Contents

1. Basic information

Physician	Patient	Specimen
Ordering Physician: -	Name: -	Specimen ID: -
Institution: MDx	Cancer Type: -	Specimen Type: Formalin fixed paraffin-embedded tissue
Ordered Test Item: COMPASS Tissue	Gender: -	Specimen Collection Date: -
Report Date:	Date of Birth:	Specimen Receipt Date: -

2. Genetic alterations and relevant therapies

Tier I – Strong Clinical Significance

Genomic Variation	VAF/Copy Number	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
SVIL-RET NM_021738.2; NM_020975.4 rearrangement	29.4%	Sensitive: Pralsetinib* (A) Selpercatinib* (A) Resistance: Afatinib* (D) Erlotinib* (D) Gefitinib* (D)	Sensitive: Cabozantinib* (A) Lenvatinib* (C) Vandetanib* (C) Sorafenib* (D)	Sensitive: BOS172738 (C) HS-10365 (C) RXDX-105 (C) SY-5007 (C)
KIF5B-RET NM_004521.2; NM_020975.4 rearrangement	28.6%	Sensitive: Pralsetinib* (A) Selpercatinib* (A) Resistance: Afatinib* (D) Erlotinib* (D) Gefitinib* (D)	Sensitive: Cabozantinib* (A) Lenvatinib* (C) Vandetanib* (C) Sorafenib* (D)	Sensitive: BOS172738 (C) HS-10365 (C) RXDX-105 (C) SY-5007 (C)

Tier II – Potential Clinical Significance

Genomic Variation	VAF/Copy Number	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
MDM2 NM_002392.4 copy number gain	14.0	-	-	Sensitive: Alrizomadlin (C) ASTX295 (C) Brigimadlin (C)
AURKA NM_003600.2 copy number gain	4.4	-	Sensitive: Rucaparib* (D)	Sensitive: Alisertib (D)

3. TMB & MSI Biomarker#

Biomarker	Result	Relevant Therapies (In this cancer type)
TMB	TMB-L，4.8 Muts/Mb	-
MSI	MSS	-

Clinical concordance has not been established for TMB and MSI. Information about these biomarkers is intended for Research-Use Only and may not be used to guide treatment and/or for clinical decision making. Any decision on the patient's treatment is at the sole discretion of the treating physician and must be considered in combination with other relevant patient information.

Note:

1. The variant classification system used in this report is based on joint consensus recommendations of the AMP, ASCO, and CAP. Tier I, variants with strong clinical significance; Tier II, variants with potential clinical significance; Tier III, variants of unknown clinical significance; and Tier IV, variants deemed benign or likely benign (PMID: 27993330).
2. The categories of clinical and/or experimental evidence of therapeutics was divided into four levels based on the AMP/ASCO/CAP Guidelines for Interpretation of Cancer Variants (PMID: 27993330):
   Level A, approved by the FDA for specific cancer types or included in clinical guidelines;
   Level B, large scale clinical studies repeatedly confirmed and clinical expert consensus;
   Level C, FDA or other professional institutions approved in another cancer types or has been used as screening criteria for clinical trials or multiple small research support;
   Level D, preclinical studies or a few cases support.
3. The therapies listed in the report are the potential benefit targeted treatments for the patient without ranked by gene or therapy significance and the actual effect in this individual remains unknown. Clinical decisions including management and treatment select must according to professional physician instructions.
4. " * " indicates the drugs approved by FDA/EMA/Other agencies.
5. VAF stands for variant allele frequency.

4. Interpretation for relevant therapies

Sensitive therapies

Genetic Variation	Therapies	Detailed Interpretation
AURKA NM_003600.2 copy number gain	Rucaparib Alisertib	**Gene Description:** AURKA (Aurora Kinase A) encodes a cell cycle-regulated kinase that is involved in microtubule formation and/or stabilization at the spindle pole during chromosome segregation and plays a role in tumor development and progression. Amplification and overexpression of Aurka has been identified in a variety of solid tumor types, including breast cancer (PMID: 22825030). **Variant Description:** A copy number gain alteration in AURKA is identified in this case. **Drug Interpretation:** **Rucaparib** Rucaparib is a potent mammalian poly(ADP-ribose) polymerase (PARP) 1, 2 and 3 inhibitor with anticancer properties. In a preclinical study, everolimus demonstrated unefficacy in cancer cell lines with PIK3CA and KRAS/BRAF mutation, beacause PI3K pathway activating mutations were sensitive to everolimus, indicating KRAS/BRAF mutations were the possible cause of resistance. [PMID: 20664172] **Alisertib** Alisertib is a second-generation, orally bioavailable, highly selective small molecule inhibitor of the serine/threonine protein kinase Aurora A kinase(AURKA) with potential antineoplastic activity. In vitro studies, it had shown that Alisertib combined with docetaxel can effectively inhibit the growth of upper gastrointestinal adenocarcinoma cell lines with increased AURKA copy number, and induce apoptosis. In vivo xenograft experiments, it also showed that Alisertib combined with docetaxel had anti-tumor activity towards upper gastrointestinal adenocarcinoma with AURKA amplification. [22972611]
SVIL-RET NM_021738.2;NM_020975.4 rearrangement	Pralsetinib Selpercatinib Cabozantinib Lenvatinib Vandetanib Sorafenib BOS172738 HS-10365 RXDX-105 SY-5007	**Gene Description:** RET (Ret Proto-Oncogene) encodes receptor tyrosine kinase that activates downstream MAPK and PI3K/AKT signaling pathways, and plays a role in cell differentiation, growth, migration and survival (PMID: 24561444, PMID: 29134959, PMID: 32094155). RET activating mutations, fusions, amplification and/or overexpression has been associated with a variety of cancers including lung (PMID: 30257958) and colorectal (PMID: 30210625, PMID: 30038711). **Variant Description:** SVIL-RET rearrangement, results a fusion gene which contain promoter region to intron 1 of SVIL gene in 5'and intron 11 to terminator of RET gene.This fusion preserves the complete kinase domain of the RET gene, and may lead to the functional activation(PMID: 32326537). **Drug Interpretation:** **Pralsetinib** Pralsetinib (BLU-667) is an orally bioavailable selective inhibitor of mutant forms of and fusion products involving the proto-oncogene receptor tyrosine kinase RET, with potential antineoplastic activity. The NCCN guideline recommends Pralsetinib (category 2A) for the first-line treatment of patients with RET rearrangement. Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). 281 pts with RET fusion+ NSCLC had received pralsetinib of whom 260 had measurable disease at baseline per BICR. The ORR was 63.1% in pts with prior platinum treatment and 77.6% , Median overall survival was 44.3 months in pre-treated pts and not reached in treatment-naïve pts. [2022 ESMO Abstract 1170P] [NCT03037385]A retrospective efficacy and safety analysis was performed on data from patients with RET fusion positive NSCLC who were enrolled in the pralsetinib Italian expanded access program (EAP) between July 2019 and October 2021. The most frequent gene fusion partner was KIF5B (77%). Brain metastases were known in 17 patients (28%) at the time of pralsetinib treatment. 13 patients were treatment naïve, 47 were pretreated. The ORR was 66% in the evaluable population (n=58). The DCR was 79%. After a median follow-up of 10.1 months, the median progression free survival was 8.9 months. In patients with measurable brain metastases (n = 6) intracranial ORR was 83%, and intracranial DCR was 100%. [2022 ESMO Abstract 1124P]

		Selpercatinib Selpercatinib is a selective RET kinase inhibitor. The NCCN guideline recommends selpercatinib (category 2A) for the treatment of patients with RET rearrangement positive NSCLC. Efficacy was demonstrated in total of 316 patients with locally advanced or metastatic RET fusion-positive NSCLC. Patients received selpercatinib until disease progression or unacceptable toxicity.Among 69 treatment-naïve patients, ORR was 83% with a DOR of 20.3 months . Among 247 patients previously treated with platinum-based chemotherapy, ORR was 62% with a DOR of 31.6 months. [2024 ELCC Abstract 35P; NCT03157128]In the open-label, multi-center phase II LIBRETTO-321 study, Chinese patients with advanced solid tumors harboring RET alterations received selpercatinib 160 mg twice daily. Of 77 enrolled patients, 47 had RET fusion-positive NSCLC. After 9.7 months of median follow-up, IRC-assessed ORR in the PAS (n = 26) was 69.2% and 94.4% of responses were ongoing; the ORR was 87.5% and 61.1% in treatment-naïve and pre-treated patients, respectively. IRC-assessed ORR in all patients with NSCLC (n = 47) was 66.0%. Among five patients with measurable CNS metastases at baseline, four (80%) achieved an IRC-assessed intracranial response. [PMID: 35923928] **Cabozantinib** Cabozantinib is an orally bioavailable, small molecule receptor tyrosine kinase (RTK) inhibitor. The NCCN guideline recommends cabozantinib (category 2A) for the treatment of patients with RET rearrangement positive non-small cell lung cancer (NSCLC) .Researchers conducted open-label, Simon two-stage, single-centre, phase 2, single-arm trial to assess the activity of cabozantinib in patients with RET-rearranged lung cancers.26 patients with RET-rearranged lung adenocarcinomas were enrolled and given cabozantinib; 25 patients were assessable for a response. KIF5B-RET was the predominant fusion type identified in 16 (62%) patients. The study met its primary endpoint, with confirmed partial responses seen in seven of 25 response-assessable patients (overall response 28%). [PMID: 27825636] [NCT01639508] **Lenvatinib** Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). This open label, phase 2 study enrolled pts with RET-positive lung adenocarcinoma. Pts received lenvatinib 24 mg/d in 28-d cycles until disease progression or unacceptable toxicity. 25 Pts with RET-positive NSCLC enrolled (KIF5B-RET: 13, other RET fusion: 12). Tumor shrinkage occurred in the majority of pts; ORR was 16% (confirmed PRs). DCR was 76%. [2016 EMSO Abstract 1204PD] **Vandetanib** Vandetanib is an oral kinase inhibitor of tumour angiogenesis and tumour cell proliferation with the potential for use in a broad range of tumour types. This is a multi-institution, open-label, phase II trial . The purpose of this study is to investigate the efficacy and safety of vandetanib in patients with advanced NSCLC harboring RET gene rearrangement. Eighteen patients (12 males, 6 females) were enrolled. three patients (17%) had partial remission and another eight patients had stable disease. [2016 ASCO Abstract 9013]This was a multicenter, single-arm phase II study to evaluate the efficacy and safety of vandetanib in pts with advanced RET-rearranged NSCLC who failed at least one prior chemotherapy. A total of 19 pts (10 KIF5B-RET, 6 CCDC6-RET, and 3 unknown-RET) were enrolled in this study and 17 pts were eligible for efficacy analysis. Among 17 eligible pts, ORR was 53% of which 9 partial responses met the primary endpoint, and disease control rate was 88%. The median progression-free survival (PFS) was 4.7 months. According to RET fusion subtypes, ORR and median PFS were 83% (5/6) and 8.3 months in pts with CCDC6-RET versus 20% (2/10) and 2.9 months in those with KIF5B-RET. The median overall survival was 11.1 months. [2016 ASCO Abstract 9012] **Sorafenib** Sorafenib is a synthetic compound targeting growth signaling and angiogenesis. The concentration needed for 50% growth inhibition (GI (50)) by sorafenib was 0.14 mumol/L for the PTC cells with the RET/PTC1 rearrangement, and 2.5 mumol/L for PTC cells with a BRAF mutation, both readily achievable serum concentrations. After 3 weeks of oral administration of sorafenib (80

