ACT Onco® + Report

PATIENT		
Identifier: 陳俊華		Patient ID: 49325293
Date of Birth: Jan 08, 1961		Gender: Male
Diagnosis: Pancreatic cancer		
ORDERING PHYSICIAN		
Name: 許劭榮醫師		Tel: 886-228712121
Facility: 臺北榮總		
Address: 臺北市北投區石牌路二段 201 號		
SPECIMEN		
Specimen ID: S11275278H	Collection site: Pancreas	Type: FFPE tissue
Date received: Jun 09, 2023	Lab ID: AA-23-03768	D/ID: NA

ABOUT ACTOnco®+

The test is a next-generation sequencing (NGS)-based assay developed for efficient and comprehensive genomic profiling of cancers. This test interrogates coding regions of 440 genes associated with cancer treatment, prognosis and diagnosis. Genetic mutations detected by this test include small-scale mutations like single nucleotide variants (SNVs), small insertions and deletions (InDels) (≤ 15 nucleotides) and large-scale genomic alterations like copy number alterations (CNAs). The test also includes an RNA test, detecting fusion transcripts of 13 genes.

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Probable Effects in Patient's Cancer Type		Probable Sensitive in Other Cancer Types
	Sensitive	Resistant	
Not detected			

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
KRAS G12D	-	Cetuximab, Panitumumab

Note:

- The above summary tables present genomic variants and biomarkers based on the three-tiered approach proposed by US FDA for reporting tumor profiling NGS testing. "Variants/biomarkers with evidence of clinical significance" refers to mutations that are widely recognized as standard-of-care biomarkers (FDA level 2/AMP tier 1). "Variants/biomarkers with potential clinical significance" refers to mutations that are not included in the standard of care but are informational for clinicians, which are commonly biomarkers used as inclusion criterial for clinical trials (FDA level 3/AMP tier 2).
- The therapeutic agents and possible effects to a given drug are based on mapping the variants/biomarkers with ACT Genomics clinical knowledge database. The mapping results only provide information for reference, but not medical recommendation.
- Please refer to corresponding sections for more detailed information about genomic alteration and clinical relevance listed above.

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TESTING RESULTS

VARIANT(S) WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Allele Frequency
GNAS	R201C	16.2%
KRAS	G12D	33.5%
TP53	E286Q	27.4%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	*CDKN2A*	Homozygous deletion	0
Chr17	*TP53*	Heterozygous deletion	1
Chr9	*PTCH1*	Heterozygous deletion	1

- Fusions

Fusion Gene & Exon	Transcript ID
No fusion gene detected in this sample	

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	0.0 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

Note:
- Variant(s) enlisted in the SNV table may currently exhibit no relevance to treatment response prediction. Please refer to INTERPRETATION for more biological information and/or potential clinical impacts of the variants.
- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 33% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3A		
KRAS G12D	Cetuximab, Panitumumab	**resistant**

Therapies associated with benefit or lack of benefit are based on biomarkers detected in this tumor and published evidence in professional guidelines or peer-reviewed journals.

Level	Description
1	FDA-recognized biomarkers predictive of response or resistance to FDA approved drugs in this indication
2	Standard care biomarkers (recommended by the NCCN guideline) predictive of response or resistance to FDA approved drugs in this indication
3A	Biomarkers predictive of response or resistance to therapies approved by the FDA or NCCN guideline in a different cancer type
3B	Biomarkers that serve as inclusion criteria for clinical trials (minimal supportive data required)
4	Biomarkers that show plausible therapeutic significance based on small studies, few case reports, or preclinical studies

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IMMUNE CHECKPOINT INHIBITORS (ICIs)

No genomic alterations detected to confer sensitivity or lack of benefit to immune checkpoint therapies.

- Other Biomarkers with Potential Clinical Effects for ICIs

Genomic Alterations	Potential Clinical Effects
Not detected	

Note: Tumor non-genomic factors, such as patient germline genetics, PDL1 expression, tumor microenvironment, epigenetic alterations or other factors not provided by this test may affect ICI response.

CHEMOTHERAPIES

No genomic alterations detected in this tumor predicted to confer sensitivity or lack of benefit to chemotherapies.

HORMONAL THERAPIES

No genomic alterations detected in this tumor predicted to confer sensitivity or lack of benefit to hormonal therapies.

