FOUNDATIONONE®CDx

PATIENT
Huang, Tsung-Chi

TUMOR TYPE
Brain glioblastoma (GBM)
COUNTRY CODE
TW

REPORT DATE
21 Mar 2022
ORDERED TEST #
ORD-1321252-01

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 Brain glioblastoma (GBM)
NAME Huang, Tsung-Chi
DATE OF BIRTH 03 March 1960
SEX Male
MEDICAL RECORD # 48284522

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 Brain
SPECIMEN ID S111-08315C (PF22036)
SPECIMEN TYPE Slide Deck
DATE OF COLLECTION 02 March 2022
SPECIMEN RECEIVED 15 March 2022

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 1 Muts/Mb

Genomic Findings

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

EGFR R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa†
CDKN2A/B CDKN2B loss, CDKN2A loss
IKZF1 rearrangement exon 4
MTAP loss
TERT promoter -124C>T

2 Disease relevant genes with no reportable alterations: ***IDH1, PDGFRA***

† See About the Test in appendix for details.

Report Highlights

- Variants with **diagnostic implications** that may indicate a specific cancer type: ***EGFR* amplification** (p. 4), ***TERT* promoter -124C>T** (p. 8)
- Targeted therapies with potential clinical benefit **approved in another tumor type**: **Cetuximab** (p. 9), **Erlotinib** (p. 9), **Gefitinib** (p. 10), **Panitumumab** (p. 10)
- Evidence-matched **clinical trial options** based on this patient's genomic findings: (p. 11)
- Variants with **prognostic implications** for this tumor type that may impact treatment decisions: ***TERT* promoter -124C>T** (p. 8)

BIOMARKER FINDINGS

Microsatellite status - MS-Stable

Tumor Mutational Burden - 1 Muts/Mb

GENOMIC FINDINGS

***EGFR* -** R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

8 Trials *see p. 11*

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	Cetuximab
	Erlotinib
	Gefitinib
	Panitumumab

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

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Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
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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

Low-level MSI has been reported in 5-9% of glioblastoma (GBM) samples[6-8]. A large-scale study did not find high-level microsatellite instability (MSI-H) in any of 129 GBM samples[6], although a small-scale study reported MSI-H in 4 of 15 pediatric GBMs and 1 of 12 adult GBMs[9]. The frequency of MSI has been reported to be increased in relapsed compared to primary GBM[6], in GBMs with a previous lower grade astrocytoma[7], and in giant cell GBM compared to classic GBM[8].

FINDING SUMMARY

Microsatellite instability (MSI) is a condition of genetic hypermutability that generates excessive amounts of short insertion/deletion mutations in the genome; it generally occurs at microsatellite DNA sequences and is caused by a deficiency in DNA mismatch repair (MMR) in the tumor[10]. 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[10-12]. 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[13-15]. MSS status indicates MMR proficiency and typically correlates with intact expression of all MMR family proteins[10,12,14-15].

BIOMARKER

Tumor Mutational Burden

RESULT
1 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[16-18], anti-PD-1 therapies[16-19], and combination nivolumab and ipilimumab[20-25]. In glioma, a lack of association between TMB and clinical benefit from immune checkpoint inhibitors has been reported[16,26-27]. However, multiple case studies have reported that patients with ultramutated gliomas driven by POLE mutations have benefited from treatment with anti-PD-1[28-29] or anti-PD-L1[30] therapies. Therefore, although increased TMB alone may not be a strong biomarker for PD-1 or PD-L1 inhibitors in this cancer type, these agents may have efficacy for patients with glioma harboring both high TMB and POLE mutation.

FREQUENCY & PROGNOSIS

Glioblastoma (GBM) harbors a median TMB of 2.7 mutations per megabase (muts/Mb), and 4.2% of cases have high TMB (>20 muts/Mb)[31]. For pediatric patients, high TMB has been reported in a subset of high-grade gliomas, frequently in association with mutations in mismatch repair or proofreading genes and in TP53, whereas BRAF alterations or other oncogene fusions were observed more frequently in brain tumors harboring low TMB[32-33]. Increased TMB has been reported to correlate with higher tumor grade in glioma[34] and glioblastoma (GBM) tissue samples with biallelic mismatch repair deficiency (bMMRD)[28], as well as with shorter OS of patients with diffuse glioma[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 below levels that would be predicted to be associated with sensitivity to PD-1- or PD-L1-targeting immune checkpoint inhibitors, alone or in combination with other agents[16,26-30].

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GENE
EGFR

ALTERATION
R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

TRANSCRIPT ID
NM_005228

CODING SEQUENCE EFFECT
323G>A

VARIANT ALLELE FREQUENCY (% VAF)
0.86%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

In multiple glioblastoma (GBM) studies, the presence of EGFRvIII has not predicted clinical benefit from first-generation EGFR TKIs such as erlotinib[47-52] or gefitinib[50,53]. However, case reports have described patients with EGFRvIII-positive GBM responding to erlotinib[54-57]. In a retrospective study of patients with GBM treated with erlotinib or gefitinib, co-expression of EGFRvIII with PTEN protein was the strongest predictor of response (P<0.001)[58], suggesting that activity in this setting is dependent on PTEN status[59-60]. However, a prospective Phase 2 trial testing erlotinib monotherapy for patients with EGFRvIII and PTEN-positive recurrent glioblastoma reported minimal efficacy and was terminated[52]. The second-generation EGFR TKIs afatinib and dacomitinib have shown minimal efficacy for patients with EGFRvIII glioblastoma (GBM)[61-64]. A Phase 1/2 study of afatinib, temozolomide, or the combination for patients with GBM reported clinical benefit, including for patients with EGFRvIII; however, temozolomide alone and in combination exhibited better responses than afatinib monotherapy[61-62]. A Phase 2 trial of dacomitinib for patients with EGFR-amplified GBM reported a DCR of 26% (5/19) among patients with EGFR amplification and EGFRvIII; however, the trial failed to meet its primary endpoint of 6-month PFS[63]. A retrospective biomarker analysis of another Phase 2 study of dacomitinib for patients with GBM found no association between EGFRvIII and clinical benefit[64]. A patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFRvIII, experienced progression of the EGFRvIII-positive tumor during treatment with osimertinib[65]. Novel approaches that specifically target EGFRvIII in glioblastoma (GBM), such as the vaccine rindopepimut, are under investigation in both clinical and preclinical studies. A Phase 2 trial reported significant improvement in OS for patients with EGFRvIII-positive GBM with rindopepimut in combination with bevacizumab compared to bevacizumab alone (HR=0.53, p=0.01)[66]. However, a Phase 3 study of rindopepimut combined with temozolomide compared to temozolomide alone in newly diagnosed EGFRvIII-positive GBM patients was terminated after the interim analysis, due to a lack of clinical benefit as measured by OS (20 vs. 20 months)[67]. For patients with non-small cell lung cancer, EGFR activating mutations may predict sensitivity to EGFR TKIs, including erlotinib[68], gefitinib[69], afatinib[70], dacomitinib[71], and osimertinib[72]; however, the data for patients with other tumor types are limited[64,73-77]. A case study of a patient with multiple glioblastoma (GBM) tumors, one of which harbored EGFR amplification and multiple missense mutations, reported a near-CR of the EGFR-amplified and -mutated tumor to osimertinib[65]. A case series of 11 patients with bithalamic gliomas with EGFR mutations suggested that treatment with EGFR inhibitors, including osimertinib, prolonged patient survival relative to other types of treatment; however, no patients attained PR or SD[76]. Another case series of 2 patients with osimertinib-treated bithalamic gliomas with EGFR exon 20 insertion mutations reported that one patient experienced no progression at 4 months of treatment and that another patient did not progress until after 6 months of treatment[78]. Clinical studies of the second-generation EGFR TKIs afatinib and dacomitinib for patients with EGFR-amplified gliomas have shown limited efficacy[61,63-64,79-80]; however, a small subset of patients has experienced clinical benefit[63-64,79]. Multiple studies have failed to find a positive association between increased EGFR expression and clinical benefit from erlotinib or gefitinib for patients with glioblastoma[58,81-83]. There are conflicting data on the efficacy of anti-EGFR antibodies for the treatment of EGFR-amplified tumors. A meta-analysis of colorectal cancer patients treated with second-line or higher cetuximab or panitumumab observed an association between EGFR copy number gain and increased OS and PFS[84]. However, studies in head and neck squamous cell carcinoma and gastric cancer found either no association or a negative association between EGFR copy number gain and survival after treatment with first-line cetuximab or panitumumab in combination with chemotherapy[85-86]. The Phase 3 INTELLANCE trial of depatuxizumab mafodotin (ABT-414), an EGFR-targeted antibody-drug conjugate with a toxic payload, in patients with EGFR-amplified glioblastoma (GBM) was stopped for futility. Interim analysis demonstrated improved median PFS (mPFS) of ABT-414 monotherapy compared with placebo (HR=0.84); however, no OS benefit was observed (HR=1.01). Improved mPFS was also observed in patients harboring EGFRvIII (HR=0.73) but without an OS improvement (HR=0.95)[87]. The Phase 2 INTELLANCE trial demonstrated clinical benefit for EGFR-amplified GBM for the combination of ABT-414, temozolomide, and radiotherapy (HR=0.66, p=0.017), but there was no evidence of efficacy for ABT-414 monotherapy (HR=1.04, p=0.83)[88].

