MAYO CLINIC

1-800-533-1710

MayoComplete Solid Tumor Panel

MCSTP

PATIENT NAME				ORDER NUMBER
IMPLEMENTATION, TEST T				**O020000406**
PATIENT ID X100458433	DATE OF BIRTH 05/01/1973	AGE 50 Y	SEX Female	REQUESTED BY CLIENT TESTING
COLLECTED 3/20/2024, 7:00 AM	RECEIVED 3/20/2024, 1:52 PM	REPORTED 4/5/2024, 1:27 PM		
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RESULT

Variant	AMP Tier	FDA Approved Therapies	FDA Approved Therapies (for other tumor type)	Clinical Trials
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	1A	Yes	Yes	Yes
Microsatellite STABLE (1.4%)	2C	None	None	Yes
MET c.3028+1G>A (MET exon 14 skipping)	1A	Yes	None	Yes
BRCA2 c.3680_3681del (p.L1227fs*5) and heterozygous loss	2C	None	Yes	Yes
TP53 homozygous loss	2C	None	None	None
MDM2 amplification (Copy number: 20.1)	2D	None	None	None

PROVIDED DIAGNOSIS: LUNG ADENOCARCINOMA

INTERPRETATION

RNA testing revealed MET exon 14 skipping; there was no evidence of fusions.

Tumor Mutational Burden (TMB)/Microsatellite Instability (MSI):
TMB: HIGH (15.0 mutations/Mb)
MSI: STABLE (MSS)

Immunotherapies have been FDA approved for adult and pediatric advanced stage solid tumors with high tumor mutational burden (TMB-H, defined as ten or more mutations per megabase) and/or high microsatellite instability (MSI-H)/defective DNA mismatch repair (dMMR) [PMID: 28596308, PMID: 29355075, PMID: 30787022].

1) MET c.3028+1G>A (MET exon 14 skipping) (VAF: 42%)

GENE/VARIANT SUMMARY
MET splice site 3082+1G>A (NM_001127500) is predicted to be an activating mutation.

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Met protein, also known as c-Met or hepatocyte growth factor receptor (HGFR), which is a receptor tyrosine kinase that is activated by the ligand HGF; Met activation results in signaling mediated partly through the Ras/Raf/MAPK and PI3K pathways to promote proliferation [PMID:22042966]. Additionally, Met protein activation or overexpression promotes angiogenesis, resistance to apoptosis, proliferation, and invasion of cancer cells [PMID:12684423, PMID:22042966, PMID:22270953, PMID:22553051].

This alteration disrupts a splice junction adjacent to exon 14 of the 1390-amino acid Met protein (IGV, UniProt). Alterations that disrupt the exon 14 consensus splice sites have been reported to result in skipping of exon 14, which results in the deletion of part of the juxtamembrane domain; the loss of exon 14 has been reported to result in the stabilization and activation of Met, due in part to loss of interaction with the ubiquitin ligase Cbl [PMID:16397241, PMID:25971938]. Therefore, this alteration is expected to be activating. Additionally, MET exon 14 skipping mutations have been associated with sensitivity to Met inhibitors, including capmatinib and tepotinib [PMID:25769807, PMID:25971938, PMID:32469185, PMID:32877583].

MET mutations have been reported in 0.5-7% of lung adenocarcinoma samples analyzed [COSMIC (May 2023); cBioPortal for Cancer Genomics (May 2023)]. A meta-analysis of 21156 NSCLC cases from 25 studies has reported MET exon 14 mutations in less than 1% (10/21156) of samples [PMID:33996610].

THERAPEUTIC IMPLICATIONS
Drug sensitivity: Increased Met expression, possibly as a result of MET mutation or amplification, may lead to enhanced Met activation and may therefore confer sensitivity to Met inhibitors [PMID:20303741, PMID:22042947].