		mg/kg/d) in mice, small (94% reduction compared with controls) or no tumor growth was detected in mice inoculated with PTC cells bearing the RET/PTC1 rearrangement. [PMID: 18676765] **BOS172738** BOS172738 is an investigational, potent, selective oral RET kinase inhibitor. NCT03780517 is a phase 1 study consisting of a dose-escalation and dose-expansion phase. During the escalation, 67 patients with RET-altered advanced solid tumors received once-daily oral doses of BOS172738 (10-150 mg). BOS172738 demonstrated broad anti-tumor activity with an investigator-assessed ORR of 33% (n=18/54), a NSCLC ORR of 33% (n=10/30), MTC ORR of 44% (n=7/16, including 1 complete response) and one patient with RET fusion+ pancreatic cancer reported a partial response. Responders included patients with brain metastases with one patient whose brain lesion decreased by 43%. The median duration of response has not been reached. Many patients remain on study, including the longest of 659 days, at data cutoff [2021 ASCO Abstract 3008] [NCT03780517] **HS-10365** HS-10365 is a highly potent and selective tyrosine kinase inhibitor, and the preclinical studies have indicated its favorable safety and antitumor activity in RET-altered tumor models. This study (NCT05207787) recruited patients (pts) with RET-altered advanced solid tumors, including RET fusion-positive (+) NSCLC, RET-mutated medullary thyroid carcinoma and so on. As of Dec.15th 2022, 31 RET fusion+ NSCLC pts with RET TKI-naïve were received HS-10365 at 6 doses, including 25 previously received platinum-based chemotherapy pts and 6 treatment-naïve pts. The ORR was 70.0% (21/30, 95% CI 50.6%-85.3%), with 66.7% (16/24) in pretreated pts and 83.3% (5/6) in treatment naïve pts. Furthermore, the DCR was 96.7% (29/30, 95% CI 82.8%-99.9%), with 95.8% (23/24) in pretreated pts and 100% (6/6) in treatment naïve pts. Meanwhile, 25 of 31 pts remained on treatment and responses were ongoing [2023 AACR Abstract CT201, NCT05207787]. **RXDX-105** RXDX-105 is an orally available, highly selective kinases inhibitor of RET. Pts with advanced solid tumors were enrolled in a Phase 1/1b dose escalation study followed by dose expansion at the RP2D. RXDX-105 was given orally at doses ranging from 20 - 350 mg QD. As of 30Jun2017, 144 (55 Ph 1; 89 Ph 1b) pts (73F; 71M) received RXDX-105. Of the 91 pts treated in Ph 1b, 21 pts had NSCLC harboring RET fusions confirmed by NGS, were RETi naïve, and evaluable for efficacy. Of these, 13 harbored the KIF5B-RET fusion. The other 8 pts had a variety of non-KIF5B-RET fusions; 6 of these 8 pts achieved a confirmed PR for an ORR of 75%. Median DOR has not yet been reached. None of the 13 pts with KIF5B-RET fusions had a RECIST response, although 4 had SD lasting ≥ 6 months. Overall, time on treatment ranges from 0.5+ to 14.5+ months. [NCT01877811] [2017 ESMO Abstract LBA19-A] **SY-5007** SY-5007 is a highly potent RET inhibitor that selectively targets RET fusions and mutations. This pivotal phase II study aimed to evaluate the efficacy and safety of SY-5007, a novel, highly selective RET inhibitor, in Chinese patients with advanced, positive RET NSCLC. As of the data cutoff date on January 16, 2024, the trial enrolled 105 patients, with a median follow-up of 4.57 months. The BICR-assessed overall ORR was 77.1% and DCR was 83.8%. The investigator-assessed overall ORR was 77.1% and DCR was 90.5%. In treatment-naive patients (cohort 1, n=56), SY-5007 showed an ORR of 83.9% and a DCR of 91.1%. In pre-treated patients (cohort 2, n=49), SY-5007 exhibited an ORR of 69.4% and a DCR of 89.8%. For 29 patients with baseline brain metastasis, the ORR and DCR were 69.0% and 86.2%. Meanwhile, the ORR and DCR for 76 patients without baseline brain metastasis were 80.3% and 92.1%. Among 10 patients with baseline intracranial target lesions, intracranial ORR and DCR were 80.0% and 100%. Median PFS, DoR or OS were not reached (2024 ASCO Abstract 3106; NCT05278364).
KIF5B-RET NM_004521.2;NM_020975.4 rearrangement	Pralsetinib Selpercatinib Cabozantinib Lenvatinib Vandetanib Sorafenib	**Gene Description:** KIF5B (Kinesin Family Member 5B) is a microtubule motor protein involved in cargo transportation (PMID: 12743033), including lysosome and mitochondria transportation (PMID: 30058692).RET (Ret Proto-Oncogene) encodes receptor tyrosine kinase that activates downstream MAPK and PI3K/AKT signaling pathways, and plays a role in cell differentiation, growth, migration and survival (PMID: 24561444, PMID:

	BOS172738 HS-10365 RXDX-105 SY-5007	29134959, PMID: 32094155). RET activating mutations, fusions, amplification and/or overexpression has been associated with a variety of cancers including lung (PMID: 30257958) and colorectal (PMID: 30210625, PMID: 30038711). **Variant Description:** KIF5B-RET gene rearrangement is the rearrangement of the KIF5B gene and RET gene.RET rearrangements include KIF5B-RET, CCDC6-RET, NCOA4-RET and TRIM33-RET, etc. In the rearrangement, the kinase region of RET is retained, but the promoter is changed, which leads to the activation of RET gene. **Drug Interpretation:** **Pralsetinib** Pralsetinib (BLU-667) is an orally bioavailable selective inhibitor of mutant forms of and fusion products involving the proto-oncogene receptor tyrosine kinase RET, with potential antineoplastic activity. The NCCN guideline recommends Pralsetinib (category 2A) for the first-line treatment of patients with RET rearrangement. Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). 281 pts with RET fusion+ NSCLC had received pralsetinib of whom 260 had measurable disease at baseline per BICR. The ORR was 63.1% in pts with prior platinum treatment and 77.6% , Median overall survival was 44.3 months in pre-treated pts and not reached in treatment-naïve pts. [2022 ESMO Abstract 1170P] [NCT03037385]A retrospective efficacy and safety analysis was performed on data from patients with RET fusion positive NSCLC who were enrolled in the pralsetinib Italian expanded access program (EAP) between July 2019 and October 2021. The most frequent gene fusion partner was KIF5B (77%). Brain metastases were known in 17 patients (28%) at the time of pralsetinib treatment. 13 patients were treatment naïve, 47 were pretreated. The ORR was 66% in the evaluable population (n=58). The DCR was 79%. After a median follow-up of 10.1 months, the median progression free survival was 8.9 months. In patients with measurable brain metastases (n = 6) intracranial ORR was 83%, and intracranial DCR was 100%. [2022 ESMO Abstract 1124P] **Selpercatinib** Selpercatinib is a selective RET kinase inhibitor. The NCCN guideline recommends selpercatinib (category 2A) for the treatment of patients with RET rearrangement positive NSCLC. Efficacy was demonstrated in total of 316 patients with locally advanced or metastatic RET fusion-positive NSCLC. Patients received selpercatinib until disease progression or unacceptable toxicity.Among 69 treatment-naïve patients, ORR was 83% with a DOR of 20.3 months . Among 247 patients previously treated with platinum-based chemotherapy, ORR was 62% with a DOR of 31.6 months. [2024 ELCC Abstract 35P; NCT03157128]In the open-label, multi-center phase II LIBRETTO-321 study, Chinese patients with advanced solid tumors harboring RET alterations received selpercatinib 160 mg twice daily. Of 77 enrolled patients, 47 had RET fusion-positive NSCLC. After 9.7 months of median follow-up, IRC-assessed ORR in the PAS (n = 26) was 69.2% and 94.4% of responses were ongoing; the ORR was 87.5% and 61.1% in treatment-naïve and pre-treated patients, respectively. IRC-assessed ORR in all patients with NSCLC (n = 47) was 66.0%. Among five patients with measurable CNS metastases at baseline, four (80%) achieved an IRC-assessed intracranial response. [PMID: 35923928] **Cabozantinib** Cabozantinib is an orally bioavailable, small molecule receptor tyrosine kinase (RTK) inhibitor. The NCCN guideline recommends cabozantinib (category 2A) for the treatment of patients with RET rearrangement positive non-small cell lung cancer (NSCLC) .Researchers conducted open-label, Simon two-stage, single-centre, phase 2, single-arm trial to assess the activity of cabozantinib in patients with RET-rearranged lung cancers.26 patients with RET-rearranged lung adenocarcinomas were enrolled and given cabozantinib; 25 patients were assessable for a response. KIF5B-RET was the predominant fusion type identified in 16 (62%) patients. The study met its primary endpoint, with confirmed partial responses seen in seven of 25 response-assessable patients (overall response 28%). [PMID: 27825636] [NCT01639508] **Lenvatinib** Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors

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MDM2 NM_002392.4 copy number gain	Alrizomadlin ASTX295 Brigimadlin	**Gene Description:** MDM2 (MDM2 Proto-Oncogene) encodes a nuclear-localized E3 ubiquitin ligase, which promotes tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. Amplification and/or overexpression of MDM2 has been identified in several cancer types (PMID: 23303139, PMID: 31440117) and amplification is common in liposarcoma (PMID: 30237864). **Variant Description:** A copy number gain alteration in MDM2 is identified in this case. **Drug Interpretation:** **Alrizomadlin** Alrizomadlin is a novel MDM2 inhibitor that blocks the interaction of MDM2 and p53. A preclinical trials of Alrizomadlin targeting the MDM2-p53 pathway demonstrate that Alrizomadlin-mediated p53 activation promotes anti-tumor immunity in the tumor microenvironment regardless of the Trp53 status of the tumor itself. [PMID: 31779710] As of December 25, 2020, 84 pts had been treated in 6 cohorts: melanoma (n = 26), NSCLC (n = 23), ATM mutation (n = 9), liposarcoma (n = 14), urothelial (n = 9), and MPNST (n = 3). In the PD-1/PD-L1 inhibitor-failed melanoma cohort, there was 1 confirmed PR out of 5 pts with uveal melanoma, 2 PR (1 confirmed and 1 unconfirmed) of 5 pts with mucosal melanoma, and 1 confirmed PR of 11 pts with cutaneous melanoma. ORR in the melanoma cohort was 17.4% (4/23 evaluable pts), and the DCR was 60.9% (14/23). In the MPNST cohort, 1 of 3 pts had an unconfirmed ongoing PR. In I-O drug-failed NSCLC (n = 14 evaluable) and urothelial (n = 5 evaluable) cohorts, each reported 1 confirmed PR. [2021 ASCO Abstract 2506] **ASTX295** ASTX295 is a potent, next generation MDM2 antagonist with a shorter half-life aimed at reducing on-target bone marrow toxicity. ASTX295-01 is a first-in-human, open-label, multicenter, phase 1/2 study that enrolled 83 patients with wild-type TP53. Following treatment with ASTX295, multiple objective responses were observed, including 1 NSCLC patient and 3 liposarcoma (LPS) patients (a tumor type commonly associated with MDM2 amplification). The ORR for LPS was 7.9%, with PFS of 7.95 and 9.66 months, and a 16-week disease control rate of 69.2% and 72.0%. Five GBM patients were enrolled, 4 of whom had MDM2 amplification, and 3 of them showed tumor regression. [2024 AACR Abstract CT066] **Brigimadlin** Brigimadlin (BI 907828), a highly potent mouse double minute-2 (MDM2)-p53 antagonist, has shown potent preclinical antitumour activity.

		A phase I study is evaluating BI 907828 in pts with advanced solid tumours. At data cut off (April 2023), 140 pts had been enrolled to receive BI 907828. At data cut off, 16/140 pts (11.4%) had a confirmed PR, and 89 pts had SD, giving a DCR of 75.0%. Preliminary mPFS was 7.8 months; 36 pts (25.7%) had PFS >6 months. A total of 10 pts with advanced biliary tract cancer (BTC) received BI 907828; of these, 3 (30%) had a confirmed PR and 5 had SD (DCR 80%). Two pts with BTC achieved PFS >12 months. [2023 ESMO Abstract 673P; NCT03449381] Brightline-2: A Study to Test Whether BI 907828 Helps People With Cancer in the Biliary Tract, Pancreas, Lung or Bladder is recruiting. [NCT05512377]

Resistant therapies

Genetic Variation	Therapies	Detailed Interpretation
SVIL-RET NM_021738.2; NM_020975.4 rearrangement	Afatinib Erlotinib Gefitinib	**Gene Description:** RET (Ret Proto-Oncogene) encodes receptor tyrosine kinase that activates downstream MAPK and PI3K/AKT signaling pathways, and plays a role in cell differentiation, growth, migration and survival (PMID: 24561444, PMID: 29134959, PMID: 32094155). RET activating mutations, fusions, amplification and/or overexpression has been associated with a variety of cancers including lung (PMID: 30257958) and colorectal (PMID: 30210625, PMID: 30038711). **Variant Description:** SVIL-RET rearrangement, results a fusion gene which contain promoter region to intron 1 of SVIL gene in 5'and intron 11 to terminator of RET gene.This fusion preserves the complete kinase domain of the RET gene, and may lead to the functional activation(PMID: 32326537). **Drug Interpretation:** **Afatinib, Erlotinib, Gefitinib** Afatinib is a an orally bioavailable anilino-quinazoline derivative and potent, irreversible inhibitor of the receptor tyrosine kinase (RTK) epidermal growth factor receptor (ErbB; EGFR) family, with antineoplastic activity. Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. Gefitinib is the first selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that binds to the adenosine triphosphate (ATP)-binding site of the enzyme. By inhibiting EGFR tyrosine kinase, the downstream signaling cascades are also inhibited, resulting in inhibited malignant cell proliferation. Multiple case reports indicate that RET rearrangement may be a potential resistance mechanism to EGFR TKIs in EGFR mutant NSCLC. [PMID: 26187428]
KIF5B-RET NM_004521.2; NM_020975.4 rearrangement	Afatinib Erlotinib Gefitinib	**Gene Description:** KIF5B (Kinesin Family Member 5B) is a microtubule motor protein involved in cargo transportation (PMID: 12743033), including lysosome and mitochondria transportation (PMID: 30058692).RET (Ret Proto-Oncogene) encodes receptor tyrosine kinase that activates downstream MAPK and PI3K/AKT signaling pathways, and plays a role in cell differentiation, growth, migration and survival (PMID: 24561444, PMID: 29134959, PMID: 32094155). RET activating mutations, fusions, amplification and/or overexpression has been associated with a variety of cancers including lung (PMID: 30257958) and colorectal (PMID: 30210625, PMID: 30038711). **Variant Description:** KIF5B-RET gene rearrangement is the rearrangement of the KIF5B gene and RET gene.RET rearrangements include KIF5B-RET, CCDC6-RET, NCOA4-RET and TRIM33-RET, etc. In the rearrangement, the kinase region of RET is retained, but the promoter is changed, which leads to the activation of RET gene. **Drug Interpretation:** **Afatinib, Erlotinib, Gefitinib** Afatinib is a an orally bioavailable anilino-quinazoline derivative and potent, irreversible inhibitor of the receptor tyrosine kinase (RTK) epidermal growth factor receptor (ErbB; EGFR) family, with antineoplastic activity. Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. Gefitinib is the first selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that binds to the adenosine triphosphate

		(ATP)-binding site of the enzyme. By inhibiting EGFR tyrosine kinase, the downstream signaling cascades are also inhibited, resulting in inhibited malignant cell proliferation. Multiple case reports indicate that RET rearrangement may be a potential resistance mechanism to EGFR TKIs in EGFR mutant NSCLC. [PMID: 26187428]

Note:

Clinical trials only show some relevant results, and clinical trials are updated in real time. For comprehensive clinical trial information, please refer to www.clinicaltrials.gov.

5. Interpretation for polymorphism variants related with chemotherapies

Drug Classes	Test Content	Drug name	Gene	dbSNP	Genotype	Variant-Drug Phenotype Annotation	Evidence Level
5-Fluorouracil (5-Fu), Fluoropyrimidines	Drug efficacy	5-Fu+Oxaliplatin	*GSTP1*	rs1695	AA	Associated with poorer response to treatment	2A
	Drug toxicity	5-Fu or Capecitabine	*DPYD*	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
			MTHFR	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
		5-Fu+Leucovorin or Tegafur+Leucovorin	*UMPS*	rs1801019	GG	Associated with decreased risk of drug toxicity	2B
		Fluoropyrimidine-based therapy	***DPYD***	**rs67376798**	**TT**	**Associated with decreased risk of drug toxicity**	**1A**
			DPYD	**rs55886062**	**AA**	**Associated with decreased risk of drug toxicity**	**1A**
			DPYD	**rs3918290**	**CC**	**Associated with decreased risk of drug toxicity**	**1A**
Anthracyclines	Drug toxicity	Anthracyclines	*CBR3*	rs1056892	AG	Associated with increased risk of drug toxicity	2B
		Epirubicin	*GSTP1*	rs1695	AA	Associated with decreased risk of drug toxicity	2A
	Drug efficacy	Epirubicin	*GSTP1*	rs1695	AA	Associated with better response to treatment	2A
Aromatase inhibitors	Drug efficacy	Letrozole, Anastrozole	*CYP19A1*	rs4646	CC	Associated with poorer response to treatment	3
		Anastrozole	*ABCB1*	rs2032582	AC	Associated with poorer response to treatment	3
	Drug toxicity	Anastrozole	*ABCB1*	rs1045642	AG	Associated with increased risk of drug toxicity	3
Capecitabine	Drug toxicity	Capecitabine-Based Chemotherapy	*MTHFR*	rs1801131	GT	Associated with increased risk of drug toxicity	2A
			DPYD	rs2297595	TT	Associated with decreased risk of drug toxicity	2A
		5-Fu or Capecitabine	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
		Capecitabine	***DPYD***	**rs67376798**	**TT**	**Associated with decreased risk of drug toxicity**	**1A**
			DPYD	**rs55886062**	**AA**	**Associated with decreased risk of drug toxicity**	**1A**
			DPYD	**rs3918290**	**CC**	**Associated with decreased risk of drug toxicity**	**1A**
Cyclophosphamide	Drug toxicity	Cyclophosphamide	*XRCC1*	rs25487	CT	Associated with decreased risk of drug toxicity	3
			MTHFR	rs1801133	GG	Associated with decreased risk of drug toxicity	2A
		Cyclophosphamide+Epirubicin	*GSTP1*	rs1695	AA	Associated with decreased risk of drug toxicity	2A
	Drug efficacy	Cyclophosphamide	*XRCC1*	rs25487	CT	Associated with poorer response to treatment	3
			SOD2	rs4880	AA	Associated with better response to treatment	2B
		Cyclophosphamide+Epirubicin	*GSTP1*	rs1695	AA	Associated with better response to treatment	2A