OTHERS

No genomic alterations detected in this tumor predicted to confer sensitivity or lack of benefit to other therapies.

Note:
Therapeutic implications provided in the test are based solely on the panel of 440 genes sequenced. Therefore, alterations in genes not covered in this panel, epigenetic and post-transcriptional and post-translational factors may also determine a patient's response to therapies. In addition, several other patient-associated clinical factors, including but not limited to, prior lines of therapies received, dosage and combinations with other therapeutic agents, patient's cancer types, sub-types, and/or stages, may also determine the patient's clinical response to therapies.

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VARIANT INTERPRETATION

GNAS R201C

Biological Impact

GNAS encodes the alpha subunit of the stimulator G protein (Gs-alpha), a guanine-nucleotide binding protein (G protein) involved in the hormonal regulation of adenylate cyclase[1]. The common mutations of GNAS have been identified in tumors, including R201C, R201H, and Q227R, resulting in constitutive activation of Gs-alpha and its effector adenylate cyclase, leading to increased cAMP accumulation, and constitutive cAMP signaling, associated with excessive proliferation and tumor development[2][3][1]. GNAS activation may affect downstream MAPK and Wnt signaling pathway, suggesting activating mutation of GNAS can modify cell growth and may be oncogenic[3].

R201C (corresponding to R844C in isoform XLas-1) is located in the GTP-binding domain of the GNAS short isoform 1 (UniProtKB). This mutation results in a loss of the GTPase activity of GNAS protein leading to constitutive downstream pathway activation, cell proliferation, and tumor formation in vivo[3][4].

Therapeutic and prognostic relevance

Low expression of GNAS has been reported to associate with both poor overall survival and PSA progression-free survival in prostate cancer[5].

A case report showed that an advanced pancreatic ductal adenocarcinoma patient harboring EGFR G1022S, GNAS R201C, KRAS G12D, MTOR D258fs, and NF1 D1976fs in ctDNA showed a response to trametinib. The following ctDNA analysis showed the GNAS R201C, as well as EGFR G1022S, KRAS G12D, MTOR D258fs, and NF1 D1976fs, were no longer detected at 19 weeks treatment[6].

KRAS G12D

Biological Impact

The V-Ki-Ras2 Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (KRAS) gene encodes a small GTPase protein, a member of the RAS family of small GTPases, which catalyze the hydrolysis of GTP to GDP. RAS proteins cycle between an active (GTP-bound) and an inactive (GDP-bound) state, to activate the downstream oncogenic pathways, including the PI3K/AKT/mTOR and MAPK pathways[7]. KRAS mutations occur primarily in three hotspots G12, G13 and Q61, and less frequently in codon A146[7][8]. These are activating mutations that lead to constitutive activation and persistent stimulation of the downstream signaling pathways[9][10]. Mutations in KRAS have been reported in a diverse spectrum of human malignancies, including pancreatic carcinomas (>80%)[7][11], colon carcinomas (40-50%)[12][13], and lung carcinomas (30-50%)[14][15], but are also present in biliary tract malignancies, endometrial cancer, cervical cancer, bladder cancer, liver cancer, myeloid leukemia and breast cancer[8].

G12D is a hotspot mutation located in the GTP binding region of the KRAS protein (UniProtKB). This mutation results in decreased KRAS GTPase activity, increased activation of downstream signaling, and promotes tumor formation in preclinical studies[16][17][18].

Therapeutic and prognostic relevance

Cetuximab and panitumumab are FDA-approved for treating RAS wild-type metastatic colorectal cancer. The NCCN for CRC recommends that patients with any known KRAS or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab.

KRAS mutation has been determined as an inclusion criterion for the trials evaluating MEK inhibitors efficacies in various types of solid tumors (NCT03704688, NCT02399943, NCT02285439, NCT03637491, NCT04214418).

KRAS mutations are associated with a lack of efficacy of EGFR TKIs[19][20][21]. Some case reports suggest that MEK

inhibitors may benefit patients with KRAS mutations, as shown in cervical and ovarian cancer cases (Am J Clin Exp Obstet Gynecol 2015;2(3):140-143)[22][23]. However, a randomized Phase II study did not find trametinib to be superior to docetaxel in KRAS-mutant non-small cell lung cancer patients[24]. MEK inhibitors as a monotherapy have limited response[25].

Combining MEK and mTOR inhibitors is being evaluated as a potential strategy in RAS-mutant CRC[26][27]. The combination of trametinib and palbociclib has resulted in objective responses in KRAS mutant models[28].