Crizotinib and cabozantinib target multiple kinases, including Met, and have been approved for certain indications [PMID:34237250, PMID:24002501, PMID:23292257, PMID:23319867, PMID:26406150, PMID:25667280, PMID:25470694, PMID:23724913].

In addition, the kinase inhibitors capmatinib and tepotinib have been approved by the FDA, EMA and PMDA, for the treatment of adult patients with metastatic non-small cell lung cancer and a MET exon 14 skipping mutation [PMID:32469185, PMID:32877583].

Drug resistance: MET amplification or elevated Met expression has been implicated in acquired resistance to Egfr inhibitors in some cancer types; studies are currently investigating combination therapy with Met inhibitors and Egfr inhibitors in this setting [PMID:21273060, PMID:17463250, PMID:23527257, PMID:23729478]. Met activation has been implicated as one key mechanism of resistance to Egfr-targeted therapy in NSCLC [PMID:29631966, PMID:30823937, PMID:30676858, PMID:17463250, PMID:24167634, PMID:20489150].

FDA Approved Drugs: Tepotinib. Capmatinib.

2) BRCA2 c.3680_3681del (p.L1227fs*5) (VAF: 56%) and heterozygous loss

GENE/VARIANT SUMMARY

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BRCA2 L1227fs*5 (NM_000059) is an inactivating mutation.
Heterozygous loss was also detected, indicating likely biallelic inactivation of BRCA2.

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [PMID:12228710]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [PMID:21731065, PMID:28079255].

The alteration reported here is expected to effectively truncate the 3418-amino acid Brca2 protein prior to the C-terminal Rad51 binding domain and three nuclear localization signals crucial to Brca2 protein function; truncating mutations including T3195* and Y3308* have been reported to result in Brca2 inactivation [PMID:18607349, PMID:17515903, PMID:10570174, PMID:25847274, PMID:18593900]. In addition, this alteration is likely to elicit nonsense-mediated decay [PMID:27618451, PMID:29121514, PMID:9644970, PMID:25741868]. Therefore, this alteration is expected to be inactivating.

BRCA2 mutations have been reported in 1.1-7.3% of lung adenocarcinoma samples analyzed [COSMIC (May 2023); cBioPortal for Cancer Genomics, May (2023)].

THERAPEUTIC IMPLICATIONS
Drug sensitivity: Inactivating BRCA2 alterations have been reported to predict sensitivity to platinum-based chemotherapy and PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, which are FDA-approved in specific indications [PMID:30110579, PMID:28546758, PMID:26187614, PMID:27908594, PMID:28474297].

The PARP inhibitor olaparib has been approved by the FDA for use in advanced ovarian cancer, metastatic Her2 negative breast cancer, and pancreatic adenocarcinoma patients with germline BRCA1/2 mutations as well as for castration-resistant adult prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA1/2 mutations; rucaparib has been approved by the FDA for advanced ovarian cancer and castration-resistant prostate cancer patients with either germline or somatic BRCA1/2 mutations [PMID:22452356, PMID:26187614, PMID:27908594, PMID:28751443, PMID:28916367, PMID:28578601, PMID:30689707, PMID:31157963, PMID:32795228].

Olaparib in combination with abiraterone and prednisone or prednisolone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer with deleterious BRCA mutation as determined by an FDA-approved companion diagnostic test.

In addition, talazoparib in combination with enzalutamide has been FDA-approved for the treatment of metastatic castration-resistant prostate cancer patients with tumors harboring germline or somatic alteration in one or more homologous recombination repair genes, including BRCA2 mutation [PMID:37285865].

Furthermore, niraparib in combination with abiraterone acetate plus prednisone has been approved by the FDA for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) harboring deleterious or suspected deleterious BRCA1/2 mutations [PMID:36952634].

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Loss of Brca2 expression has been reported to enhance sensitivity to cisplatin in preclinical studies of NSCLC [PMID:24974076, PMID:27473273].

Drug resistance: None.

FDA Approved Drugs: None.