Etoposide	Drug toxicity	Etoposide	*SLIT1*	rs2784917	AG	Associated with decreased risk of drug toxicity	4
			ABCB1	rs1045642	AG	Associated with decreased risk of drug toxicity	3
Gemcitabine	Drug toxicity	Gemcitabine	*RRM1*	rs9937	AA	Associated with increased risk of drug toxicity	4
			CDA	rs60369023	GG	Associated with decreased risk of drug toxicity	3
			CDA	rs2072671	AA	Associated with decreased risk of gastrointestinal toxicity and neutropenia, increased risk of hematologic toxicity	2B
Irinotecan	Drug toxicity	Irinotecan	*UGT1A1*	rs8175347	6TA/6TA	Associated with decreased risk of drug toxicity	2A
			UGT1A1	rs4148323	AG	Associated with moderate risk of drug toxicity	2A
			C8orf34	rs1517114	GG	Associated with decreased risk of drug toxicity	2B
Methotrexate	Drug toxicity	Methotrexate	*MTHFR*	rs1801133	GG	Associated with decreased risk of drug toxicity	3
			MTRR	rs1801394	AA	Associated with decreased risk of drug toxicity	2B
			ABCB1	rs1045642	AG	Associated with increased risk of drug toxicity	2A
	Drug efficacy	Methotrexate	*ATIC*	rs4673993	TT	Associated with poorer response to treatment	2B
Pemetrexed	Drug efficacy	Pemetrexed	*MTHFR*	rs1801133	GG	Associated with better response to treatment	3
Platinum-Based Chemotherapy	Drug toxicity	Cisplatin	*XPC*	rs2228001	GT	Associated with increased risk of drug toxicity	1B
		Platinum compounds	*GSTP1*	rs1695	AA	Associated with increased risk of drug toxicity	2A
		Cisplatin, Platinum, Platinum compounds	*ERCC1*	rs3212986	CC	Associated with increased risk of drug toxicity	2B
		Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with increased risk of drug toxicity	2B
			XRCC1	rs25487	CT	Associated with decreased risk of drug toxicity	2B
	Drug efficacy	Carboplatin	*MTHFR*	rs1801133	GG	Associated with poorer response to treatment	2A
		Platinum compounds	*XRCC1*	rs1799782	GA	Associated with better response to treatment	NA
		Carboplatin, Cisplatin, Oxaliplatin, Platinum, Platinum compounds	*ERCC1*	rs11615	AA	Associated with poorer response to treatment	2B
			XRCC1	rs25487	CT	Associated with poorer response to treatment	2B
Taxanes	Drug toxicity	Paclitaxel	*ABCB1*	rs1045642	AG	Associated with increased risk of drug toxicity	3
			SOD2	rs4880	AA	Associated with increased risk of drug toxicity	3
		docetaxel	*ERCC1*	rs3212986	CC	Associated with increased risk of drug toxicity	3
			ERCC1	rs11615	AA	Associated with increased risk of drug toxicity	3

		Taxanes	*ABCB1*	rs2032582	CA	Associated with moderate risk of drug toxicity	3
	Drug efficacy	Paclitaxel+Cisplatin	*TP53*	rs1042522	CC	Associated with better response to treatment	2B
		Paclitaxel	*ABCB1*	rs2032582	CA	Associated with moderate response to treatment	3
Vinca alkaloids	Drug efficacy	Vincristine	*ABCB1*	rs1045642	AG	Associated with poorer response to treatment	3

Note:

1. The level of variant-drug associations evidence is based on PharmGKB website, for more detailed information please see http://www.pharmgkb.org/page/clinAnnLevels.

   Level 1A：Annotation for a variant-drug combination in a CPIC- or medical society–endorsed pharmacogenomics guideline, or implemented at a PGRN site, or in another major health system;

   Level 1B： Annotation for a variant-drug combination in which the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant P-values, and, preferably with a strong effect size;

   Level 2A： Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely;

   Level 2B： Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small;

   Level 3: Annotation for a variant–drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association;

   Level 4： Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.
2. The variant-drug correlation relationship derived from multiple independent studies, therefore, the interpretations of the same class of drug for the tested individual may be inconsistent. The final drug instruction needs to combine with the specific clinical situation.
3. The detection results are only based on the analysis of tumor samples and lack of control, the results of some loci may be specific to tumor tissues due to factors such as loss of heterozygosity.

6. Immune checkpoint inhibitors predictive biomarkers

Detected of Indicator or gene for immune checkpoint inhibitor*

Biomarker/Variant		Result	Clinical Interpretation
Biomarkers for predicting efficacy			
Tumor mutation burden (TMB)		**TMB-L**	**-**
Microsatellite instability (MSI)		**MSS**	**-**
Affect the treatment effect - positive correlation			
PD-L1 amplification		-	-
PBRM1 inactivating mutation (Renal clear cell carcinoma)		-	-
MLH1 deleterious mutation		-	-
MSH2 deleterious mutation		-	-
MSH6 deleterious mutation		-	-
PMS2 deleterious mutation		-	-
POLE mutation (driver)		-	-
POLD1 mutation (driver)		-	-
Other DNA damage repair (DDR) pathway genes	*ATM* mutation	-	-
	ATR mutation	-	-
	BAP1 mutation	-	-
	BLM mutation	-	-
	BRCA1 mutation	-	-
	BRCA2 mutation	-	-
	BRIP1 mutation	-	-
	CHEK1 mutation	-	-
	CHEK2 mutation	-	-
	ERCC2 mutation	-	-
	ERCC3 mutation	-	-
	ERCC4 mutation	*ERCC4* p.V756M(24.4%)	May increase the benefit rate of PD-1/PD-L1 inhibitors
	ERCC5 mutation	-	-
	FANCA mutation	-	-
	FANCC mutation	-	-
	MRE11A mutation	-	-
	NBN mutation	-	-
	RAD50 mutation	-	-

	RAD51 mutation	-	-
	RAD51B mutation	-	-
	RAD51D mutation	-	-
	RAD54L mutation	-	-
TP53 mutation		-	-
KRAS mutation		-	-
Affect the treatment effect - negative correlation			
PTEN inactivating mutation		-	-
JAK1 inactivating mutation		-	-
JAK2 inactivating mutation		-	-
B2M inactivating mutation		-	-
EGFR mutation (L858R/EX19del)		-	-
ALK rearrangement		-	-
STK11 inactivating mutation		-	-
KEAP1 inactivating mutation		-	-
11q13 amplification		-	-
MDM2 amplification		*MDM2* copy number gain(14.0)	Increase the risk of hyper progress when treated with PD-1/PD-L1 inhibitors
MDM4 amplification		-	-
DNMT3A inactivating mutation		-	-
Indicator affecting prognosis of immune checkpoint inhibitor therapy			
HLA-I Zygosity (At least one of type A, B, C is homozygous)		-	-

* Clinical concordance has not been established for predictive biomarkers for immune checkpoint inhibitors (ICI). Information about these biomarkers is intended for Research-Use Only and may not be used to guide treatment and/or for clinical decision making. Any decision on the patient's treatment is at the sole discretion of the treating physician and must be considered in combination with other relevant patient information.

Note:

1. "-" denotes no alterations were detected in this individual.
2. The interpretation of the detection results of *PBRM1* inactivating mutations is only applicable to renal clear cell carcinoma.
3. The indicators/gene clinical interpretations listed above are for reference only, and the specific decisions need to refer to professional physician instructions.
4. For a detailed interpretation, showed in Interpretation for biomarker of checkpoint inhibitor.
5. POLE and POLD1 mutations are restrict to currently reported mutations that may lead to hypermutation in tumor, resulting in tumor mutation burden increase.
6. HLA-I results analyzed by the phenotypes of HLA-A, HLA-B and HLA-C loci detected from tumor samples. Due to the lack of control samples, HLA-I typing cannot be accurately analyzed and It is possible that show homozygosity because of the occurrence of HLA-LOH in the tumor tissue.