Sorafenib has been shown to be beneficial in KRAS-mutant CRC/NSCLC, and KRAS-amplified melanoma[29][30][31]. KRAS mutations in exon 2 (codon 12 or 13) and codon 61 have been associated with poor prognosis in CRC[32].

Patients with KRAS or BRAF mutations in low-grade serous carcinoma of the ovary or peritoneum had better overall survival than those with wild-type genes[33]. In ovarian serous borderline tumor, KRAS G12V mutation was linked to shorter survival time[34].

TP53 E286Q, Heterozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[35]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[36].

E286Q is a missense mutation that lies within the DNA-binding domain (DBD) of the p53 protein (UniProtKB). Cell-based assay suggested that E286Q is a loss-of-function mutant that fails to suppress the transcription of Nrf2 and results in cisplatin chemoresistance in lung cancer cells[37].

Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)[38].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib[39]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat[40].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53[41][42][43]. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)[44]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[45][46]. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[47].

CDKN2A Homozygous deletion

Biological Impact

The Cyclin-Dependent Kinase Inhibitor 2A (CDKN2A) gene encodes the p16 (p16INK4a) and p14 (ARF) proteins. p16INK4a binds to CDK4 and CDK6, inhibiting these CDKs from binding D-type cyclins and phosphorylating the retinoblastoma (RB) protein whereas p14 (ARF) blocks the oncogenic activity of MDM2 by inhibiting MDM2-induced degradation of p53[48][49][50]. CDKN2A has been reported as a haploinsufficient tumor suppressor with one copy loss that may lead to weak protein expression and is insufficient to execute its original physiological functions[51]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[52][53].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[54][55]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[56][57][58]. However, there are clinical studies that demonstrated CDKN2A nuclear expression, CDKN2A/CDKN2B co-deletion, or CDKN2A inactivating mutation was not associated with clinical benefit from CDK4/6 inhibitors, such as palbociclib and ribociclib, in RB-positive patients[59][60][61].CDKN2A loss or mutation has been determined as an inclusion criterion for the trial evaluating CDK4/6 inhibitors efficacy in different types of solid tumors (NCT02693535, NCT02187783).

The phase II TAPUR trial demonstrated clinical benefits to palbociclib monotherapy in advanced NSCLC or head and neck cancer harboring a CDKN2A mutation or copy number loss. However, pancreatic and biliary cancer patients harboring a CDKN2A mutation or copy number loss did not demonstrate an objective response or stable disease when treated with palbociclib monotherapy for 16 weeks (DOI: 10.1200/JCO.2021.39.15_suppl.6043)[62][63].

Notably, the addition of several CDK4/6 inhibitors to hormone therapies, including palbociclib in combination with letrozole, ribociclib plus letrozole, and abemaciclib combines with fulvestrant, have been approved by the U.S. FDA for the treatment of ER+ and HER2- breast cancer[55][64][65].

In a Phase I trial, a KRAS wild-type squamous non-small cell lung cancer (NSCLC) patient with CDKN2A loss had a partial response when treated with CDK4/6 inhibitor abemaciclib[57]. Administration of combined palbociclib and MEK inhibitor PD-0325901 yield promising progression-free survival among patients with KRAS mutant non-small cell lung cancer (NSCLC) (AACR 2017, Abstract CT046). Moreover, MEK inhibitor in combination with CDK4/6 inhibitor demonstrates significant anti-KRAS-mutant NSCLC activity and radiosensitizing effect in preclinical models[66].

A retrospective analysis demonstrated that concurrent deletion of CDKN2A with EGFR mutation in patients with non-small cell lung cancer (NSCLC), predicts worse overall survival after EGFR-TKI treatment[67].

PTCH1 Heterozygous deletion

Biological Impact

The PTCH1 (protein patched homolog 1) gene encodes a multi-pass transmembrane receptor for sonic hedgehog (shh), a tumor suppressor that acts to repress shh signaling in the absence of ligand[68]. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth[69][70]. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma[71][72][73][74]. Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma[72]. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in mice[69][75].