3) TP53 homozygous loss

GENE/VARIANT SUMMARY
TP53 homozygous loss is an inactivating alteration.

The TP53 gene encodes the tumor suppressor p53, a protein that is involved in the DNA damage cell cycle checkpoint and causes cell cycle arrest when it senses DNA damage. p53 can also activate DNA repair genes or induce apoptosis in the presence of DNA damage. Alterations in TP53 typically result in a loss of p53 protein function. Additionally, some alterations are predicted to have oncomorphic or gain-of-function properties leading to downstream oncogenic effects, including genomic instability and excessive cell proliferation [PMID:9039259, PMID:15625370, PMID:11400116, PMID:12826609, PMID:21760960, PMID:18802452].

Homozygous deletion of TP53, which is located at chromosome 17p13, has been associated with a loss of TP53 mRNA and p53 protein expression [PMID:2143022].

Homozygous deletion of TP53 has been reported in 0.0-1.7% of lung adenocarcinoma cases (cBioPortal for Cancer Genomics, May 2023).

THERAPEUTIC IMPLICATIONS
Drug sensitivity: At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines [PMID:24583792, PMID:21541192, PMID:24982341].

Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function [PMID:21087899, PMID:20107315, PMID:21799033]. Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors. Chk1 inhibitors in combination with chemotherapy are also under investigation in clinical trials.

Aurora kinase A inhibition, which may be relevant for tumors with TP53 mutations, is not expected to be relevant for a tumor with reduction or loss of p53 expression as reported here [PMID:21994418, PMID:25398437].

Drug resistance: Mutations in TP53 may increase resistance to ionizing radiation therapy [PMID:14576853,

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PMID:25913131].

FDA Approved Drugs: None.

4) MDM2 amplification (Copy number: 20.1)

GENE/VARIANT SUMMARY
MDM2 amplification is an activating alteration.

MDM2 encodes the E3 ubiquitin protein ligase, Mdm2, which mediates the ubiquitination and subsequent degradation of p53, Rb1, and other proteins [PMID:15053880, PMID:15632057, PMID:16337594].

MDM2 gene amplification, which is located at chromosome 12q15, has been correlated with elevated Mdm2 protein expression, as measured by immunohistochemistry, and frequently with the inactivation of p53 [PMID:32352245, PMID:18646312, PMID:18521196, PMID:10065155]. MDM2 functions as an oncogene, and MDM2 amplification has been shown to play a role in cell proliferation, invasion, and metastasis [PMID:16980628, PMID:2026149, PMID:16243710, PMID:10065155].

Amplification of MDM2 has been reported in 3.6-13% of lung adenocarcinoma cases (cBioPortal for Cancer Genomics, May 2023).

THERAPEUTIC IMPLICATIONS
Drug sensitivity: Mdm2 antagonists, which disrupt the Mdm2-p53 interaction, leading to reactivation of p53, are being studied in multiple tumor types [PMID:20975744, PMID:14704432, PMID:15715460, PMID:23165797, PMID:20422343]. Several other classes of Mdm2-p53 disrupting molecules have also been found to have activity, including novel benzodiazepine derivatives [PMID:15715460].

Preclinical studies in pancreatic, breast, and colon cancer cell lines suggest that Mdm2 inhibitors may increase sensitivity of tumors to platinum-based therapies [PMID:20156675, PMID:21623005].

Drug resistance: Amplification of MDM2 or MDM4 has been associated with hyperprogression following treatment with anti-PD-1 or anti-PD-L1 inhibitors in one study. Hyperprogression was defined as a time to treatment less than two months, greater than 50% increase in tumor burden as compared with pre-immunotherapy, and greater than two-fold increase in progression pace [PMID:28351930].

One study reported that four NSCLC patients harboring both EGFR sensitizing mutations and MDM2 amplification exhibited progressive disease following gefitinib treatment, with follow-up preclinical analysis indicating that MDM2 amplification induced erlotinib resistance in a NSCLC cell model [PMID:32611363].