7. PARP inhibitors efficacy prediction

Gene	Result	Clinical Interpretation
BRCA1	-	***BRCA1* and *BRCA2* gene:** NCCN Guidelines recommend patients with germline or somatic BRCA1/2 mutated ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma treat with Olaparib and Rucaparib; ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma cancer in HRD-positive status that defined by either a deleterious or suspected deleterious BRCA mutation or genomic instability are recommended treat with Niraparib; breast cancer patients with germline BRCA1/2 mutation are recommended to treat with Olaparib or Talazoparib; pancreatic adenocarcinoma carrying deleterious germline BRCA1/2 mutation are recommended to use Olaparib as maintenance treatment; Rucaparib is recommended for patients with prostate cancer whose tumor have deleterious germline or somatic BRCA1/2 mutations; prostate cancer carrying HRR mutations (including BRCA1/2) are recommended to use Olaparib. **Other homologous recombination repair (HRR) pathway genes:** CHEK1/CHEK2, BRCA1/2, BRIP1, CDK12, ATM/ATR, FANCA/C/D2/E/F/G/L/M, MRE11A, NBN, RAD50/51, RAD51B/C/D, RAD54L, PALB2, BAP1, BLM, RECQL, RECQL4, WRN, FAM175A, BARD1, EMSY, ERCC1, ATRX genes play a role in the repair process of homologous recombination (HR), and PARP inhibitors can comprehensively defect tumor cells with homologous recombination deficiency (HRD). NCCN Guidelines recommend prostate cancer with HRR mutations (including BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B/C/D, RAD54L gene mutations) use Olaparib as second-line treatment. Multiple clinical studies have shown that patients with deficiency in HRR gene can receive benefit from PARP inhibitors treatment (PMID: 2610020; 28588062; 2015 ESMO-ECC Abstract 435; 2015 ASCO Abstract 5508; ESMO 2019 TRITON2 Updated Analyses; 2019 ASCO Abstract 3006; ESMO 2019: GALAHAD). The clinical trials that PARP inhibitors used for the treatment of solid tumors with HRR gene deficiency (including breast cancer, prostate cancer, melanoma, and non-small cell lung cancer) are ongoing (NCT03344965, NCT03967938, NCT03742895, NCT02952534, NCT04171700, NCT02401347, NCT02854436).
BRCA2	-	
ATM	-	
ATR	-	
ATRX	-	
BAP1	-	
BARD1	-	
BLM	-	
BRIP1	-	
CDK12	-	
CHEK1	-	
CHEK2	-	
C11orf30	-	
ERCC1	-	
FAM175A	-	
FANCA	-	
FANCC	-	
FANCD2	-	
FANCE	-	
FANCF	-	
FANCG	-	
FANCL	-	
FANCM	-	
MRE11A	-	
NBN	-	
PALB2	-	
RAD50	-	
RAD51	-	
RAD51B	-	
RAD51C	-	
RAD51D	-	
RAD54L	-	
RECQL	-	
RECQL4	-	
WRN	-	

Note: "-" denotes no alterations were detected in this individual.

8. Interpretation of Immune checkpoint inhibitors predictive biomarkers

Interpretation of TMB & MSI Biomarker

Tumor Mutation Burden (TMB):TMB-L
Tumor mutation burden (TMB) refers to the number of somatic mutations in the coding region, usually indicated as the total number of somatic mutations within each MB tumor genome region. GenePlus TMB database already accumulated TMB results derived from more than 10,000 cases of Chinese solid tumor. TMB is divided into high TMB (TMB-H) and low TMB (TMB-L) based on the TMB values distribution in Geneplus database. The top quartile TMB distribution is used as the cut-off value to define TMB-H. It is necessary to mention that TMB values evaluation may be affected by low tumor cell content. Colorectal cancers use TMB values corresponding to MSI-H to divide TMB high/low. The results of TMB are divided into two types: TMB-H, which means high tumor mutation burden; TMB-L, which means low tumor mutation burden. Several studies have shown that tumors with TMB-H (including NSCLC, colorectal cancer, melanoma, endometrial cancer, and glioma) are sensitive to pembrolizumab/nivolumab treatment and have more good benefits (2016 ASCO Abstract 9017; PMID: 25765070; 26028255;27159395; 27486176; 27001570; 27671167). Studies have also shown that urothelial carcinoma with high tumor mutation burden is sensitive to atezolizumab treatment (PMID: 26952546).
Microsatellite Instability (MSI):MSS
MSI (microsatellite instability, MSI) refers to the phenomenon that the sequence of microsatellites increases or decreases. Microsatellite (MS), also called Short Tandem Repeats (STRs) or Simple Sequence Repeat (SSRs), consists of repeated sequences of 1–6 nucleotides. This report uses NGS panel detection and is based on the 1021 Panel platform. The MSI status can be accurately judged by the microsatellite instability score of case samples, and the therapeutic efficacy of immune checkpoint inhibitors can be evaluated. Here are 2 types of MSI results: MSI-H, which means microsatellites are highly unstable; MSS, which means microsatellites are stable. FDA approved pembrolizumab for solid tumors with MSI-H or dMMR (highly unstable microsatellites or MMR defects) and approved for MSI-H or dMMR colorectal cancer as the first-line treatment. FDA approved nivolumab for the treatment of children or adults who have progressed after 5-FU/oxaliplatin/irinotecan treatment with MSI-H or dMMR metastatic colorectal cancer. The NCCN clinical practice guidelines for colorectal cancer indicate that pembrolizumab/nivolumab can be used for the treatment of patients with dMMR/MSI-H colorectal cancer.

The treatment effect - positive correlation

The treatment effect - negative correlation

***MDM2* amplification**
Findings:*MDM2* copy number gain(14.0)
MDM2 (MDM2 Proto-Oncogene) encodes a nuclear-localized E3 ubiquitin ligase, which promotes tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation. Amplification and/or overexpression of MDM2 has been identified in several cancer types and amplification is common in liposarcoma. Multiple studies have shown that MDM2/MDM4 amplification are supposed to be associated with hyperprogression on immune checkpoint inhibitors in diverse cancers. Champiat et al. have reported of 131 evaluable patients who received anti-PD-1/PD-L1 inhibitors, 12 patients (9%) were considered as having hyperprogressive disease which defined as a RECIST progression of tumor growth rate increased ≥2 fold upon immunotherapy treatment compared with the first evaluation (PMID: 27827313). In another study, among 155 patients after anti-PD-1/PD-L1 monotherapy, in all six individuals with MDM2/MDM4 amplification experienced time-to-failure < 2 months, and four of these patients present accelerated tumor growth rate, with 2.3-. 7.1-. 7.2- and 42.3- fold increase compared to that before immunotherapy (PMID: 28351930).

Indicator affecting prognosis of immune checkpoint inhibitor therapy

HLA-I	Somatic HLA-I heterozygosity or homozygous
HLA-A	Heterozygosity
HLA-B	Heterozygosity
HLA-C	Heterozygosity
The anti-tumor activity of immune checkpoint inhibitor therapy is related to CD8+ T cells. The recognition of cancer cells by CD8+ T cells is achieved by HLA-I (human leukocyte antigen class I) molecules presenting tumor antigens. HLA alleles have the characteristics of polymorphism and codominance. HLA-I loci subdivided into HLA-A, HLA-B and	

HLA-C. When a patient's HLA-I is homozygous at least one locus, this patient is expected to present less and less diverse tumor neoantigens to T cells compared to patients who are heterozygous at all three loci. In two cohorts, patients with heterozygous HLA-I showed longer OS than those with homozygous alleles, cohort1: HR=1.4 (1.02-1.9), P-value=0.036; cohort2: HR=1.31 (1.03- 1.7), P-value=0.028; among 32 patients with heterozygous HLA-I but at least one locus with LOH (loss of heterozygosity), patients with HLA-I LOH have a higher survival risk (P = 0.05, HR = 1.60, 95% CI 1.03-2.43), and these patients mainly with low mutation burden (P = 0.0006, HR = 3.68, 95% CI 1.64-8.23)(PMID: 29217585).

Note:

1. The clinical interpretation of indicators/genes listed in this report is for reference only, and specific decisions should be based on clinical reality.

9. TIER III - Variants of unknown significance

Single nucleotide variants, small size deletion/duplication

Gene	Transcript	c.HGVS	p.HGVS	Functional Region	VAF
FAT1	NM_005245.3	c.7777G>A	p.A2593T	EX10	38.4%
ERCC4	NM_005236.2	c.2266G>A	p.V756M	EX11	24.4%
TBX3	NM_016569.3	c.211G>T	p.A71S	EX1	19.6%

Copy number variations

Gene	Transcript	Variant Type	Functional Region	Copy Number
GNAS	NM_000516.4	copy number gain	all exon	14.8
IFNG	NM_000619.2	copy number gain	all exon	12.6
XRCC2	NM_005431.1	copy number gain	all exon	9.4
MYC	NM_002467.4	copy number gain	all exon	9.0
RAD52	NM_134424.2	copy number gain	all exon	7.0
KDM5A	NM_001042603.1	copy number gain	all exon	6.6
PCK1	NM_002591.3	copy number gain	all exon	5.0
GRIN2A	NM_001134407.1	copy number gain	all exon	4.8
EXT1	NM_000127.2	copy number gain	all exon	4.4
TERC	NR_001566.1	copy number gain	all exon	4.0

Gene rearrangement

Gene	Transcript	Variant Type	Functional Region	VAF
-	-	-	-	-

Note:

1. "-" denotes no alterations were detected in this individual.
2. The variant classification system used in this report is based on joint consensus recommendations of the AMP, ASCO, and CAP. Tier I, variants with strong clinical significance; Tier II, variants with potential clinical significance; Tier III, variants of unknown clinical significance; and Tier IV, variants deemed benign or likely benign (PMID: 27993330).
3. The table above only shows the functional mutations within analytical range.
4. The detection could not distinguish between somatic mutations and germline mutations effectively without control sample analysis. Polymorphism is filtered through the Thousand Genome Database and ExAC Database. The above table only lists the functional alterations of the important gene coding regions with a frequency of <0.01 in the two databases.
5. VAF, the abbreviation of variant allele frequency, represents the proportion of the mutant alleles accounted in the sum of wild type and mutant allele at a chromosome position.
6. Researches suggested that variant allele frequency or copy number of cell free DNA in peripheral blood may not be linearly correlated with that of DNA in tumor tissues.