FREQUENCY & PROGNOSIS

Across several genomic studies of CNS tumors, EGFR amplification has been reported in 16.9% of anaplastic astrocytomas, and 39.7% of glioblastoma multiformes (GBMs)[89-92]. Across several genomic studies of CNS tumors, EGFR alterations have been reported in 13.2% of anaplastic astrocytomas, 5.3-15.9% of glioblastoma multiformes (GBMs), and 0% of pilocytic astrocytomas[89-92]. In the glioblastoma (GBM) TCGA dataset, putative high-level amplification of EGFR has been found in 48% of cases and mutation has been found in 21% of cases[90]. Missense mutations in the EGFR extracellular domain have been found in 10-15% of GBMs and approximately half have a low-level amplification of the mutated allele[93-94]. One study detected EGFR alterations in 50% (117/232) of IDH-wildtype GBM samples analyzed, including 41% (95/232) with a co-occurring EGFR amplification and mutation, 26% (61/232) with an EGFR domain truncation event, such as EGFRvIII, and 2.2% (5/232) with an EGFR fusion event[95]. EGFRvIV alteration has been reported in 7 out of 35 high-grade glioma tumors (EGFRvIVa - 5/7 and EGFRvIVb - 2/7)[96]. The EGFRvIII mutation has been variously reported in 6-46% of GBM samples[58,96-103]. No definitive correlation has been identified between EGFR amplification and length of survival in patients with GBM[104-105]; however, EGFR amplification has been associated with prolonged survival in patients over the age of 60 with GBM[106]. The link between EGFRvIII status and prognosis is unclear, although some studies suggest that it may be linked to improved survival and response to chemotherapy[107].

FINDING SUMMARY

EGFR encodes the epidermal growth factor

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receptor, which belongs to a class of proteins called receptor tyrosine kinases. In response to signals from the environment, EGFR passes biochemical messages to the cell that stimulate it to grow and divide[108]. Amplification of EGFR has been associated with increased expression of EGFR mRNA and protein in several cancer types[109-111]. A mutation of the EGFR gene, referred to as EGFRvIII, results from a gene rearrangement that deletes exons 2-7. This alteration causes an in-frame deletion of 801 base pairs encoding part of the extracellular ligand-binding domain[97]. This deletion has shown to result in ligand-independent (constitutive) phosphorylation and activation of EGFR, as well as consequent tumorigenesis[97,112]. The EGFR rearrangement seen here is an EGFR kinase domain duplication (EGFR-KDD). EGFR-KDDs, including in-frame tandem duplications of exons 18-25 or exons 18-26, have been shown to be activating and oncogenic[113-116]. Other EGFR-KDD alterations, such as duplication of exons 17-25 or exons 14-26, have been observed in patients with lung adenocarcinoma or lung squamous cell carcinoma, respectively[117]. A patient with lung adenocarcinoma with an EGFR exon 18-25 duplication had a PR to afatinib[113]. The variants EGFRvIVa and EGFRvIVb lack exons 25-27 and exons 25-26, respectively, resulting in truncation downstream of the protein kinase domain[118]. C-terminal truncations of EGFR, including EGFRvIVa, EGFRvIVb, truncation at amino acids 1056 (deletion of exon 27), and deletion of residues 1010-1152 have been reported to lead to cellular transformation and tumor formation in mouse xenografts, and to be sensitive to EGFR-targeting therapies, including erlotinib and cetuximab[118-120]. EGFR mutations that have been characterized in biochemical assays to be activating, as observed here, are predicted to confer sensitivity to EGFR-targeted therapies[93,121-137].

POTENTIAL DIAGNOSTIC IMPLICATIONS

The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[138].

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GENE
CDKN2A/B

ALTERATION
CDKN2B loss, CDKN2A 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[139-142]. Although case studies have reported that patients with breast cancer or uterine leiomyosarcoma harboring CDKN2A loss responded to palbociclib treatment[143-144], multiple other clinical studies have shown no significant correlation between p16INK4a loss or inactivation and therapeutic benefit of these agents[145-151]; it is not known whether CDK4/6 inhibitors would be beneficial in this case. Although preclinical studies have suggested that loss of p14ARF function may be associated with reduced sensitivity to MDM2 inhibitors[152-153], the clinical relevance of p14ARF as a predictive biomarker is not clear. There are no drugs that directly target the mutation or loss of CDKN2B in cancer. Because the p15INK4b protein encoded by CDKN2B is known to inhibit CDK4, tumors with CDKN2B mutation or loss may predict sensitivity to CDK4/6 inhibitors, such as ribociclib, abemaciclib, and palbociclib[146,148-149,154-156].

FREQUENCY & PROGNOSIS

Concurrent putative homozygous deletion of CDKN2A and CDKN2B has been reported in 35% of patients with gliomas[91] and detected more frequently in patients with glioblastoma multiforme (GBM; 58%)[90] than in those with lower grade gliomas (13%) (cBioPortal, Sep 2021)[157-158]. In other studies, loss of CDKN2A/B by deletion has been reported in up to 78% of astrocytomas (including anaplastic astrocytomas and GBM)[103,159-160]. A study found homozygous deletion of both p16INK4a and p14ARF in 26% (13/50) of glioblastomas (GBMs); 18% (9/50) of cases showed homozygous deletion of the p14ARF-encoding locus alone[161]. One study detected CDKN2A/B loss in 69% (161/232) and mutation in 2.6% (6/232) of IDH-wildtype GBM samples analyzed[95]. Decreased p14ARF and p16INK4a expression levels were found to be tightly associated in a study of glioma samples[162]. Homozygous deletion of the genomic region including CDKN2A and CDKN2B has been found to be associated with poor prognosis in GBM and likely serves as an early event in GBM progression[159,163]. In addition, expression of p16INK4a has been found to be lower in patients with high grade malignant gliomas compared to patients with low grade gliomas, and loss of p16INK4a expression has been associated with shorter overall survival in pilocytic astrocytomas[164-165].

