21189386
253. Casper M, et al. Fam. Cancer (2014) pmid: 24420788
254. Smith LM, et al. Pancreatology (2009) pmid: 20110747
255. Ciriello G, et al. Cell (2015) pmid: 26451490
256. Nature (2014) pmid: 24476821
257. Nature (2015) pmid: 25631445
258. Jones DH, et al. Mol Clin Oncol (2017) pmid: 28781807
259. Kim SM, et al. Biochem. Biophys. Res. Commun. (2006) pmid: 16682010
260. Kang D, et al. Genes Chromosomes Cancer (2013) pmid: 23011637
261. Chen Y, et al. PLoS ONE (2014) pmid: 24874471
262. Morishita M, et al. Biochim. Biophys. Acta (2011) pmid: 21664949
263. Hirai H, et al. Cancer Biol. Ther. (2010) pmid: 20107315
264. Bridges KA, et al. Clin. Cancer Res. (2011) pmid: 21799033
265. Rajeshkumar NV, et al. Clin. Cancer Res. (2011) pmid: 21389100
266. Osman AA, et al. Mol. Cancer Ther. (2015) pmid: 25504633
267. Xu L, et al. Mol. Cancer Ther. (2002) pmid: 12489850
268. Xu L, et al. Mol. Med. (2001) pmid: 11713371
269. Camp ER, et al. Cancer Gene Ther. (2013) pmid: 23470564
270. Kim SS, et al. Nanomedicine (2015) pmid: 25240597
271. Pirollo KF, et al. Mol. Ther. (2016) pmid: 27357628
272. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27601554
273. Moore et al., 2019; ASCO Abstract 5513
274. Leijen S, et al. J. Clin. Oncol. (2016) pmid: 27998224
275. Oza et al., 2015; ASCO Abstract 5506
276. Lee J, et al. Cancer Discov (2019) pmid: 31315834
277. Méndez E, et al. Clin. Cancer Res. (2018) pmid: 29535125
278. Seligmann JF, et al. J Clin Oncol (2021) pmid: 34538072
279. Gourley et al., 2016; ASCO Abstract 5571
280. Park H, et al. ESMO Open (2022) pmid: 36084396
281. Gerlinger M, et al. Nat. Genet. (2014) pmid: 24487277
282. Nature (2013) pmid: 23792563
283. Guo G, et al. Nat. Genet. (2011) pmid: 22138691
284. Sato Y, et al. Nat. Genet. (2013) pmid: 23797736
285. Davis CF, et al. Cancer Cell (2014) pmid: 25155756
286. Szymańska K, et al. Cancer Lett. (2010) pmid: 20137853
287. Gad S, et al. Br. J. Cancer (2007) pmid: 17133269
288. de Velasco G, et al. Br. J. Cancer (2018) pmid: 29674707
289. Noon AP, et al. BJU Int. (2012) pmid: 21756282
290. Brown CJ, et al. Nat. Rev. Cancer (2009) pmid: 19935675
291. Joerger AC, et al. Annu. Rev. Biochem. (2008) pmid: 18410249
292. Kato S, et al. Proc. Natl. Acad. Sci. U.S.A. (2003) pmid: 12826609
293. Kamada R, et al. J. Biol. Chem. (2011) pmid: 20978130
294. Zerdoumi Y, et al. Hum. Mol. Genet. (2017) pmid: 28472496
295. Yamada H, et al. Carcinogenesis (2007) pmid: 17690113
296. Bougeard G, et al. J. Clin. Oncol. (2015) pmid: 26014290
297. Sorrell AD, et al. Mol Diagn Ther (2013) pmid: 23355100
298. Nichols KE, et al. Cancer Epidemiol. Biomarkers Prev. (2001) pmid: 11219776
299. Kleihues P, et al. Am. J. Pathol. (1997) pmid: 9006316
300. Gonzalez KD, et al. J. Clin. Oncol. (2009) pmid: 19204208
301. Lalloo F, et al. Lancet (2003) pmid: 12672316
302. Mandelker D, et al. Ann. Oncol. (2019) pmid: 31050713
303. Hematology Am Soc Hematol Educ Program (2018) pmid: 30504320
304. Zhang X, et al. PLoS ONE (2013) pmid: 23991038
305. Holland DG, et al. EMBO Mol Med (2011) pmid: 21337521
306. Sircoulomb F, et al. EMBO Mol Med (2011) pmid: 21328542
307. Reynisdottir I, et al. Cancer Med (2013) pmid: 24156016

308. Yang G, et al. Oncol. Rep. (2014) pmid: 24481460
309. Ma F, et al. Oncol. Rep. (2014) pmid: 25017610
310. Bazarov AV, et al. Breast Cancer Res. (2011) pmid: 21635707
311. Slorach EM, et al. Genes Dev. (2011) pmid: 21317240