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Therapeutic and prognostic relevance

Vismodegib and sonidegib are small molecule inhibitors of SMO approved by the U.S. FDA for the treatment of patients with basal cell carcinoma[76][77][78][79].A heavily pretreated patient with metastatic medulloblastoma harboring loss-of-heterozygosity and somatic mutation of PTCH1 showed rapid regression of the tumor after treated with vismodegib[80]. Furthermore, a phase II study demonstrated that vismodegib treatment results in extended progression-free survival (PFS) in patients with loss-of-heterozygosity, SHH-driven medulloblastoma[81]. In the phase II MyPathway trial, three advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment[82]. In a clinical study, two patients with Sonic Hedgehog (SHH) activated medulloblastoma harboring PTCH1 loss-of-function mutations demonstrated partial responses to sonidegib treatment[83].

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US FDA-APPROVED DRUG(S)

Sonidegib (ODOMZO)

Sonidegib is a Hedgehog signaling pathway inhibitor by blocking its key component, smoothened (smo). Sonidegib is developed and marketed by Novartis under the trade name ODOMZO.

- FDA Approval Summary of Sonidegib (ODOMZO)

BOLT[78] NCT01327053	**Basal cell carcinoma** (Approved on 2015/07/24)
	-
	Sonidegib [ORR(%): 58.0]

Vismodegib (ERIVEDGE)

Vismodegib is a cyclopamine-competitive antagonist and acts as a first-in-class Hedgehog signaling pathway inhibitor by blocking its key component smoothened (smo). Vismodegib is developed by Genentech and marketed by Roche under the trade name ERIVEDGE.

- FDA Approval Summary of Vismodegib (ERIVEDGE)

ERIVANCE BCC[76] NCT00833417	**Basal cell carcinoma** (Approved on 2012/01/30)
	-
	Vismodegib [ORR (mBCC)(%): 30.3, ORR (laBCC)(%): 42.9]

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

Trials were searched by applying filters: study status, patient's diagnosis, intervention, location and/or biomarker(s). Please visit https://clinicaltrials.gov to search and view for a complete list of open available and updated matched trials.

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

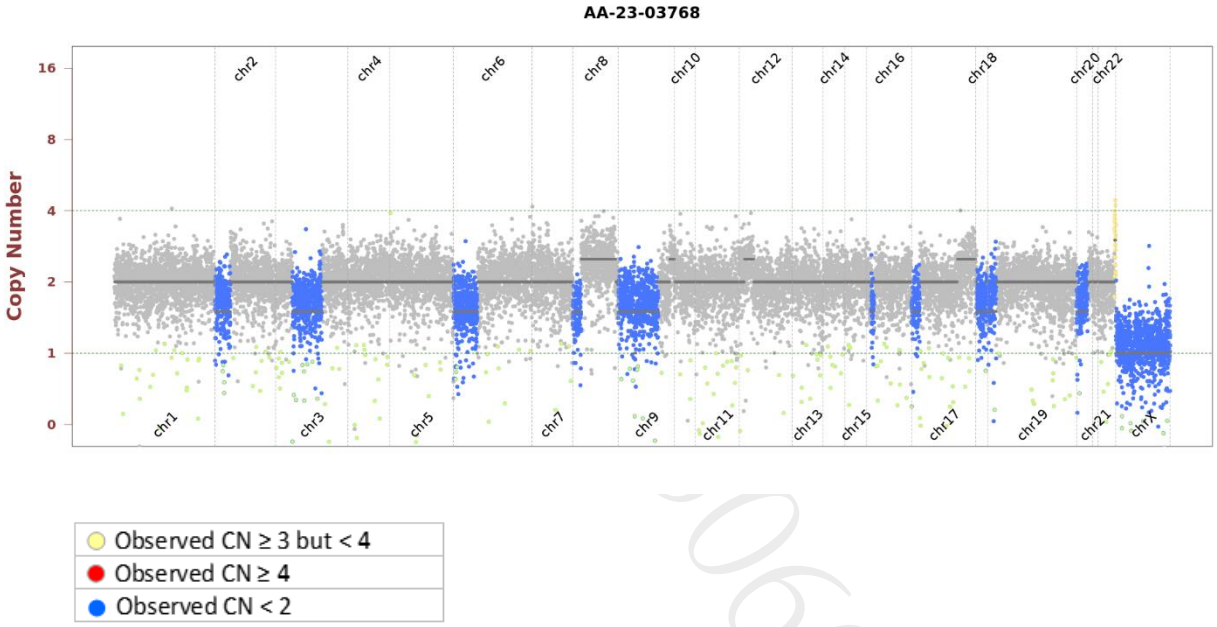
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
GNAS	R201C	8	c.601C>T	NM_000516	COSM27887	16.2%	655
KRAS	G12D	2	c.35G>A	NM_004985	COSM521	33.5%	2795
TP53	E286Q	8	c.856G>C	NM_000546	COSM44250	27.4%	496

- Copy Number Alterations

Observed copy number (CN) for each evaluated position is shown on the y-axis. Regions referred to as amplification or deletion are shown in color. Regions without significant changes are represented in gray.