FDA Approved Drugs: None.

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Sequencing coverage greater than or equal to 100X was observed in 96.6% of targeted regions.

Low coverage regions (< 100X coverage):
ABL1 (5'UTR); AMER1 (5'UTR); ARAF (5'UTR); ARID1A (Exon 1); ATRX (5'UTR, Exon 1); BARD1 (5'UTR); BCR (5'UTR, Exon 17); BTK (5'UTR); CBFB (5'UTR); CDH1 (5'UTR, Exon 1); CEBPA (5'UTR, Exon 1); COP1 (5'UTR); DNMT1 (5'UTR, Exon 5); DOT1L (Exon 13); EIF4E (Exon 7); EPCAM (5'UTR); EPHA5 (5'UTR); ETV4 (5'UTR); ETV5 (Promoter); FANCA (5'UTR, Exon 1); FANCE (5'UTR, Exon 1); FGF3 (5'UTR, Exon 1, Promoter); FGF4 (5'UTR, Exon 1, Promoter); FGF8 (Exon 3); FLT3 (Exon 1); FLT4 (Exon 1); FOXA1 (Promoter); FOXO1 (5'UTR); GATA1 (3'UTR, 5'UTR); GATA2 (5'UTR); GATA4 (5'UTR, Exon 2); GNA11 (5'UTR); GNAS (5'UTR); GRIN2A (5'UTR); H3-3A (3'UTR); IDH2 (5'UTR, Exon 1); KDM6A (Exon 9); KEAP1 (5'UTR); LAMP1 (5'UTR); LZTR1 (5'UTR); MALT1 (5'UTR); MAP2K2 (3'UTR, 5'UTR); MAP3K1 (5'UTR, Exon 1); MEF2B (3'UTR); MLLT3 (Exon 1); MST1 (Exon 7); MST1R (5'UTR); MYD88 (Promoter); NF2 (5'UTR); NFKBIA (5'UTR); NOTCH3 (Exon 24); PDGFRA (Exon 2); PIK3R2 (3'UTR, 5'UTR); PRKDC (5'UTR); PRSS8 (5'UTR); PTCH1 (5'UTR); RAB35 (5'UTR, Exon 1); RAC1 (5'UTR); RANBP2 (Exon 11, Exon 19); RB1 (5'UTR, Exon 15); RBM10 (Exon 8); RECQL4 (Exon 2); RPS6KA4 (3'UTR); SDHA (5'UTR, Exon 1); SDHB (5'UTR); SETBP1 (5'UTR); SH2B3 (5'UTR, Exon 2); SOX10 (5'UTR); STAG2 (Exon 21); STAT5A (Exon 9); STAT5B (Exon 8); STK11 (3'UTR); SUZ12 (3'UTR, 5'UTR); TERT (5'UTR); TFE3 (5'UTR, Exon 1, Promoter); TGFBR1 (5'UTR); TMPRSS2 (5'UTR); TP53 (3'UTR); TSC2 (3'UTR); XIAP (5'UTR, Exon 4); ZBTB7A (3'UTR); ZNF703 (5'UTR)

Evidence-based sequence variant classification was performed according to the 2017 AMP/ASCO/CAP Joint consensus recommendation [PMID 27993330] as follows: Tier 1 - Variant with strong clinical significance; Tier 2 - Variant with potential clinical significance; Tier 3 - Variant of unknown (uncertain) clinical significance; Tier 4 - Benign or likely benign variant. Tiers 1 and 2 variants are clinically significant mutations and rearrangements. Only Tiers 1 and 2 variants are interpreted.