10. Appendix

Variant Interpretation

FAT1 c.7777G>A(p.A2593T)

FAT1 (FAT Atypical Cadherin 1) is a transmembrane atypical cadherin that regulates cell growth via inhibition of the Yap1 pathway, and is involved in cell migration and invasion (PMID: 23076869, PMID: 29565465). FAT1 homozygous deletions have been identified in glioblastoma, astrocytoma and oral cancers (PMID: 23076869, PMID: 23354438), and mutations have been observed in several tumor types including glioblastoma, head and neck squamous cell carcinoma, colorectal, and esophageal cancer (PMID: 23354438, PMID: 23076869, PMID: 29565465), and T-cell acute lymphoblastic leukemia (PMID: 24972153).
A missense alteration in FAT1,p.A2593T, is identified in this case.
SIFT predict result of the mutation is benign, PolyPhen-2 predict result of the mutation is benign, The results of the predict are for reference only.

ERCC4 c.2266G>A(p.V756M)

ERCC4 (ERCC Excision Repair 4, Endonuclease Catalytic Subunit) encoded protein forms a complex with ERCC1 and is involved in the 5' incision made during nucleotide excision repair. ERCC4 mutations results in xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, and XFE progeria and therefore, may be associated with increased cancer risk (PMID: 26074087).
A missense alteration in ERCC4,p.V756M, is identified in this case.
SIFT predict result of the mutation is benign, PolyPhen-2 predict result of the mutation is benign, The results of the predict are for reference only.

TBX3 c.211G>T(p.A71S)

TBX3 (T-Box Transcription Factor 3) is a member of a phylogenetically conserved family of genes that share a common DNA-binding domain, the T-box. This protein functions in embryogenesis, cell cycle control, and cellular senescence (PMID: 22002537, PMID: 31669645). Overexpression of Tbx3 has been identified in cancers including breast, pancreatic, liver (PMID: 30578408), bladder, melanoma (PMID: 24025717), rhabdomyosarcoma (PMID: 32098189), and hypopharyngeal carcinoma (PMID: 31897121).
A missense alteration in TBX3,p.A71S, is identified in this case.
SIFT predict result of the mutation is benign, PolyPhen-2 predict result of the mutation is deleterious, The results of the predict are for reference only.

GNAS copy number gain

GNAS (GNAS Complex Locus) is a GTPase that is activated upon ligand binding of a G-protein coupled receptor, and is involved in mediating hormone response (PMID: 23640210, PMID: 25851935). Hotspot mutations impair Gnas GTPase activity, resulting in constitutive pathway activation and are common in a variety of tumor types (PMID: 23640210).
A copy number gain alteration in GNAS is identified in this case.

IFNG copy number gain

IFNG (Interferon Gamma) encodes a soluble cytokine that is a member of the type II interferon class that possesses antiviral activity and immunoregulatory functions. The protein is a potent activator of macrophages and has antiproliferative effects on transformed cells and it can potentiate the antiviral and antitumor effects of the type I interferons.
A copy number gain alteration in IFNG is identified in this case.

XRCC2 copy number gain

XRCC2 (X-Ray Repair Cross Complementing 2) encodes a member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage. XRCC2 variants may confer increased cancer risk in a variety of cancers including, breast and skin cancers (PMID: 15723711).
A copy number gain alteration in XRCC2 is identified in this case.

MYC copy number gain

MYC (MYC Proto-Oncogene, BHLH Transcription Factor) is a proto-oncogene and encodes a nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. Amplification, overexpression, and rearrangement of MYC is commonly observed in solid and hematological tumors (PMID: 28587062), such as lung cancer (PMID: 32014901) and diffuse large B-Cell lymphoma (PMID: 32074595).
A copy number gain alteration in MYC is identified in this case.

RAD52 copy number gain

RAD52 (RAD52 Homolog, DNA Repair Protein) is involved in double-stranded break repair and plays a central role in genetic recombination and DNA repair by promoting the annealing of complementary single-stranded DNA and by stimulation of the RAD51 recombinase. RAD52 mutations have been reported in large-scale sequencing studies (PMID: 21720365, PMID: 21798893).

A copy number gain alteration in RAD52 is identified in this case.

KDM5A copy number gain

KDM5A (Lysine Demethylase 5A) encodes a member of the Jumonji, AT-rich interactive domain 1 (JARID1) histone demethylase protein family. The encoded protein regulates gene transcription through chromatin remodeling to promote cell growth and differentiation (PMID: 30650517). KDM5A overexpression has been reported in a number of cancers including breast cancer (PMID: 22937203).
A copy number gain alteration in KDM5A is identified in this case.

PCK1 copy number gain

PCK1 (Phosphoenolpyruvate Carboxykinase 1) is a main control point for the regulation of gluconeogenesis.
A copy number gain alteration in PCK1 is identified in this case.

GRIN2A copy number gain

GRIN2A (Glutamate Ionotropic Receptor NMDA Type Subunit 2A) encodes a member of the glutamate-gated ion channel protein family and is a subunit of the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are both ligand-gated and voltage-dependent, and are associated with the efficiency of synaptic transmission. These receptors are permeable to calcium ions, and activation results in a calcium influx into post-synaptic cells, which results in the activation of several signaling cascades. Somatic mutations in GRIN2A are frequently observed in melanoma (PMID: 21499247, PMID: 27659111, PMID: 28986867, PMID: 24739903) and decreased expression has been observed in nasopharyngeal carcinoma (PMID: 26681223).
A copy number gain alteration in GRIN2A is identified in this case.

EXT1 copy number gain

EXT1 (Exostosin Glycosyltransferase 1) encodes an endoplasmic reticulum-resident type II transmembrane glycosyltransferase involved in the chain elongation step of heparan sulfate biosynthesis. Mutations in this gene cause the type I form of multiple exostoses.
A copy number gain alteration in EXT1 is identified in this case.

TERC copy number gain

TERC (Telomerase RNA Component) is the RNA component of telomerase that serves as template for new telomeric repeats, therefore is essential for telomerase function and regulates chromosomal stability and cell senescence (PMID: 27245259).
A copy number gain alteration in TERC is identified in this case.

Quality Control Results

Quality Control Index		Result	Criterion
Tumor Cell Content Assessment	Tumor Cell Content[1]	-	30%
DNA Quality Assessment	DNA Amount (ng)[2]	-	≥100
DNA Library Quality Assessment	DNA Library Amount (ng)[3]	-	≥600
Sequencing Quality Assessment	Average effective sequencing depth[4]	1251	≥500
	Fraction of target covered with ≥ 300x[5]		
	Fraction of base quality ≥ Q30[6]	97%	≥80%
Overall Assessment[7]		PASS	

Note:

1. Tumor Cell Content: The tumor cell content of the submitted samples evaluated under the microscope after HE staining. If the sample does not meet the conditions required for pathological evaluation, this item will not be involved in the quality control overall assessment results
2. DNA Amount (ng) : The total amount of DNA extracted from the tested samples.
3. DNA Library Amount (ng) : The total amount of DNA fragments that are constructed with adapters and barcodes, which also known as DNA library.
4. Average effective sequencing depth : Average sequencing depth on target without duplicated reads.
5. Fraction of target covered with ≥ 300x : The proportion of bases that sequencing depth reach or above 300x on target,

this index reflecting the coverage uniformity of sequencing.

6. Fraction of base quality ≥ Q30 : The proportion of base quality in sequencing data that reach or above Q30, that is the probability of base recognition accuracy rate exceeds 99.9%.
7. Overall Assessment : The quality control overall assessment results are divided into two levels: "PASS" and "RISK". The reliability of test results may be affected when the overall quality assessment result is "risk".

Genes Assayed

Genes with full coding exonic regions, flanking regions and splice variants included for the detection of substitutions, insertion-deletions (indels), and copy-number alterations (CNAs)