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OTHER DETECTED VARIANTS

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
BRD4	Splice region	-	c.3169+8G>T	NM_058243	-	50.1%	688
FANCD2	H1320Y	40	c.3958C>T	NM_001018115	-	49.5%	977
HR	R825P	11	c.2474G>C	NM_005144	-	48.1%	77
INSR	Splice region	-	c.1483+3A>C	NM_000208	-	56.3%	1005
KAT6A	T1263I	17	c.3788C>T	NM_006766	-	54.0%	809
KMT2D	G2346S	31	c.7036G>A	NM_003482	COSM7325165	33.7%	416
MUC16	G1978S	1	c.5932G>A	NM_024690	-	50.7%	1580
POLE	K2223R	48	c.6668A>G	NM_006231	-	63.2%	701
RNF43	R389C	9	c.1165C>T	NM_017763	COSM4651313	50.7%	639
TBX3	T45M	1	c.134C>T	NM_016569	-	41.0%	761

Note:

- This table enlists variants detected by the panel other than those with clinical relevance (reported in Testing Result section). The clinical impact of a genetic variant is determined according to ACT Genomics in-house clinical knowledge database. A negative result does not necessarily indicate absence of biological effect on the tumor. Some variants listed here may possibly have preclinical data or may show potential clinical relevance in the future.

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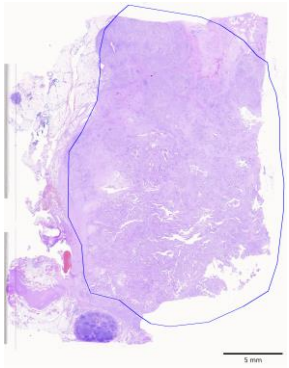
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Mar 11, 2023
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11275278H
- Collection site: Pancreas
- Examined by: Dr. Yeh-Han Wang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 40%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 50%
  3. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the whole slide (%): 0%
  4. The percentage of necrotic cells (including necrotic tumor cells) in total cells in the encircled areas in the whole slide (%): 0%
  5. Additional comment: NA
- Manual macrodissection: Performed on the highlighted region
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 854x
- Target Base Coverage at 100x: 94%

RNA test

- Average unique RNA Start Sites per control GSP2: 100

LIMITATIONS

1. This test does not provide information of variant causality and does not detect variants in non-coding regions that could affect gene expression. This report does not report polymorphisms and we do not classify whether a mutation is germline or somatic. Variants identified by this assay were not subject to validation by Sanger or other technologies.
2. The possibility cannot be excluded that certain pathogenic variants detected by other sequencing tools may not be reported in the test because of technical limitation of bioinformatics algorithm or the NGS sequencing platform, e.g. low coverage.
3. This test has been designed to detect fusions in 13 genes sequenced. Therefore, fusion in genes not covered by this test would not be reported. For novel fusions detected in this test, Sanger sequencing confirmation is recommended if residue specimen is available.

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NEXT-GENERATION SEQUENCING (NGS) METHODS

DNA test

Extracted genomic DNA was amplified using primers targeting coding exons of analyzed genes and subjected to library construction. Barcoded libraries were subsequently conjugated with sequencing beads by emulsion PCR and enriched using Ion Chef system. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific).

Raw reads generated by the sequencer were mapped to the hg19 reference genome using the Ion Torrent Suite. Coverage depth was calculated using Torrent Coverage Analysis plug-in. Single nucleotide variants (SNVs) and short insertions/deletions (InDels) were identified using the Torrent Variant Caller plug-in. VEP (Variant Effect Predictor) was used to annotate every variant using databases from Clinvar, COSMIC and Genome Aggregation database. Variants with coverage ≥ 20, allele frequency ≥ 5% and actionable variants with allele frequency ≥ 2% were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at 100x ≥ 85% with a mean coverage ≥ 500x.