A complete gene list is available online (www.mayoclinic.org; test code MCSTP)

CLINICAL TRIALS

Markers	Trial ID	Title	Locations/Contact
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	United States: AL AZ CA CT FL GA IL IN ME MI NC ND NE NH NM NY OH OR PA SC SD TN TX UT VA WA WI(Pam Mangat MS; tapur@asco.org)
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT03809624	An Open-Label Multicenter First-in-Human Dose-Escalation Phase 1 / 2 Study of INBRX-105 and INBRX-105 in Combination With Pembrolizumab in Patients With Locally Advanced or Metastatic Solid Tumors	United States: AZ CA GA IN KY MA MI MO NE OR PA TX UT VA(Amanda Sweeney; clinicaltrials@inhibrx.com; 858-500-7833)

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Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT04198766	An Open-Label Multicenter First-in-Human Dose-Escalation Multicohort Phase 1/2 Study of INBRX-106 and INBRX-106 in Combination With Pembrolizumab in Subjects With Locally Advanced or Metastatic Solid Tumors	United States: CA GA IA IL KY MI NE OR TN TX VA WI(Amanda Sweeney Trial Manager; clinicaltrials@inhibrx.com; 858-500-7833)
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT04787042	A First-In-Human Phase 1/2 Open-Label Study of Intravenous ST-067 Subcutaneous ST-067 With or Without Obinutuzumab Pre-Treatment and ST-067 in Combination With Pembrolizumab in Subjects With Advanced Solid Malignancies	United States: AZ CO CT FL MA NY OR(Beatrice McQueen Ph.D.; beatrice@simchatherapeutics.com; 805-300-3912)
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT05199272	A Phase 1/2a Multicenter Open-Label Dose-Escalation and Expansion Study of Intravenously Administered 23ME-00610 in Patients With Advanced Solid Malignancies	United States: CA GA MI NY OH OR TN TX VA(Study Inquiry; studyinquiry@23andme.com; (650) 963-8997)
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT05592626	A Phase 1/2 First-in-Human Open-Label Dose Escalation and Expansion Study of STAR0602 a Selective T Cell Receptor (TCR) Targeting Bifunctional Antibody-fusion Molecule in Subjects With Unresectable Locally Advanced or Metastatic Solid Tumors That Are Antigen-rich (START-001)	United States: MA MD NY(Ke Liu MD PhD; kliu@marengotx.com; +1 (617) 917-4980)
Tumor Mutational Burden HIGH (15.0 mutations/Mb)	NCT05904496	A Phase 1a/1b Study Investigating the Safety Tolerability Pharmacokinetics Pharmacodynamics and Preliminary Antitumor Activity of the DGK¿ Inhibitor BGB-30813 Alone or in Combination With the Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients With Advanced or Metastatic Solid Tumors	United States: NJ TX(Study Director; clinicaltrials@beigene.com; 1-877-828-5568)
Microsatellite STABLE (1.2%)	NCT05572684	A Phase 1b/2 Open-Label Safety Tolerability and Efficacy Study of NC410 Plus Pembrolizumab for Participants With Advanced Unresectable and/or Metastatic Immune Checkpoint Inhibitor (ICI) Refractory Solid Tumors or ICI Naïve MSS/MSI-Low Solid Tumors	United States: AZ CO KY LA MD NJ OH TX VA WA(Associate Director Clinical Operations at NextCure Inc.; NCClin@nextcure.com; 859-468-8632)
MET c.3028+1G>A (MET exon 14 skipping)	NCT03175224	Phase 1 / 2 Multicenter Study of the Safety Pharmacokinetics and Preliminary Efficacy of APL-101 in Subjects With Non-Small Cell Lung Cancer With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advance Solid Tumors	United States: CA DE FL MA MD MN MO NC OH PA SC TN TX WI WV(Vivian Huey; clinops@apollomicsinc.com; 6502094055)