ABL1	*ACVR1B*	*AKT1*	*AKT2*	*AKT3*	*ALK*	*APC*	*AR*	*ARAF*	*ARID1A*
ARID1B	*ARID2*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*	*AXIN2*
AXL	*B2M*	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCOR*	*BLM*	*BMPR1A*	*BRAF*
BRCA1	*BRCA2*	*BRD4*	*BRIP1*	*BTK*	*CARD11*	*CASP8*	*CBFB*	*CBL*	*CCND1*
CCND2	*CCND3*	*CCNE1*	*CD274*	*CDC73*	*CDH1*	*CDK12*	*CDK4*	*CDK6*	*CDK8*
CDKN1A	*CDKN1B*	*CDKN2A*	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	*CHEK2*	*CIC*	*CREBBP*
CRKL	*CSF1R*	*CTCF*	*CTNNA1*	*CTNNB1*	*CUL3*	*CYLD*	*DAXX*	*DDR1*	*DDR2*
DICER1	*DNMT3A*	*DOT1L*	*EGFR*	*EIF1AX*	*C11orf30*	*EP300*	*EPAS1*	*EPCAM*	*EPHA2*
EPHA3	*EPHA5*	*EPHB1*	*EPHB6*	*ERBB2*	*ERBB3*	*ERBB4*	*ERCC1*	*ERCC3*	*ERCC4*
ERCC5	*ERG*	*ERRFI1*	*ESR1*	*EXT1*	*EXT2*	*EZH2*	*FAM123B*	*FAM175A*	*FANCA*
FANCC	*FANCD2*	*FANCE*	*FANCF*	*FANCG*	*FANCL*	*FANCM*	*FAS*	*FAT1*	*FAT2*
FBXW7	*FGF19*	*FGF3*	*FGF4*	*FGFR1*	*FGFR2*	*FGFR3*	*FGFR4*	*FH*	*FLCN*
FLT1	*FLT3*	*FLT4*	*FOXA1*	*FOXL2*	*FOXP1*	*FUBP1*	*GALNT12*	*GATA3*	*GNA11*
GNAQ	*GNAS*	*GRIN2A*	*GRM3*	*HDAC1*	*HGF*	*HNF1A*	*HOXB13*	*HRAS*	*IDH1*
IDH2	*IFNG*	*IFNGR1*	*IGF1R*	*IKBKE*	*IKZF1*	*IL7R*	*INPP4B*	*IRF2*	*IRS2*
JAK1	*JAK2*	*JAK3*	*JUN*	*KDM5A*	*KDM5C*	*KDM6A*	*KDR*	*KEAP1*	*KIT*
KRAS	*LRP1B*	*MAF*	*MAP2K1*	*MAP2K2*	*MAP2K4*	*MAP3K1*	*MAPK1*	*MAX*	*MCL1*
MDM2	*MDM4*	*MED12*	*MEF2B*	*MEN1*	*MET*	*MITF*	*MLH1*	*MLH3*	*MLL*
MLL2	*MLL3*	*MPL*	*MRE11A*	*MS4A1*	*MSH2*	*MSH3*	*MSH6*	*MST1R*	*MTOR*
MUTYH	*MYC*	*MYCL1*	*MYCN*	*MYD88*	*NBN*	*NCOR1*	*NF1*	*NF2*	*NFE2L2*
NFKBIA	*NKX2-1*	*NOTCH1*	*NOTCH2*	*NOTCH3*	*NPM1*	*NRAS*	*NSD1*	*NTHL1*	*NTRK1*
NTRK2	*NTRK3*	*PALB2*	*PARK2*	*PARP1*	*PAX5*	*PBRM1*	*PCK1*	*PDCD1*	*PDCD1LG2*
PDGFRA	*PDGFRB*	*PDK1*	*PIK3CA*	*PIK3CB*	*PIK3CG*	*PIK3R1*	*PIK3R2*	*PMS1*	*PMS2*
POLD1	*POLE*	*POT1*	*PPP2R1A*	*PRDM1*	*PRKAR1A*	*PTCH1*	*PTCH2*	*PTEN*	*PTPN11*
PTPRD	*RAC1*	*RAD50*	*RAD51*	*RAD51B*	*RAD51C*	*RAD51D*	*RAD52*	*RAD54L*	*RAF1*
RARA	*RB1*	*RBM10*	*RECQL*	*RECQL4*	*RET*	*RHOA*	*RICTOR*	*RINT1*	*RNF43*
ROS1	*RPTOR*	*RUNX1*	*SDHA*	*SDHAF2*	*SDHB*	*SDHC*	*SDHD*	*SERPINB 3*	*SERPINB4*
SETD2	*SF3B1*	*SLX4*	*SMAD2*	*SMAD3*	*SMAD4*	*SMARCA4*	*SMARCB1*	*SMO*	*SOCS1*
SOX2	*SOX9*	*SPOP*	*SRC*	*STAG2*	*STAT3*	*STK11*	*SUFU*	*SYK*	*TBX3*
TCF7L2	*TERC*	*TET2*	*TGFBR2*	*TMEM127*	*TMPRSS2*	*TNFAIP3*	*TNFRSF14*	*TOP1*	*TOP2A*
TP53	*TSC1*	*TSC2*	*TSHR*	*U2AF1*	*VEGFA*	*VHL*	*WRN*	*WT1*	*XPO1*
XRCC2	*ZMAT3*								

Genes with select intronic regions, promoter regions and fusion breakpoint for detection of gene rearrangements

ALK	*BCL2L11*	*BRAF*	*BRCA1*	*BRD4*	*CD74*	*EGFR*	*EML4*	*ERG*	*ETV6*
EZR	*FGFR1*	*FGFR2*	*FGFR3*	*KIF5B*	*KIT*	*MAML2*	*MET*	*MSH2*	*MYC*
MYCL1	*NCOA4*	*NOTCH2*	*NTRK1*	*NTRK2*	*NTRK3*	*PDGFRA*	*RAF1*	*RET*	*ROS1*
RSPO2	*SDC4*	*SLC34A2*	*TERT*	*TFE3*	*TMPRSS2*	*TPM3*	*PMS2*		

Genes with partial coding exons of 709 genes

ABCA13	*ABCB1*	*ABCC1*	*ABCC11*	*ABCC2*	*ABCG2*	*ABL2*	*ACACA*	*ACIN1*	*ACTB*

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ACTG1	ACTG2	ACVR2A	ACVRL1	ADAM29	ADAMTS5	ADCY1	AFF1	AFF2	AFF3
AHNAK	AKAP9	ALB	AMOT	ANGPT1	ANK3	ANKRD11	ANKRD30A	ANKRD30B	APEX1
APOBEC3B	ARAP3	ARFGEF1	ARFGEF2	ARHGAP29	ARHGAP35	ARID4B	ARID5B	ARNT	ASCL4
ASH1L	ASMTL	ASPM	ASTN1	ASXL2	ATIC	ATP11B	ATP12A	ATP1A1	ATP2B3
BAZ2B	BBC3	BBS9	BCAS1	BCL10	BCL11A	BCL11B	BCL2A1	BCL2L11	BCL3
BCL6	BCL9	BCORL1	BCR	BIRC3	BMPR2	BNC2	BPTF	BRD2	BRD3
BRSK1	BRWD1	BTLA	BUB1	C15orf23	C15orf55	C1QA	C1S	C3orf70	C7orf53
C8orf34	CACNA1E	CADM2	CALR	CAMTA1	CASP1	CASQ2	CBLB	CBR1	CBR3
CCDC168	CCNA1	CCNB3	CCT3	CCT5	CCT6B	CD22	CD33	CD5L	CD74
CDA	CDH11	CDH18	CDH23	CDK13	CHD1	CHD1L	CHD4	CHD6	CHD8
CHD9	CHFR	CHI3L1	CHN1	CIITA	CLDN18	CLP1	CLSPN	CLTC	CNOT3
CNOT4	CNTN1	CNTN5	CNTNAP1	CNTNAP5	COL1A1	COL2A1	COL5A1	COL5A2	COL5A3
COPS2	CPS1	CRIPAK	CRLF2	CRNKL1	CRTC1	CSF1	CSF3R	CSMD1	CSMD3
CSNK1A1	CSNK1G3	CTLA4	CTNNA2	CTNND1	CUX1	CXCR4	CYBA	CYP19A1	CYP1A1
CYP1B1	CYP2A13	CYP2C8	CYP2D6	CYP3A4	CYP3A5	DCC	DDX3X	DDX5	DEK
DHX35	DHX9	DIAPH1	DIS3L2	DLC1	DMD	DNAH6	DNAJB1	DNM2	DNMT1
DNMT3B	DOCK2	DOCK7	DPYD	DRGX	DTX1	DUSP22	DYSF	E2F3	EBF1
ECT2L	EED	EEF1A1	EGFL7	EGR3	EIF2AK3	EIF2C3	EIF3A	EIF4A2	EIF4G3
ELAC2	ELF1	ELF3	ELMO1	ELN	EME2	EMID2	EML4	EPC1	EPHA1
EPHA4	EPHA7	EPHB2	EPHB4	EPOR	EPPK1	EPS15	ERBB2IP	ERCC2	ESR2
ETS1	ETV1	ETV5	ETV6	EWSR1	EZR	F8	FAM131B	FAM135B	FAM157B
FAM46C	FAM5C	FAP	FASLG	FAT3	FAT4	FCGR1A	FCGR2A	FCGR2B	FCGR3A
FCRL4	FGF10	FGF12	FGF14	FGF23	FGF6	FLG	FLI1	FLNC	FMN2
FN1	FNDC4	FOXA2	FOXO1	FOXO3	FOXQ1	FRMPD4	FUS	FXR1	FYN
FZD1	G3BP1	G3BP2	GAB2	GABRA6	GATA1	GATA2	GFRAL	GIGYF1	GKN2
GLB1L3	GLI1	GLI2	GLI3	GMPS	GNA13	GNG2	GPC3	GPR124	GPS2
GPX1	GRB7	GSK3B	GSTM5	GSTP1	GUSB	H3F3A	H3F3B	H3F3C	HCLS1
HCN1	HDAC4	HDAC9	HECW1	HEY1	HIST1H1C	HIST1H1D	HIST1H1E	HIST1H2AC	HIST1H2AG
HIST1H2AL	HIST1H2AM	HIST1H2BC	HIST1H2BD	HIST1H2BJ	HIST1H2BK	HIST1H2BO	HIST1H3B	HIST1H3C	HIST1H3D
HIST1H3F	HIST1H3G	HIST1H3H	HIST1H3I	HIST1H4I	HIST3H3	HLA-A	HLA-B	HLA-C	HLF
HMCN1	HNF1B	HNRPDL	HOXA11	HOXA13	HOXA3	HOXA9	HOXC13	HOXD11	HOXD13
HSD3B1	HSP90AA1	HSP90AB1	HSPA8	HSPD1	HSPH1	ICK	ICOSLG	ID3	IFITM3
IGF1	IGF2	IGF2R	IGLL5	IKZF2	IKZF3	IL10	IL1RAPL1	IL21R	IL6
IL6ST	IMPG1	ING1	INHBA	INPP4A	INPPL1	INSR	IRF4	IRF6	IRS1
ITGB3	ITK	ITSN1	JARID2	KALRN	KAT6A	KAT6B	KCNJ5	KCNQ2	KDM2B
KEL	KIF5B	KLF4	KLHL6	KLK1	KRTAP5-5	L3MBTL1	LAMA2	LATS1	LATS2
LCP1	LEF1	LGALS8	LIFR	LPHN2	LPP	LRP2	LRP4	LRP5	LRP6
LRRC7	LRRK2	LYN	LZTS1	MACF1	MAD1L1	MAGI2	MAML2	MAML3	MAP3K13
MAPK3	MCC	MCM3	MDC1	MECOM	MEF2C	MGA	MIB1	MIOS	MKL1
MLL4	MLLT3	MMP11	MMP2	MN1	MNDA	MNX1	MSH4	MSN	MSR1
MTHFR	MTRR	MUC5B	MYH11	MYH14	MYH9	MYO3A	MYOD1	NAP1L1	NAV3
NCAM2	NCF2	NCF4	NCK1	NCOA3	NCOA4	NCOR2	NCSTN	NDUFA13	NFATC4
NFE2L3	NKX3-1	NLRC3	NOD1	NOS3	NOTCH4	NQO1	NR1I2	NR2F2	NR4A2
NRG1	NRP2	NRXN1	NTM	NUMA1	NUP107	NUP210	NUP93	NUP98	OBSCN
OGDH	OMD	OPCML	OR11G2	OR2T4	OR4A15	OR4C6	OR5L2	OR6F1	P2RY8
P4HB	PABPC1	PABPC3	PAG1	PAK1	PAK3	PASK	PAX3	PAX7	PC
PCDH18	PCSK6	PCSK7	PDCD11	PDE4DIP	PDGFB	PDILT	PER1	PGR	PHF1