Variants reported in Genome Aggregation database with > 1% minor allele frequency (MAF) were considered as polymorphisms. ACT Genomics in-house database was used to determine technical errors. Clinically actionable and biologically significant variants were determined based on the published medical literature.

The copy number alterations (CNAs) were predicted as described below:
Amplicons with read counts in the lowest 5th percentile of all detectable amplicons and amplicons with a coefficient of variation ≥ 0.3 were removed. The remaining amplicons were normalized to correct the pool design bias. ONCOCNV (an established method for calculating copy number aberrations in amplicon sequencing data by Boeva et al., 2014) was applied for the normalization of total amplicon number, amplicon GC content, amplicon length, and technology-related biases, followed by segmenting the sample with a gene-aware model. The method was used as well for establishing the baseline of copy number variations.

Tumor mutational burden (TMB) was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The TMB calculation predicted somatic variants and applied a machine learning model with a cancer hotspot correction. TMB may be reported as “TMB-High”, “TMB-Low” or “Cannot Be Determined”. TMB-High corresponds to ≥ 7.5 mutations per megabase (Muts/Mb); TMB-Low corresponds to < 7.5 Muts/Mb. TMB is reported as “Cannot Be Determined” if the tumor purity of the sample is < 30%.

Classification of microsatellite instability (MSI) status is determined by a machine learning prediction algorithm. The change of a number of repeats of different lengths from a pooled microsatellite stable (MSS) baseline in > 400 genomic loci are used as the features for the algorithm. The final output of the results is either microsatellite Stable (MSS) or microsatellite instability high (MSI-H).

RNA test

Extracted RNA was reverse-transcribed and subjected to library construction. Sequencing was performed according to Ion Proton or Ion S5 sequencer protocol (Thermo Fisher Scientific). To ensure sequencing quality for fusion variant analysis, the average unique RNA Start Sites (SS) per control Gene Specific Primer 2 (GSP 2) should be ≥ 10.

The fusion analysis pipeline aligned sequenced reads to the human reference genome, identified regions that map to noncontiguous regions of the genome, applied filters to exclude probable false-positive events and, annotated previously characterized fusion events according to Quiver Gene Fusion Database, a curated database owned and maintained by ArcherDX. In general, samples with detectable fusions need to meet the following criteria: (1) Number of unique start sites (SS) for the GSP2 ≥ 3; (2) Number of supporting reads spanning the fusion junction ≥ 5; (3) Percentage of supporting reads spanning the fusion junction ≥ 10%; (4) Fusions annotated in Quiver Gene Fusion Database.

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DATABASE USED

- Reference genome: Human genome sequence hg19
- COSMIC v.92
- Genome Aggregation database r2.1.1
- ClinVar (version 20210404)
- ACT Genomics in-house database
- Quiver Gene Fusion Database version 5.1.18