FINDING SUMMARY

CDKN2A encodes two different, unrelated tumor suppressor proteins, p16INK4a and p14ARF, whereas CDKN2B encodes the tumor suppressor p15INK4b[166-167]. 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[168-169]. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via a mechanism of MDM2 inhibition[170-171]. One or more alterations observed here are predicted to result in p16INK4a loss of function[172-193]. One or more alterations seen here are predicted to result in p14ARF loss of function[176,193-196]. CDKN2B alterations such as seen here are predicted to inactivate p15INK4b[197].

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[198]. Mutation carriers within families may develop either or both types of cancer, and melanoma cases may be referred to as familial or hereditary melanoma[199-200]. CDKN2A is the most implicated gene in familial melanoma, with germline mutations present in 16% to 20% of familial melanoma cases[201-203]. 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[204-206]. In the appropriate clinical context, germline testing of CDKN2A is recommended.

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GENE
IKZF1

ALTERATION
rearrangement exon 4

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

There are no therapeutic options to directly target IKZF1 alterations. Preclinical studies have reported that the immunomodulatory therapy lenalidomide, which is approved in certain hematological malignancies, causes degradation of Ikaros and Aiolos (encoded by IKZF3); degradation of these transcription factors has been shown to be necessary and sufficient for the activity of lenalidomide[207-209]. However, it is unknown whether this approach is relevant for solid tumors with IKZF1 alterations (PubMed, Jan 2022).

FREQUENCY & PROGNOSIS

IKZF1 alterations occur at a relatively low frequency in various solid tumor types, including cutaneous melanoma (up to 7%)[210-211], lung adenocarcinoma (up to 7%)[120,212], uterine endometrioid carcinoma (5%)[42], stomach adenocarcinoma (4%)[213-214], colorectal adenocarcinoma (2-3%)[45,215], and small cell lung cancer (up to 3%)[216-217], but the functional and prognostic impact of IKZF1 alterations in solid tumors has not been established[218-221]. IKZF1 alterations have been predominantly studied in the context of acute lymphoblastic leukemia (ALL) and have been found in 15% of pediatric B-cell ALL cases and more than 70% of BCR-ABL1-positive ALL cases[222-224]. IKZF1 deletions have been associated with poor outcomes in ALL, including reduced overall survival and increased risk of recurrence[225-228].

FINDING SUMMARY

IKZF1 encodes the Ikaros family zinc finger protein 1, a transcription factor and chromatin remodeling protein that is considered to be a tumor suppressor[229-230]. IKZF1 alterations that result in disruption or loss of the zinc-finger motifs (amino acids 117-514) are predicted to lead to a loss of Ikaros function[230-232].

GENE
MTAP

ALTERATION
loss

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Preclinical and limited clinical evidence indicate that MTAP inactivation produces specific metabolic vulnerabilities. MTAP inactivation may confer sensitivity to MAT2A inhibitors[233]. 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[234]. Although preclinical data have suggested that MTAP loss sensitizes cells to PRMT5 inhibition[233,235-236], MTAP loss may not be a biomarker of response to previously developed small-molecule SAM-uncompetitive PRMT5 inhibitors[237]; dual PRMT1 and PRMT5 inhibition may be more effective[238-240]. In preclinical cancer models, MTAP inactivation showed increased sensitivity to inhibitors of purine synthesis or purine analogs, especially upon addition of exogenous MTA, which is converted to adenine in normal cells, thereby providing competition to purine poisons lacking in MTAP-deficient cells[241-251]. 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 stable disease in 23.6% (13/55) of patients[252].

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[253-254]; such events have been correlated with poor prognosis in a variety of cancer types, including hepatocellular carcinoma[255], gastrointestinal stromal tumors[256], mantle cell lymphoma (MCL)[257], melanoma[258-259], gastric cancer[260], myxofibrosarcoma[261], nasopharyngeal carcinoma[262], ovarian carcinoma[253] and non-small cell lung cancer[263]. MTAP loss was not prognostic in pediatric B-cell acute lymphocytic leukemia[264] or in astrocytoma[265]. However, MTAP has also been reported to be overexpressed in colorectal cancer (CRC) samples[266], and MTAP retention is thought to be important for prostate cancer growth due to continuous supply of SAM[267]. Germline SNPs in MTAP have been correlated with the development of cutaneous melanoma[268-269], esophageal cancer[270-271], osteosarcoma[272], and CRC[273].

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[274-275]. Decreased expression of MTAP leads to MTA accumulation within tumor cells and their microenvironment[255,276-277], thereby reducing intracellular arginine methylation[233,235,278] and altering cell signaling[277,279]. 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.

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GENE
TERT

ALTERATION
promoter -124C>T

TRANSCRIPT ID
NM_198253

CODING SEQUENCE EFFECT
-124C>T

VARIANT ALLELE FREQUENCY (% VAF)
44.0%

POTENTIAL TREATMENT STRATEGIES

— Targeted Therapies —

Therapeutic options for targeting tumors with TERT mutations are limited, although a variety of approaches have been investigated, including immunotherapies using TERT as a tumor-associated antigen and antisense oligonucleotide- or peptide-based therapies. TERT peptide vaccines showed limited anticancer efficacy in clinical trials[280]; however, in one preclinical study, the combination of a TERT peptide vaccine and anti-CTLA-4 therapy suppressed tumor growth[281]. A Phase 2 study of the TERT inhibitor imetelstat for patients with advanced non-small cell lung cancer reported no improvement in PFS or OS[282].

FREQUENCY & PROGNOSIS

TERT promoter mutations have been reported in 51-59% of gliomas[283-284], most frequently in glioblastoma (GBM, 54-84%), gliosarcoma (81%), oligodendroglioma (78%), and historically in oligoastrocytomas (25-31%) but less frequently in lower grade astrocytomas (10-18%) and in only 1% of ependymomas[283-287]. In patients with glioblastoma (GBM), the prevalence of TERT promoter mutation is lower in pediatric primary GBM (11%) and adult secondary GBM (28%) compared with adult primary GBM (58-83%)[283,285]. One study detected TERT promoter mutations in 78% (181/232) of IDH-wildtype GBM samples analyzed[95]. TERT promoter mutation has been shown to be significantly associated with increased TERT gene expression in astrocytoma, oligodendroglioma, and GBM[288]. TERT promoter mutations significantly associate with poor prognosis in patients with GBM, although this correlation may be due to the association with primary GBM as opposed to IDH-positive secondary GBM[283,285,288-289]. In the context of IDH-wildtype glioma, TERT mutations are associated with reduced OS (NCCN CNS Cancers Guidelines, v2.2021).

FINDING SUMMARY

Telomerase reverse transcriptase (TERT, or hTERT) is a catalytic subunit of the telomerase complex, which is required to maintain appropriate chromosomal length[290]. Activation of TERT is a hallmark of cancer, being detected in up to 80-90% of malignancies and absent in quiescent cells[291-293]. Mutations within the promoter region of TERT that confer enhanced TERT promoter activity have been reported in two hotspots, located at -124 bp and -146 bp upstream of the transcriptional start site (also termed C228T and C250T, respectively)[294-296], as well as tandem mutations at positions –124/–125 bp and –138/–139 bp[294].