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MET c.3028+1G>A (MET exon 14 skipping)	NCT04270591	A Phase Ib/II Open-Label Multicenter Study to Evaluate the Efficacy and Safety of Glumetinib (SCC244) a Selective MET Inhibitor in Patients With Advanced Non-Small Cell Lung Cancer Harboring MET-alterations	United States: KY(Shun LU Doctor; shun_lu@hotmail.com; +86-21-22200000ext2153)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05117242	A Phase 2 Multicenter Randomized Open-Label Trial of GEN1046 as Monotherapy and in Combination Pembrolizumab Therapy in Subjects With Relapsed /Refractory Metastatic Non-Small Cell Lung Cancer After Treatment With Standard of Care Therapy With an Immune Checkpoint Inhibitor	United States: CA FL MI PA WI(Genmab A/S Trial Information; clinicaltrials@genmab.com; +45 70202728)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05456256	Phase II Trial of LP-300 in Combination With Carboplatin and Pemetrexed in Never Smoker Patients With Relapsed Advanced Primary Adenocarcinoma of the Lung After Treatment With Tyrosine Kinase Inhibitors (The HARMONIC Study)	United States: CA IL NJ NY TX VA(Ernest Kitt; ekitt@lanternpharma.com; 972-277-1136)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05488314	A Phase 1/2 Study Evaluating the Safety and Efficacy of Amivantamab and Capmatinib Combination Therapy in Unresectable Metastatic Non-small Cell Lung Cancer	United States: AL CA VA(Study Contact; Participate-In-This-Study@its.jnj.com; 844-434-4210)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05553834	A Phase II Study of PCSK9 Inhibitor Alirocumab and PD-1 Inhibitor Cemiplimab in Patients With Metastatic Refractory To Prior Anti PD-1 Non-small Cell Lung Cancer: TOP2201	United States: NC(Scott Antonia MD; scott.antonia@duke.edu; 919 681 9509)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05567055	A Phase 2 Open-label Study to Determine the Central Nervous System Efficacy of Capmatinib in NSCLC Patients With Brain Metastases With cfDNA Positive MET Alterations	United States: PA(Jennifer Ruth RN BSN; ruthj2@upmc.edu; 412-623-8963)
MET c.3028+1G>A (MET exon 14 skipping)	NCT05617313	A Phase II Study of GT103 in Combination With Pembrolizumab in Refractory Metastatic Non-Small Cell Lung Cancer	United States: IL MI NC NJ VA(Jeffrey Clarke MD; jeffrey.clarke@duke.edu; 919-684-8111)

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MET c.3028+1G>A (MET exon 14 skipping)	NCT05983432	A Phase 1 Study Evaluating the Safety Tolerability and Efficacy of BL-B01D1 in Subjects With Metastatic or Unresectable Non-Small Cell Lung Cancer	United States: FL SC TX(Elizabeth D Lotz MBA; elizabeth.lotz@systimmune.com; (425) 453-6841)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	United States: AL AZ CA CT FL GA IL IN ME MI NC ND NE NH NM NY OH OR PA SC SD TN TX UT VA WA WI(Pam Mangat MS; tapur@asco.org)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT03428802	A Basket Trial of Pembrolizumab in Patients With Advanced Solid Tumors and Genomic Instability	United States: NJ NY(Eugenia Girda MD; eg535@cinj.rutgers.edu; 732-235-2465)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT03742895	A Phase 2 Study of Olaparib Monotherapy in Participants With Previously Treated Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer	United States: MD NJ NY WA(Toll Free Number; Trialsites@merck.com; 1-888-577-8839)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT04550494	A Pharmacodynamics-Driven Trial of Talazoparib an Oral PARP Inhibitor in Patients With Advanced Solid Tumors and Aberrations in Genes Involved in DNA Damage Response	United States: FL MD OK(A P Chen)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT04657068	A Phase I/IIa Open-label Multi-center Study to Assess the Safety Tolerability Pharmacokinetics and Preliminary Efficacy of the ATR Kinase Inhibitor ART0380 Administered Orally as Monotherapy and in Combination to Patients With Advanced or Metastatic Solid Tumors	United States: AL AR CO FL OK PA TN TX(Sarah Cannon Development Innovations; CANN.InnovationsMedical@sarahcannon.com; 844-710-6157)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT04826341	A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors	United States: MD(Rasa Vilimas R.N.; vilimasrj@mail.nih.gov; (240) 858-3158)