PHF6	*PIK3C2A*	*PIK3C2B*	*PIK3C2G*	*PIK3C3*	*PIM1*	*PKD1L2*	*PKHD1*	*PLAG1*	*PLCB1*
PLCG1	*PLCG2*	*PLK1*	*PLXNA1*	*PLXNB2*	*PNRC1*	*POLQ*	*POM121*	*POM121L12*	*POU2AF1*
PPM1D	*PPP1R17*	*PPP6C*	*PRDM16*	*PREX2*	*PRF1*	*PRKAA1*	*PRKCB*	*PRKCI*	*PRKDC*
PRRX1	*PRX*	*PSG2*	*PSIP1*	*PSMB1*	*PSMB5*	*PTGS1*	*PTGS2*	*PTPN13*	*PTPN2*
PTPRB	*PTPRK*	*PTPRO*	*PTPRS*	*PTPRT*	*PTPRU*	*RAB35*	*RAC2*	*RAD21*	*RAD54B*
RANBP2	*RASA1*	*RASGRP1*	*RBL1*	*REL*	*RELN*	*RFC1*	*RGS3*	*RHEB*	*RHOH*
RHOT1	*RIT1*	*RNASEL*	*ROBO1*	*ROBO2*	*ROBO3*	*ROCK1*	*RPGR*	*RPS6KB1*	*RPS6KB2*
RSPO2	*RSPO3*	*RUNX1T1*	*RUNX2*	*RXRA*	*RYR1*	*RYR2*	*SBDS*	*SCUBE2*	*SDC4*
SEC31A	*SEMA3A*	*SEMA3E*	*SEMA6A*	*SERPINA7*	*SETBP1*	*SETDB1*	*SF1*	*SF3A1*	*SFPQ*
SGCZ	*SGK1*	*SH2B3*	*SH2D1A*	*SH3PXD2A*	*SHH*	*SI*	*SIN3A*	*SLC16A1*	*SLC1A2*
SLC22A16	*SLC22A18*	*SLC22A2*	*SLC22A3*	*SLC34A2*	*SLCO1B3*	*SLIT1*	*SLIT2*	*SMARCD1*	*SMARCE1*
SMC1A	*SMC1B*	*SNCAIP*	*SNTG1*	*SNX29*	*SOD2*	*SOS1*	*SOX10*	*SOX17*	*SPEN*
SPRR3	*SPSB4*	*SPTA1*	*SRD5A2*	*SRGAP1*	*SRGAP3*	*SRSF2*	*SRSF7*	*STAG1*	*STAT1*
SUCLG1	*SUCLG2*	*SULT1A1*	*SUZ12*	*SVEP1*	*SYNCRIP*	*SYNE1*	*TAF1*	*TAF15*	*TAF1L*
TAL1	*TBL1XR1*	*TBX15*	*TBX22*	*TCEB1*	*TCF12*	*TCF3*	*TCF4*	*TCL1A*	*TEC*
TENM3	*TERT*	*TET1*	*TFDP1*	*TFDP2*	*TFE3*	*TGFBR1*	*THBS2*	*TJP1*	*TLE1*
TLL2	*TLR4*	*TLX3*	*TMEM132D*	*TNFSF11*	*TNN*	*TP53BP1*	*TP63*	*TP73*	*TPM3*
TPR	*TRAF2*	*TRAF7*	*TRIM24*	*TRIM58*	*TRIO*	*TRPC5*	*TRRAP*	*TSHZ2*	*TSHZ3*
TTF1	*TUBA3C*	*TUBB3*	*TUSC3*	*TXNIP*	*TYMS*	*TYR*	*UBE2D2*	*UBR5*	*UGT1A1*
UMPS	*UPF3B*	*USH2A*	*USP6*	*USP8*	*VEZF1*	*VIM*	*VTCN1*	*WASF3*	*WDR90*
WDTC1	*WHSC1*	*WHSC1L1*	*WIPF1*	*WNK1*	*WNT5A*	*WSCD2*	*WWOX*	*WWP1*	*WWP2*
XIAP	*XPC*	*XRCC1*	*XRCC3*	*YAP1*	*YY1AP1*	*ZBTB16*	*ZC3H11A*	*ZFHX3*	*ZFP36L1*
ZFP36L2	*ZFPM2*	*ZIC3*	*ZNF217*	*ZNF384*	*ZNF521*	*ZNF638*	*ZNF750*	*ZNF804B*	

Test Methodology

The COMPASS Tissue test is a qualitative test that uses NGS technology. FFPE samples were microscopically examined by pathologist to enable macrodissection of regions with enriched tumour content. Genomic DNA is extracted from FFPE tumour tissue sections and undergo library construction and hybridization-based capture of all coding exons of 312 genes, introns/promoters/fusion breakpoint regions of 38 genes and partial coding exons of 709 genes (single and multinucleotide substitutions, insertions, deletions and indel(s), copy number alterations). Hybrid capture-selected libraries are sequenced on a MGI G400 instrument to high uniform depth (Target base coverage >300x with 99% of exons at coverage >100x). The sequence data are analyzed to detect genomic variants and signatures. Variants are reported according to HGVS nomenclature (http://www.hgvs.org/mutnomen), and classified as per the AMP classification system into tiers IA, IB, IIC, IID, III and IV. These tiers are stratified by clinical utility and previously reported data in the medical literature.

Limitations

1. The test is limited to test genomic variations on DNA level and does not involve RNA or protein level.
2. Samples with amounts or quality lower than the recommended input could compromise sequencing results; using such samples may affect the performance characteristics of the assay. Clinical validity performance of this test for predicting treatment effect of any specific therapeutic product has not been established.
3. Scientific data show that not all patients carry genomic variations that are associated with targeted therapies, therefore not all subjects can be matched with targeted therapies or clear resistance mechanism.
4. This test is validated only for somatic variants and should not be used to infer or exclude any possible germline variants.
5. LIMIT OF DETECTION: This test has been validated for indels up to 25 base pairs. The limit of detection of this test is 2.5% allele frequency for single base substitutions, insertions, and deletions, and 20% tumour cellularity for fusions/rearrangement and gene amplifications.

Disclaimer

1. The selection of any, all or none of the matched therapies reported by COMPASS Tissue resides solely with the treating physician. M Diagnostics does not promise or guarantee that a specific therapeutic product will be effective in the treatment of the tested patient's disease, nor that a drug with potential lack of benefit will not provide clinical benefit to the tested patient.
2. Results of this test must always be interpreted within the clinical context and other relevant data and should not be used alone for a diagnosis of malignancy. A treating physician's decisions should not be solely based on the COMPASS Tissue test, or the information contained in this report.
3. As evidence on variants and drugs is constantly updated, previous classifications may later be modified. The interpretation of a variant is based on current available evidence at the time.
4. In no event shall M Diagnostics be liable for any actual damages, indirect damages, and/or special or consequential damages arising out of or in any way connected with the Report, your use of the Report, your reliance on the Report, or any defect or inaccurate information included within the Report.
5. Clinical concordance has not been established for TMB and MSI, as well as predictive biomarkers for immune checkpoint inhibitors (ICI). Information about these biomarkers is intended for Research-Use Only and may not be used to guide treatment and/or for clinical decision making.
6. Reliable results are dependent on adequate specimen collection and processing. This test has been validated FFPE tissues, other type of fixatives is discouraged. Improper treatment of tissue, such as decalcification, may cause PCR failure.
7. M Diagnostics pathologist HAS NOT reassessed the original diagnosis. The pathology assessment is not a confirmation of malignancy but verifies the presence of atypical cells consistent with tumour as diagnosed by the reporting pathologist. M Diagnostics assumes sample identification, and clinical diagnoses are as stated on the request form.Sequence variants were reported using Human Genome Variation Society (HGVS) nomenclature. Classification and interpretation of variants follows guidelines of American College of Medical Genetics and Genomics (ACMG), Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP).
8. Database and references used: Reference genome (GRCh37), annotation using A Locus Reference Genomic (LRG), database referencing 1000G (phase1), EXAC (0.3.1), dbSNP (147), PolyPhen2/SIFT (ensdb v73), PhyloP (46way), Clinvar (2023-7-30) and Cosmic(V80).
9. This test was developed, and its performance characteristics determined by M Diagnostics Laboratory. This test was performed in a MOH certified, SAC ISO 15189:2012 and CAP accredited laboratory and is intended for clinical purposes.

References

1. PMID: 31779710 MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment.
2. 2021 ASCO Abstract 2506 Preliminary results of a phase II study of alrizomadlin (APG-115), a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients (pts) with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic (I-O) drugs.
3. NCT03611868 A Study of APG-115 in Combination With Pembrolizumab in Patients With Metastatic Melanomas or Advanced Solid Tumors.
4. 2022 ESMO Abstract 452O A phase I dose-escalation and expansion study evaluating the safety and efficacy of the MDM2–p53 antagonist BI 907828 in patients (pts) with solid tumours.
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