POTENTIAL DIAGNOSTIC IMPLICATIONS

TERT mutations are associated with 1p/19q co-deletion in oligodendrogliomas, and are highly recurrent in IDH/ATRX-wildtype glioblastoma (GBM) (NCCN CNS Cancers Guidelines, v2.2021)[297]. The presence of EGFR gene amplification or TERT promoter mutations are indicative of diffuse astrocytic glioma with molecular features of glioblastoma, WHO grade 4 in IDH1/2-wildtype tumors (NCCN CNS Cancers Guidelines, v2.2021)[138].

Electronically signed by Erik Williams, M.D. | 21 March 2022
Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

Sample Preparation: 150 Second St., 1st Floor, Cambridge, MA 02141 · CLIA: 22D2027531
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Cetuximab

Assay findings association

EGFR
R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

AREAS OF THERAPEUTIC USE

Cetuximab is a monoclonal antibody that targets EGFR. It is FDA approved for the treatment of head and neck squamous cell carcinoma (HNSCC) and KRAS-wild-type, EGFR-expressing metastatic colorectal cancer (CRC). Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[84].

SUPPORTING DATA

A clinical trial of cetuximab with bevacizumab (an anti-VEGF monoclonal antibody) in patients with glioblastoma (GBM) did not show improved efficacy compared with bevacizumab alone[298]. In preclinical trials, cetuximab, matuzumab, and panitumumab were reported to be ineffective at blocking EGFR dimerization and activation in GBM cells expressing EGFR extracellular domain mutations[299]. However, another study demonstrated that in patients with GBM harboring EGFR amplification but lacking expression of the EGFRvIII variant, treatment with cetuximab resulted in significantly better progression-free survival (PFS) and numerical (although not statistically significant) improvement in overall survival (OS)[96]. A Phase 3 trial of combined cetuximab and platinum/5-FU in patients with HNSCC demonstrated improved response compared to platinum/5-FU alone, but EGFR amplification was not shown to predict response to this treatment[85]. A Phase 3 study of patients with pancreatic adenocarcinoma did not report any improved outcome in patients treated with a combination of cetuximab plus gemcitabine vs gemcitabine alone[300]. In a Phase 1/2 trial of 36 patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cetuximab in combination with doxorubicin, stable disease was reported in approximately 63% of patients[301]. A Phase 1 study of the combination therapy of cetuximab, erlotinib, and bevacizumab reported stable disease in 21% (7/34) of patients with non-small cell lung cancer (NSCLC)[302].

Erlotinib

Assay findings association

EGFR
R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

AREAS OF THERAPEUTIC USE

Erlotinib is a small-molecule inhibitor of EGFR. It is FDA approved as a monotherapy or in combination with ramucirumab for patients with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21 (L858R) mutations. Erlotinib is also FDA approved in combination with gemcitabine as a first-line treatment for advanced pancreatic cancer. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Amplification or activation of EGFR may predict sensitivity to therapies such as erlotinib. Responses to erlotinib have been reported for patients with EGFR rearrangements[116-117,303-305] . For patients with activating mutations in EGFR, treatment with erlotinib has been associated with improved response and lengthened time to progression[68,306-308] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[309-313] .

SUPPORTING DATA

In the MyPathway Phase 2a basket study for advanced solid tumors, 1 of 9 patients with EGFR activation mutations responded to erlotinib monotherapy; the responding patient had urethral adenocarcinoma[314]. A patient with EGFR-mutated metastatic lacrimal gland adenoid cystic carcinoma experienced clinical benefit from erlotinib treatment that was ongoing at 14 months[315]. A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. In a Phase 2 study of 65 patients with GBM or gliosarcoma, treatment with erlotinib, temozolomide, and radiotherapy resulted in longer progression-free survival relative to a historical control study utilizing a regimen of temozolomide and radiotherapy alone (19.3 months vs. 14.1 months)[316]. However, in a Phase 1/2 trial of erlotinib monotherapy in 11 patients with relapsed or refractory GBM or anaplastic astrocytoma, all patients showed disease progression and the drug showed significant toxicity[317]. In addition, a Phase 2 trial of patients with recurrent or progressive GBM treated with erlotinib and sorafenib did not meet its objective of a 30% increase in overall survival time compared with historical controls; sorafenib was found to increase erlotinib clearance[318].

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Gefitinib

Assay findings association

EGFR
R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

AREAS OF THERAPEUTIC USE

Gefitinib targets the tyrosine kinase EGFR and is FDA approved to treat non-small cell lung cancer (NSCLC) harboring exon 19 deletions or exon 21 (L858R) substitution mutations in EGFR. Please see the drug label for full prescribing information.

GENE ASSOCIATION

Activation of EGFR may predict sensitivity to therapies such as gefitinib. Clinical studies have consistently shown significant improvement in response rates and PFS for patients with EGFR-mutated non-small cell lung cancer (NSCLC) treated with gefitinib compared with chemotherapy[308,319-324] , and responses have been reported for patients with EGFR-rearranged NSCLC[116-117] . For patients with esophageal or biliary cancer treated with erlotinib or gefitinib, elevated EGFR copy number or amplification is associated with clinical responses and longer survival[309-313] . Patients with refractory advanced esophageal carcinoma and EGFR amplification derived significant overall survival benefit from gefitinib compared to placebo (HR = 0.21)[309,325] .

SUPPORTING DATA

A clinical study of patients with glioblastoma (GBM) treated with gefitinib or erlotinib found that 9/49 (18%) had tumor shrinkage of 25% or more; in this study, the extracellular domain EGFRvIII mutation was correlated with response[58]. A Phase 2 clinical study of gefitinib in patients with high-grade glioma (including GBM, anaplastic astrocytoma, and oligodendroglioma) reported 18% (5/28) disease stabilization; efficacy was not correlated with EGFR expression[81]. However, a Phase 1/2 clinical trial of gefitinib combined with radiotherapy in 178 patients with GBM reported no overall survival benefit of added gefitinib, and EGFR expression was found to be of no prognostic value for patients treated with gefitinib plus radiotherapy[82]. A Phase 2 trial of preoperative gefitinib treatment in patients with recurrent GBM reported that although EGFR phosphorylation was decreased in treated patients as compared to the control group, measurement of 12 downstream molecules revealed no significant changes[83].

Panitumumab

Assay findings association

EGFR
R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

AREAS OF THERAPEUTIC USE

Panitumumab is a monoclonal antibody that targets EGFR. It is FDA approved to treat KRAS wild-type and NRAS wild-type metastatic colorectal cancer (CRC) combined with chemotherapy or as monotherapy for patients who have progressed on prior chemotherapy. Please see the drug label for full prescribing information.

GENE ASSOCIATION

For patients with metastatic CRC receiving cetuximab or panitumumab as mono- or combination therapy, increased EGFR copy number associated with improved OS (HR=0.62) in a meta-analysis, although increased survival was not seen in populations that received first-line treatment with EGFR antibodies[84].