PATIENT NAME				ORDER NUMBER
IMPLEMENTATION, TEST T				**O020000406**
PATIENT ID X100458433	DATE OF BIRTH 05/01/1973	AGE 50 Y	SEX Female	REQUESTED BY CLIENT TESTING
COLLECTED 3/20/2024, 7:00 AM	RECEIVED 3/20/2024, 1:52 PM	REPORTED 4/5/2024, 1:27 PM		
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Markers	Trial ID	Title	Locations/Contact
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT05076396	Phase I Open-label Dose-escalating Clinical and Pharmacokinetic Study of PM14 Administered Intravenously to Patients With Advanced Solid Tumors	United States: MA TX(Carmen Kahatt MD PhD; ckahatt@pharmamar.com; 0034 91 823 4615)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT05144698	Phase I/II Trial of Autologous Rapamycin-Resistant Th1/Tc1 (RAPA-201) Cell Therapy of PD-(L)1 Resistant Solid Tumors	United States: NJ(Daniel Fowler M.D.; dan@rapatherapeutics.com; (301) 518-3104)
BRCA2 c.3680_3681del (p.L1227fs*5)	NCT05327010	Phase 2 Trial of the Combination of the BET Inhibitor ZEN003694 (ZEN-3694) and the PARP Inhibitor Talazoparib in Patients With Molecularly-Selected Solid Tumors (ComBET)	United States: CA CO GA IL KY NC PA TX VA(Timothy A Yap)

Clinical trials associated with Tiers 1 and 2 variants that have a status of recruiting are included in the table above

VARIANTS OF UNCERTAIN SIGNIFICANCE

The following VARIANTS OF UNCERTAIN SIGNIFICANCE were identified:
ALK, c.2143G>A (p.G715R) (VAF: 20%)
KDM5A, c.3005G>A (p.R1002Q) (VAF: 50%)
NOTCH3, c.592G>A (p.A198T) (VAF: 39%)
NTRK2, c.382A>C (p.T128P) (VAF: 45%)
RAD51C, c.790G>A (p.G264S) (VAF: 51%)

SPECIMEN

Tissue, Tumor

TISSUE ID

13245

METHOD

Microscopic examination was performed by a pathologist to identify areas of tumor for enrichment by macrodissection.

DNA and RNA were extracted from FFPE or cytology slides, and next generation sequencing using the Illumina TruSight Oncology 500 chemistry was performed. The following variant types and molecular profiles were evaluated: tumor mutation burden (TMB) status, microsatellite instability (MSI) status, sequence variants involving exonic regions and exon/intron boundaries of 515 genes, gene amplifications in 96 genes, homozygous deletion of 133 genes, biallelic inactivation of 31 tumor suppressor genes, fusions involving any of 55 genes, and transcript variants in 3 genes. For TMB calculation, the minimal coding region size considered for TMB calculation that is consistently meeting the required 50x minimal sequence coverage criteria is 1.1 Mb, but is 1.28 MB on average. All nonsynonymous and synonymous qualifying somatic SNVs and DELINSs that have a minimum VAF of 5% and 50x depth at the variant position are

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considered for TMB computation. Driver mutations are not included in the TMB calculation.

AMP/ASCO/CAP classifications and clinical trials and therapeutic information were powered by Qiagen Clinical Insights - Interpret One (QCI-11). Variant nomenclature is based on build GRCh37 (hg19). For targeted gene lists, details about gene transcripts (GenBank accession numbers), specific targeted regions of each gene, and additional information on this test, see www.mayocliniclabs.com (Test ID MCSTP).

DISCLAIMER

CLINICAL CORRELATIONS

Test results should be interpreted in context of clinical findings, tumor sampling, histopathology, and other laboratory data. If results obtained do not match other clinical laboratory findings, please contact the laboratory for possible interpretation. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

This test is performed to evaluate for somatic (i.e., tumor-specific) variants. Although germline (i.e., inherited) alterations may be detected, this test cannot distinguish between germline and somatic alterations. Follow-up germline testing using non-neoplastic (normal) tissue can be performed for confirmation of suspected clinically relevant germline alterations. Germline testing should be performed along with genetic counselling.

The clinical trials provided are current as of the date that the report was generated and may not include all clinical trials available. Additional clinical trials can be found at clinicaltrials.gov. Data interpretation including therapeutic matching (FDA approved drugs, NCCN guidelines and clinical trials) with the variants identified are based on the primary tumor type.

The presence or absence of a genetic variant may not be predictive of response to therapy in all patients.

TECHNICAL LIMITATIONS

Variant Allele Frequency:

Variant allele frequency (VAF) is the percentage of sequencing reads supporting a specific variant divided by the total sequencing reads at that position. In somatic testing, VAF should be interpreted in the context of several factors including, but not limited to: tumor purity/heterogeneity/copy number status (ploidy, gains/losses, loss of heterozygosity) and sequencing artifact/misalignment [PMID: 27144058, PMID: 29769535].

Tumor Purity:

A tumor percentage of greater than or equal to 20% by morphological assessment is required to perform the assay and has shown to be sufficient for accurate detection of SNVs, insertions, deletions, fusions, and splice variants. However, a tumor percentage of greater than or equal to 40% is preferred to accurately detect copy number variants (CNVs), TMB, and MSI status. A tumor percentage lower than 40% may result in false negative results for MSI and/or copy number alterations and an underestimation of TMB. Performance characteristics (accuracy, reproducibility, and analytical sensitivity) are described in the laboratory test catalog.

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Detection Thresholds:

The sensitivity for SNVs, insertions, and deletions at or above 5% VAF was 97.9%. The sensitivity for variants with VAFs between 2-5% may be lower. Insertions and deletions are detected at 99.0% accuracy at or below 31 bp. The sensitivity for insertions and deletions larger than above 31 bps has not been determined. Tumor copy number variations can impact sequence coverage which in turn can impact the sensitivity for SNVs detection, and TMB calculation. A number of regions, originally included in this assay, are excluded from the reportable range due to low sequence coverage, or high background noise level. Gene amplifications and homozygous deletions are called by an in-house developed bioinformatics pipeline and are manually reviewed to optimize sensitivity and specificity. SNV, CNV, TMB and MSI markers calling may be impacted by suboptimal sequence coverage. Therefore, gene regions not achieving 100x coverage are disclaimed on the report. Amplification is defined as the presence of 6 or more copies of the gene for a diploid baseline genome. Reported copy numbers are an estimate of the identified gene copy number within the tumor purity of the specimen and are not adjusted to represent 100% tumor purity. Three supporting reads are required to call a gene fusion, and 10 supporting reads are required to call a splice/transcript variant. Tumor mutational burden (TMB) scores are classified as TMB-Low (less than 10 mutations/Mb) or TMB-High (greater than or equal to 10 mutations/Mb) in accordance with validation studies initially performed on lung cancer samples demonstrating a clinical response to immune checkpoint inhibitors, and more recently in multiple other solid tumor types, where TMB was evaluated by the TSO500 assay [PMID: 35218944]. MSI status is classified as MS-Stable (less than 20% unstable microsatellite sites) or MSI-High (greater than or equal to 20% unstable sites).

Rare polymorphisms may be present that could lead to false negative or false positive results.

A negative (wild-type) result does not rule out the presence of a mutation or rearrangement that may be present but below the limits of detection of the assay or not interrogated by the assay.

TEST CLASSIFICATION

The test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

HUSSAM AL KATEB

Code : MCR Laboratory : Mayo Clinic Laboratories - Rochester Main Campus Address : 200 FIRST STREET SW
Lab Director : WILLIAM G MORICE, II MD, PHD CLIA Certificate : 24D0404292 ROCHESTER MN 55905