SUPPORTING DATA

A Phase 1 trial of EnGeneIC delivery vehicle (EDV) targeting EGFR with panitumumab in combination with doxorubicin for 14 patients with glioblastoma (GBM) reported no responses and 28% (4/14) SDs[326]. Panitumumab has shown efficacy as monotherapy or in combination with chemotherapy for patients with KRAS-wildtype colorectal cancer[327-329] and has been investigated in a variety of other tumor types. For patients with head and neck squamous cell carcinoma (HNSCC), data are conflicting; some trials of panitumumab in various lines and with different chemotherapy combinations have shown modest benefit[330-332] and others have reported no benefit[333-335] . A Phase 3 study of chemotherapy with or without panitumumab for patients with advanced gastroesophageal cancer was terminated for futility[336]. Trials in a variety of tumor types have failed to show significant benefit for patients, including non-small cell lung cancer (NSCLC)[337-338] ; biliary tract cancers, including cholangiocarcinoma[339-340] ; and renal cell carcinoma (RCC)[341].

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

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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

EGFR

ALTERATION

R108K - subclonal, amplification, EGFRvIII, kinase domain duplication, EGFRvIVa

RATIONALE

EGFR activating mutations, rearrangements, or amplification may predict sensitivity to EGFR-targeted therapies. Strategies to overcome resistance to current agents include next-generation EGFR inhibitors and combination therapies.

NCT03239015

PHASE 2

Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event

TARGETS
EGFR, ERBB4, ERBB2, PARP, mTOR, MET, ROS1, RET, VEGFRs, BRAF, CDK4, CDK6

LOCATIONS: Shanghai (China)

NCT03783403

PHASE 1

A Study of CC-95251, a Monoclonal Antibody Directed Against SIRPα, in Subjects With Advanced Solid and Hematologic Cancers

TARGETS
CD20, EGFR, SIRP-alpha

LOCATIONS: Heidelberg (Australia), Melbourne (Australia), Edmonton (Canada), Oregon, California, Arizona, Toronto (Canada), Oklahoma, Missouri, Pennsylvania

NCT03810872

PHASE 2

An Explorative Study of Afatinib in the Treatment of Advanced Cancer Carrying an EGFR, a HER2 or a HER3 Mutation

TARGETS
EGFR, ERBB4, ERBB2

LOCATIONS: Liège (Belgium), Brussels (Belgium), Gent (Belgium)

NCT03618667

PHASE 2

GC1118 in Recurrent Glioblastoma Patients With High EGFR Amplification

TARGETS
EGFR

LOCATIONS: Seoul (Korea, Republic of)

NCT04172597

PHASE 2

A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies

TARGETS
EGFR, ERBB2, ERBB4

LOCATIONS: California

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NCT02800486

PHASE 2

Super Selective Intra-arterial Repeated Infusion of Cetuximab (Erbitux) With Reirradiation for Treatment of Relapsed/Refractory GBM, AA, and AOA

TARGETS
EGFR

LOCATIONS: New York

NCT02861898

PHASE 1/2

Super-selective Intra-arterial Repeated Infusion of Cetuximab for the Treatment of Newly Diagnosed Glioblastoma

TARGETS
EGFR

LOCATIONS: New York

NCT02303678

PHASE 1

D2C7 for Adult Patients With Recurrent Malignant Glioma

TARGETS
EGFRvIII

LOCATIONS: North Carolina

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.

ALK	***ARID1A***	***FGFR4***	***PIK3CB***
S737L	G1375A	D709G	N217D

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APPENDIX Genes Assayed in FoundationOne®CDx

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*	*ETV1*
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. 2022. 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 fractional-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. 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%.

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

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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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

MR Suite Version 6.1.0

The median exon coverage for this sample is 842x

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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. Martinez R, et al. Oncology (2004) pmid: 15331927
7. Martinez R, et al. J. Cancer Res. Clin. Oncol. (2005) pmid: 15672285
8. Martinez R, et al. Cancer Genet. Cytogenet. (2007) pmid: 17498554
9. Szybka M, et al. Clin. Neuropathol. () pmid: 12908754
10. Kocarnik JM, et al. Gastroenterol Rep (Oxf) (2015) pmid: 26337942
11. You JF, et al. Br. J. Cancer (2010) pmid: 21081928
12. Bairwa NK, et al. Methods Mol. Biol. (2014) pmid: 24623249
13. Boland CR, et al. Cancer Res. (1998) pmid: 9823339
14. Pawlik TM, et al. Dis. Markers (2004) pmid: 15528785
15. Boland CR, et al. Gastroenterology (2010) pmid: 20420947
16. Samstein RM, et al. Nat. Genet. (2019) pmid: 30643254
17. Goodman AM, et al. Mol. Cancer Ther. (2017) pmid: 28835386
18. Goodman AM, et al. Cancer Immunol Res (2019) pmid: 31405947
19. Cristescu R, et al. Science (2018) pmid: 30309915
20. Ready N, et al. J. Clin. Oncol. (2019) pmid: 30785829
21. Hellmann MD, et al. N. Engl. J. Med. (2018) pmid: 29658845
22. Hellmann MD, et al. Cancer Cell (2018) pmid: 29657128
23. Hellmann MD, et al. Cancer Cell (2018) pmid: 29731394
24. Rozeman EA, et al. Nat Med (2021) pmid: 33558721
25. Sharma P, et al. Cancer Cell (2020) pmid: 32916128
26. Zhao J, et al. Nat. Med. (2019) pmid: 30742119
27. Touat M, et al. Nature (2020) pmid: 32322066
28. Bouffet E, et al. J. Clin. Oncol. (2016) pmid: 27001570
29. Johanns TM, et al. Cancer Discov (2016) pmid: 27683556
30. Lukas RV, et al. J. Neurooncol. (2018) pmid: 30073642
31. Chalmers ZR, et al. Genome Med (2017) pmid: 28420421
32. Patel RR, et al. Pediatr Blood Cancer (2020) pmid: 32386112
33. Johnson A, et al. Oncologist (2017) pmid: 28912153
34. Draaisma K, et al. Acta Neuropathol Commun (2015) pmid: 26699864
35. Wang L, et al. BMC Cancer (2020) pmid: 32164609
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. van den Bent MJ, et al. J Clin Oncol (2009) pmid: 19204207
48. Haas-Kogan DA, et al. J Natl Cancer Inst (2005) pmid: 15956649
49. Brown PD, et al. J Clin Oncol (2008) pmid: 18955445
50. Preusser M, et al. J Neurooncol (2008) pmid: 18458820
51. Wen PY, et al. Neuro-oncology (2014) pmid: 24470557
52. Gallego O, et al. J Neurooncol (2014) pmid: 24352766
53. Uhm JH, et al. Int J Radiat Oncol Biol Phys (2011) pmid: 20510539
54. Doyle SP, et al. Oxf Med Case Reports (2018) pmid: 30410775
55. D'Alessandris QG, et al. Acta Neurochir (Wien) (2013) pmid: 23132371
56. Custodio A, et al. Clin Transl Oncol (2010) pmid: 20462843
57. D'Alessandris QG, et al. Acta Neurochir (Wien) (2018) pmid: 30306271
58. Mellinghoff IK, et al. N. Engl. J. Med. (2005) pmid: 16282176
59. Mellinghoff IK, et al. Clin Cancer Res (2007) pmid: 17255257
60. Arif SH, et al. Asian J Neurosurg () pmid: 29492119
61. Reardon DA, et al. Neuro-oncology (2015) pmid: 25140039
62. Alshami J, et al. Oncotarget (2015) pmid: 26423602
63. Sepúlveda-Sánchez JM, et al. Neuro-oncology (2017) pmid: 28575464
64. Chi AS, et al. JCO Precis Oncol (2020) pmid: 32923886
65. Makhlin I, et al. CNS Oncol (2019) pmid: 31769726
66. Reardon DA, et al. Clin Cancer Res (2020) pmid: 32034072
67. Weller M, et al. Lancet Oncol (2017) pmid: 28844499
68. Rosell R, et al. Lancet Oncol. (2012) pmid: 22285168
69. Douillard JY, et al. Br. J. Cancer (2014) pmid: 24263064
70. Sequist LV, et al. J. Clin. Oncol. (2013) pmid: 23816960
71. Mok TS, et al. J. Clin. Oncol. (2018) pmid: 29864379
72. Jänne PA, et al. N. Engl. J. Med. (2015) pmid: 25923549
73. Hong MH, et al. Cancer (2020) pmid: 32749686
74. Kim HS, et al. Oncotarget (2015) pmid: 26462025
75. Kim HS, et al. Clin. Cancer Res. (2015) pmid: 25424851
76. Mondal G, et al. Acta Neuropathol (2020) pmid: 32303840
77. Cavalieri S, et al. Eur. J. Cancer (2018) pmid: 29734047
78. Goyal A, et al. World Neurosurg (2021) pmid: 33940677
79. Tanaka S, et al. Sci Rep (2019) pmid: 30644426
80. Blumenthal DT, et al. J. Neurooncol. (2016) pmid: 27531351
81. Franceschi E, et al. Br. J. Cancer (2007) pmid: 17353924
82. Chakravarti A, et al. Int. J. Radiat. Oncol. Biol. Phys. (2013) pmid: 23182702
83. Hegi ME, et al. Mol. Cancer Ther. (2011) pmid: 21471286
84. Jiang Z, et al. PLoS ONE (2013) pmid: 23441167
85. Licitra L, et al. Ann. Oncol. (2011) pmid: 21048039
86. Smyth EC, et al. Gut (2021) pmid: 33199443
87. Lassman et al., 2019; Neuro-Oncology Abstract ACTR-21
88. Van Den Bent M, et al. Neuro Oncol (2020) pmid: 31747009
89. Jonsson P, et al. Clin. Cancer Res. (2019) pmid: 31263031
90. Brennan CW, et al. Cell (2013) pmid: 24120142
91. Ceccarelli M, et al. Cell (2016) pmid: 26824661
92. Thomas AA, et al. Neuro-oncology (2017) pmid: 28472509
93. Lee JC, et al. PLoS Med. (2006) pmid: 17177598
94. Vivanco I, et al. Cancer Discov (2012) pmid: 22588883
95. Yan et al. 2020; DOI:10.1200/PO.19.00385
96. Lv S, et al. Int. J. Oncol. (2012) pmid: 22752145
97. Nishikawa R, et al. Proc. Natl. Acad. Sci. U.S.A. (1994) pmid: 8052651
98. Shinojima N, et al. Cancer Res. (2003) pmid: 14583498
99. Nishikawa R, et al. Brain Tumor Pathol (2004) pmid: 15700833
100. Viana-Pereira M, et al. Anticancer Res. () pmid: 18507036
101. Yoshimoto K, et al. Clin. Cancer Res. (2008) pmid: 18223223
102. Larysz D, et al. Folia Neuropathol (2011) pmid: 21455841
103. Verhaak RG, et al. Cancer Cell (2010) pmid: 20129251
104. Srividya MR, et al. J. Clin. Pathol. (2010) pmid: 20702468
105. Das P, et al. J Clin Neurosci (2011) pmid: 20888234
106. Smith JS, et al. J. Natl. Cancer Inst. (2001) pmid: 11504770
107. Montano N, et al. Neoplasia (2011) pmid: 22241957
108. Ciardiello F, et al. N. Engl. J. Med. (2008) pmid: 18337605
109. Liang Z, et al. BMC Cancer (2010) pmid: 20637128
110. Bhargava R, et al. Mod. Pathol. (2005) pmid: 15920544
111. Yang YL, et al. Chin. Med. J. (2012) pmid: 22490401
112. Nedergaard MK, et al. BioDrugs (2012) pmid: 22385404
113. Gallant JN, et al. Cancer Discov (2015) pmid: 26286086
114. Ciesielski MJ, et al. Oncogene (2000) pmid: 10698499
115. Ozer BH, et al. Oncogene (2010) pmid: 19915609
116. Baik CS, et al. J Thorac Oncol (2015) pmid: 26398831
117. Wang J, et al. Int. J. Cancer (2019) pmid: 30255937
118. Pines G, et al. Oncogene (2010) pmid: 20676128
119. Cho J, et al. Cancer Res. (2011) pmid: 22001862
120. Imielinski M, et al. Cell (2012) pmid: 22980975
121. Foster JM, et al. World J Surg Oncol (2010) pmid: 20942962
122. Cai CQ, et al. Oncogene (2008) pmid: 18193092
123. Stabile LP, et al. Cancer Res. (2005) pmid: 15735034
124. Zhang W, et al. J Thorac Oncol (2006) pmid: 17409930
125. Siegfried JM, et al. J Thorac Oncol (2012) pmid: 22258476
126. U M, et al. PLoS Comput. Biol. (2014) pmid: 24743239
127. Cho J, et al. Mol. Cancer (2014) pmid: 24894453
128. Hama T, et al. Oncologist (2009) pmid: 19726454
129. Tam IY, et al. Mol. Cancer Ther. (2009) pmid: 19671738
130. Kancha RK, et al. Clin. Cancer Res. (2009) pmid: 19147750
131. Chen YR, et al. Oncogene (2006) pmid: 16205628
132. Ymer SI, et al. Cancers (Basel) (2011) pmid: 24212795
133. Razis E, et al. Clin. Cancer Res. (2009) pmid: 19789313
134. Wang H, et al. Neoplasia (2011) pmid: 21532887
135. Kim N, et al. Int. J. Cancer (2019) pmid: 31290142
136. Sueangoen N, et al. Cell Biosci (2020) pmid: 32190291
137. Lundby A, et al. Cell (2019) pmid: 31585087
138. Louis DN, et al. Neuro Oncol (2021) pmid: 34185076
139. Konecny GE, et al. Clin. Cancer Res. (2011) pmid: 21278246
140. Katsumi Y, et al. Biochem. Biophys. Res. Commun. (2011) pmid: 21871868
141. Cen L, et al. Neuro-oncology (2012) pmid: 22711607
142. Logan JE, et al. Anticancer Res. (2013) pmid: 23898052
143. Elvin JA, et al. Oncologist (2017) pmid: 28283584
144. Gao J, et al. Curr Oncol (2015) pmid: 26715889
145. Gopalan et al., 2014; ASCO Abstract 8077
146. Peguero et al., 2016; ASCO Abstract 2528
147. Konecny et al., 2016; ASCO Abstract 5557
148. DeMichele A, et al. Clin. Cancer Res. (2015) pmid: 25501126
149. Finn RS, et al. Lancet Oncol. (2015) pmid: 25524798
150. Infante JR, et al. Clin. Cancer Res. (2016) pmid:

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27542767
151. Johnson DB, et al. Oncologist (2014) pmid: 24797823
152. Van Maerken T, et al. Mol. Cancer Ther. (2011) pmid: 21460101
153. Gamble LD, et al. Oncogene (2012) pmid: 21725357
154. Shapiro et al., 2013; ASCO Abstract 2500
155. Flaherty KT, et al. Clin. Cancer Res. (2012) pmid: 22090362
156. Dickson MA, et al. J. Clin. Oncol. (2013) pmid: 23569312
157. Cerami E, et al. Cancer Discov (2012) pmid: 22588877
158. Gao J, et al. Sci Signal (2013) pmid: 23550210
159. Sottoriva A, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23412337
160. Weber RG, et al. Oncogene (2007) pmid: 16909113
161. Nakamura M, et al. Brain Pathol. (2001) pmid: 11303791
162. Chakravarti A, et al. Clin. Cancer Res. (2001) pmid: 11489817
163. Feng J, et al. Cancer (2012) pmid: 21713760
164. Raabe EH, et al. Clin. Cancer Res. (2011) pmid: 21636552
165. Liu W, et al. J. Exp. Clin. Cancer Res. (2011) pmid: 21843312
166. Quelle DE, et al. Cell (1995) pmid: 8521522
167. Mutat. Res. (2005) pmid: 15878778
168. Gazzeri S, et al. Oncogene (1998) pmid: 9484839
169. Oncogene (1999) pmid: 10498883
170. Sherr CJ, et al. Cold Spring Harb. Symp. Quant. Biol. (2005) pmid: 16869746
171. Ozenne P, et al. Int. J. Cancer (2010) pmid: 20549699
172. Ruas M, et al. Oncogene (1999) pmid: 10498896
173. Jones R, et al. Cancer Res. (2007) pmid: 17909018
174. Haferkamp S, et al. Aging Cell (2008) pmid: 18843795
175. Huot TJ, et al. Mol. Cell. Biol. (2002) pmid: 12417717
176. Rizos H, et al. J. Biol. Chem. (2001) pmid: 11518711
177. Gombart AF, et al. Leukemia (1997) pmid: 9324288
178. Yang R, et al. Cancer Res. (1995) pmid: 7780957
179. Parry D, et al. Mol. Cell. Biol. (1996) pmid: 8668202
180. Greenblatt MS, et al. Oncogene (2003) pmid: 12606942
181. Yarbrough WG, et al. J. Natl. Cancer Inst. (1999) pmid: 10491434
182. Poi MJ, et al. Mol. Carcinog. (2001) pmid: 11255261
183. Byeon IJ, et al. Mol. Cell (1998) pmid: 9660926
184. Kannengiesser C, et al. Hum. Mutat. (2009) pmid: 19260062
185. Lal G, et al. Genes Chromosomes Cancer (2000) pmid: 10719365
186. Koh J, et al. Nature (1995) pmid: 7777061
187. McKenzie HA, et al. Hum. Mutat. (2010) pmid: 20340136
188. Miller PJ, et al. Hum. Mutat. (2011) pmid: 21462282
189. Kutscher CL, et al. Physiol. Behav. (1977) pmid: 905385
190. Scaini MC, et al. Hum. Mutat. (2014) pmid: 24659262
191. Jenkins NC, et al. J. Invest. Dermatol. (2013) pmid: 23190892
192. Walker GJ, et al. Int. J. Cancer (1999) pmid: 10389768
193. Rutter JL, et al. Oncogene (2003) pmid: 12853981
194. Itahana K, et al. Cancer Cell (2008) pmid: 18538737
195. Zhang Y, et al. Mol. Cell (1999) pmid: 10360174
196. Zhang Y, et al. Cell (1998) pmid: 9529249
197. Jafri M, et al. Cancer Discov (2015) pmid: 25873077
198. Whelan AJ, et al. N Engl J Med (1995) pmid: 7666917
199. Adv Exp Med Biol (2010) pmid: 20687502
200. Hogg D, et al. J Cutan Med Surg (1998) pmid: 9479083
201. De Unamuno B, et al. Melanoma Res (2018) pmid: 29543703
202. Soura E, et al. J Am Acad Dermatol (2016) pmid: 26892650
203. Huerta C, et al. Acta Derm Venereol (2018) pmid: 29405243
204. Kaufman DK, et al. Neurology (1993) pmid: 8414022
205. Bahuau M, et al. Cancer Res (1998) pmid: 9622062
206. Chan AK, et al. Clin Neuropathol () pmid: 28699883
207. Krönke J, et al. Science (2014) pmid: 24292625
208. Lu G, et al. Science (2014) pmid: 24292623
209. Krönke J, et al. Nature (2015) pmid: 26131937
210. Hodis E, et al. Cell (2012) pmid: 22817889
211. Krauthammer M, et al. Nat. Genet. (2012) pmid: 22842228
212. Nature (2014) pmid: 25079552
213. Nature (2014) pmid: 25079317
214. Wang K, et al. Nat. Genet. (2014) pmid: 24816253
215. Seshagiri S, et al. Nature (2012) pmid: 22895193
216. George J, et al. Nature (2015) pmid: 26168399
217. Rudin CM, et al. Nat. Genet. (2012) pmid: 22941189
218. Zhang Z, et al. Anat Rec (Hoboken) (2013) pmid: 23580163
219. Yang L, et al. Oncol. Rep. (2010) pmid: 20596648
220. He LC, et al. Oncol. Rep. (2012) pmid: 22859015
221. Javierre BM, et al. Mol. Cancer Res. (2011) pmid: 21737484
222. Hematology Am Soc Hematol Educ Program (2012) pmid: 23233609
223. Leukemia (2010) pmid: 20428194
224. Mullighan CG, et al. Nature (2007) pmid: 17344859
225. Dörge P, et al. Haematologica (2013) pmid: 22875627
226. Krentz S, et al. Leukemia (2013) pmid: 22699455
227. Collins-Underwood JR, et al. Leukemia (2010) pmid: 20739952
228. Hunger SP, et al. Pediatr Blood Cancer (2011) pmid: 21370430
229. Olsson L, et al. Br. J. Haematol. (2015) pmid: 25753742
230. Payne KJ, et al. Crit Rev Oncog (2011) pmid: 22150303
231. Li Z, et al. World J Biol Chem (2011) pmid: 21765980
232. Cobb BS, et al. Genes Dev. (2000) pmid: 10970879
233. Marjon K, et al. Cell Rep (2016) pmid: 27068473
234. Heist et al., 2019; AACR-NCI-EORTC Abstract B116
235. Mavrakis KJ, et al. Science (2016) pmid: 26912361
236. Endoscopy (1989) pmid: 2691236
237. Guccione E, et al. Nat. Rev. Mol. Cell Biol. (2019) pmid: 31350521
238. Fedoriw A, et al. Cancer Cell (2019) pmid: 31257072
239. Srour N, et al. Cancer Cell (2019) pmid: 31287990
240. Gao G, et al. Nucleic Acids Res. (2019) pmid: 30916320
241. Hansen LJ, et al. Cancer Res. (2019) pmid: 31040154
242. Tang B, et al. Cancer Res. (2018) pmid: 29844120
243. Munshi PN, et al. Oncologist (2014) pmid: 24928612
244. de Oliveira SF, et al. PLoS ONE (2016) pmid: 26751376
245. Lubin M, et al. PLoS ONE (2009) pmid: 19478948
246. Tang B, et al. Cancer Biol. Ther. (2012) pmid: 22825330
247. Collins CC, et al. Mol. Cancer Ther. (2012) pmid: 22252602
248. Bertino JR, et al. Cancer Biol. Ther. (2011) pmid: 21301207
249. Coulthard SA, et al. Mol. Cancer Ther. (2011) pmid: 21282358
250. Miyazaki S, et al. Int. J. Oncol. (2007) pmid: 17912432
251. Efferth T, et al. Blood Cells Mol. Dis. () pmid: 11987241
252. Kindler HL, et al. Invest New Drugs (2009) pmid: 18618081
253. Wei R, et al. Sci Rep (2016) pmid: 27929028
254. Zhao M, et al. BMC Genomics (2016) pmid: 27556634
255. Kirovski G, et al. Am. J. Pathol. (2011) pmid: 21356366
256. Huang HY, et al. Clin. Cancer Res. (2009) pmid: 19887491
257. Marcé S, et al. Clin. Cancer Res. (2006) pmid: 16778103
258. Meyer S, et al. Exp. Dermatol. (2010) pmid: 20500769
259. Wild PJ, et al. Arch Dermatol (2006) pmid: 16618867
260. Kim J, et al. Genes Chromosomes Cancer (2011) pmid: 21412930
261. Li CF, et al. Oncotarget (2014) pmid: 25426549
262. He HL, et al. Medicine (Baltimore) (2015) pmid: 26656376
263. Su CY, et al. Eur J Surg Oncol (2014) pmid: 24969958
264. Mirebeau D, et al. Haematologica (2006) pmid: 16818274
265. Becker AP, et al. Pathobiology (2015) pmid: 26088413
266. Snezhkina AV, et al. Oxid Med Cell Longev (2016) pmid: 27433286
267. Bistulfi G, et al. Oncotarget (2016) pmid: 26910893
268. Antonopoulou K, et al. J. Invest. Dermatol. (2015) pmid: 25407435
269. Maccioni L, et al. BMC Cancer (2013) pmid: 23816148
270. Hyland PL, et al. Int J Epidemiol (2016) pmid: 26635288
271. Lin X, et al. Cancer Sci. (2017) pmid: 27960044
272. Zhi L, et al. J Cancer (2016) pmid: 27994653
273. Gu F, et al. Br. J. Cancer (2013) pmid: 23361049
274. Limm K, et al. PLoS ONE (2016) pmid: 27479139
275. Tang B, et al. G3 (Bethesda) (2014) pmid: 25387827
276. Limm K, et al. Eur. J. Cancer (2013) pmid: 23265702
277. Stevens AP, et al. J. Cell. Biochem. (2009) pmid: 19097084
278. Kryukov GV, et al. Science (2016) pmid: 26912360
279. Limm K, et al. Eur. J. Cancer (2014) pmid: 25087184
280. Nat Rev Clin Oncol (2017) pmid: 27245281
281. Duperret EK, et al. Mol Ther (2018) pmid: 29249395
282. Chiappori AA, et al. Ann Oncol (2015) pmid: 25467017
283. Killela PJ, et al. Proc. Natl. Acad. Sci. U.S.A. (2013) pmid: 23530248
284. Killela PJ, et al. Oncotarget (2014) pmid: 24722048
285. Nonoguchi N, et al. Acta Neuropathol. (2013) pmid: 23955565
286. Liu X, et al. Cell Cycle (2013) pmid: 23603989
287. Koelsche C, et al. Acta Neuropathol. (2013) pmid: 24154961
288. Arita H, et al. Acta Neuropathol. (2013) pmid: 23764841
289. Reitman ZJ, et al. Acta Neuropathol. (2013) pmid: 24217890
290. Shay JW, et al. Semin. Cancer Biol. (2011) pmid: 22015685
291. Shay JW, et al. Eur. J. Cancer (1997) pmid: 9282118
292. Kim NW, et al. Science (1994) pmid: 7605428
293. Hanahan D, et al. Cell (2000) pmid: 10647931
294. Horn S, et al. Science (2013) pmid: 23348503
295. Huang FW, et al. Science (2013) pmid: 23348506
296. Vinagre J, et al. Nat Commun (2013) pmid: 23887589
297. Weller M, et al. Nat Rev Clin Oncol (2021) pmid: 33293629
298. Hasselbalch B, et al. Neuro-oncology (2010) pmid: 20406901
299. Gajadhar AS, et al. Mol. Cancer Res. (2012) pmid: 22232519
300. Philip PA, et al. J. Clin. Oncol. (2010) pmid: 20606093
301. Slovin SF, et al. Clin Genitourin Cancer (2009) pmid: 19815486
302. Falchook GS, et al. Oncotarget (2013) pmid: 23435217
303. Konduri K, et al. Cancer Discov (2016) pmid: 27102076
304. Zhu YC, et al. Lung Cancer (2018) pmid: 29290255

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Julia Elvin, M.D., Ph.D., Laboratory Director CLIA: 22D2027531
Nimesh R. Patel, M.D., Laboratory Director CLIA: 34D2044309
Foundation Medicine, Inc. | 1.888.988.3639

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

305. Xu et al., 2018; ASCO Abstract e13538
306. Cappuzzo F, et al. Lancet Oncol. (2010) pmid: 20493771
307. Zhong WZ, et al. J. Clin. Oncol. (2019) pmid: 31194613
308. Petrelli F, et al. Clin Lung Cancer (2012) pmid: 22056888
309. Petty RD, et al. J. Clin. Oncol. (2017) pmid: 28537764
310. Philip PA, et al. J. Clin. Oncol. (2006) pmid: 16809731
311. Xie C, et al. Br J Cancer (2020) pmid: 32958820
312. Luo H, et al. JAMA Netw Open (2020) pmid: 33026449
313. Lee J, et al. Lancet Oncol. (2012) pmid: 22192731
314. Hainsworth JD, et al. J. Clin. Oncol. (2018) pmid: 29320312
315. Nie KK, et al. Chin Med J (Engl) (2018) pmid: 29998897
316. Prados MD, et al. J. Clin. Oncol. (2009) pmid: 19075262
317. Kesavabhotla K, et al. J. Exp. Ther. Oncol. (2012) pmid: 22946346
318. Peereboom DM, et al. Neuro-oncology (2013) pmid: 23328813
319. Han JY, et al. J. Clin. Oncol. (2012) pmid: 22370314
320. Maemondo M, et al. N. Engl. J. Med. (2010) pmid: 20573926
321. Mitsudomi T, et al. Lancet Oncol. (2010) pmid: 20022809
322. Mok TS, et al. N. Engl. J. Med. (2009) pmid: 19692680
323. Qi WX, et al. Curr Med Res Opin (2015) pmid: 25329826
324. Zhao H, et al. J Thorac Oncol (2015) pmid: 25546556
325. Dutton SJ, et al. Lancet Oncol. (2014) pmid: 24950987
326. Whittle JR, et al. J Clin Neurosci (2015) pmid: 26279503
327. Douillard JY, et al. Ann. Oncol. (2014) pmid: 24718886
328. Price TJ, et al. Lancet Oncol. (2014) pmid: 24739896
329. Van Cutsem E, et al. J. Clin. Oncol. (2007) pmid: 17470858
330. Vermorken JB, et al. Lancet Oncol (2013) pmid: 23746666
331. Wirth LJ, et al. Ann. Oncol. (2010) pmid: 19892746
332. Siano M, et al. Oncologist (2017) pmid: 28592616
333. Mesía R, et al. Lancet Oncol (2015) pmid: 25596660
334. Giralt J, et al. Lancet Oncol (2015) pmid: 25596659
335. Siu LL, et al. JAMA Oncol (2016) pmid: 27930762
336. Waddell T, et al. Lancet Oncol. (2013) pmid: 23594787
337. Crawford J, et al. J Thorac Oncol (2013) pmid: 24389433
338. Schuette W, et al. Clin Lung Cancer (2015) pmid: 26094080
339. Leone F, et al. Cancer (2016) pmid: 26540314
340. Vogel A, et al. Eur J Cancer (2018) pmid: 29413685
341. Rowinsky EK, et al. J. Clin. Oncol. (2004) pmid: 15210739

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