Variant Analysis:
解剖病理專科醫師朱盈霞
Ying-Hsia Chu, M.D.
病解字第 000653 號

Sign Off
解剖病理專科醫師朱盈霞
Ying-Hsia Chu, M.D.
病解字第 000653 號

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GENE LIST

SNV & CNV

ABCB1*	ABCC2*	ABCG2*	ABL1	ABL2	ADAMTS1	ADAMTS13	ADAMTS15	ADAMTS16	ADAMTS18	ADAMTS6	ADAMTS9
ADAMTSL1	ADGRA2	ADH1C*	AKT1	AKT2	AKT3	ALDH1A1*	ALK	AMER1	APC	AR	ARAF
ARID1A	ARID1B	ARID2	ASXL1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL
B2M	BAP1	BARD1	BCL10	BCL2*	BCL2L1	BCL2L2*	BCL6	BCL9	BCOR	BIRC2	BIRC3
BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTG2*	BTK	BUB1B	CALR
CANX	CARD11	CASP8	CBFB	CBL	CCNA1	CCNA	CCNB1	CCNB2	CCNB3	CCND1	CCND2
CCND3	CCNE1	CCNE2	CCNH	CD19	CD274	CD58	CD70*	CD79A	CD79B	CDC73	CDH1
CDK1	CDK12	CDK2	CDK4	CDK5	CDK6	CDK7	CDK8	CDK9	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA*	CHEK1	CHEK2	CIC	CREBBP	CRKL	CRLF2	CSF1R	CTCF	CTLA4
CTNNA1	CTNNB1	CUL3	CYLD	CYP1A1*	CYP2B6*	CYP2C19*	CYP2C8*	CYP2D6	CYP2E1*	CYP3A4*	CYP3A5*
DAXX	DCUN1D1	DDR2	DICER1	DNMT3A	DOT1L	DPYD	DTX1	E2F3	EGFR	EP300	EPCAM
EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2	ERBB3	ERBB4	ERCC1	ERCC2	ERCC3	ERCC4
ERCC5	ERG	ESR1	ESR2	ETV1	ETV4	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE
FANCF	FANCG	FANCL	FAS	FAT1	FBXW7	FCGR2B	FGF1*	FGF10	FGF14	FGF19*	FGF23
FGF3	FGF4*	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4
FOXL2*	FOXP1	FRG1	FUBP1	GATA1	GATA2	GATA3	GNA11	GNA13	GNAQ	GNAS	GREM1
GRIN2A	GSK3B	GSTP1*	GSTT1*	HGF	HIF1A	HIST1H1C*	HIST1H1E*	HNF1A	HR	HRAS*	HSP90AA1
HSP90AB1	HSPA4	HSPA5	IDH1	IDH2	IFNL3*	IGF1	IGF1R	IGF2	IKBKB	IKBKE	IKZF1
IL6	IL7R	INPP4B	INSR	IRF4	IRS1	IRS2*	JAK1	JAK2	JAK3	JUN*	KAT6A
KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT	KMT2A	KMT2C	KMT2D	KRAS	LCK	LIG1
LIG3	LMO1	LRP1B	LYN	MALT1	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAP3K7	MAPK1	MAPK3
MAX	MCL1	MDM2	MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MPL	MRE11
MSH2	MSH6	MTHFR*	MTOR	MUC16	MUC4	MUC6	MUTYH	MYC	MYCL	MYCN	MYD88
NAT2*	NBN	NEFH	NF1	NF2	NFE2L2	NFKB1	NFKBIA	NKX2-1*	NOTCH1	NOTCH2	NOTCH3
NOTCH4	NPM1	NQO1*	NRAS	NSD1	NTRK1	NTRK2	NTRK3	PAK3	PALB2	PARP1	PAX5
PAX8	PBRM1	PDCD1	PDCD1LG2	PDGFRA	PDGFRB	PDIA3	PGF	PHOX2B*	PIK3C2B	PIK3C2G	PIK3C3
PIK3CA	PIK3CB	PIK3CD	PIK3CG	PIK3R1	PIK3R2	PIK3R3	PIM1	PMS1	PMS2	POLB	POLD1
POLE	PPARG	PPP2R1A	PRDM1	PRKAR1A	PRKCA	PRKCB	PRKCG	PRKCI	PRKCQ	PRKDC	PRKN
PSMB8	PSMB9	PSME1	PSME2	PSME3	PTCH1	PTEN	PTGS2	PTPN11	PTPRD	PTPRT	RAC1
RAD50	RAD51	RAD51B	RAD51C	RAD51D	RAD52	RAD54L	RAF1	RARA	RB1	RBM10	RECQL4
REL	RET	RHOA	RICTOR	RNF43	ROS1	RPPH1	RPTOR	RUNX1	RUNX1T1	RXRA	SDHA
SDHB	SDHC	SDHD	SERPINB3	SERPINB4	SETD2	SF3B1	SGK1	SH2D1A*	SLC19A1*	SLC22A2*	SLCO1B1*
SLCO1B3*	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOCS1*	SOX2*	SOX9	SPEN	SPOP
SRC	STAG2	STAT3	STK11	SUFU	SYK	SYNE1	TAF1	TAP1	TAP2	TAPBP	TBX3
TEK	TERT	TET1	TET2	TGFBR2	TMSB4X*	TNF	TNFAIP3	TNFRSF14	TNFSF11	TOP1	TP53
TPMT*	TSC1	TSC2	TSHR	TYMS	U2AF1	UBE2A*	UBE2K	UBR5	UGT1A1*	USH2A	VDR*
VEGFA	VEGFB	VHL	WT1	XIAP	XPO1	XRCC2	ZNF217				

*Analysis of copy number alterations NOT available.

FUSION

ALK	BRAF	EGFR	FGFR1	FGFR2	FGFR3	MET	NRG1	NTRK1	NTRK2	NTRK3	RET	ROS1

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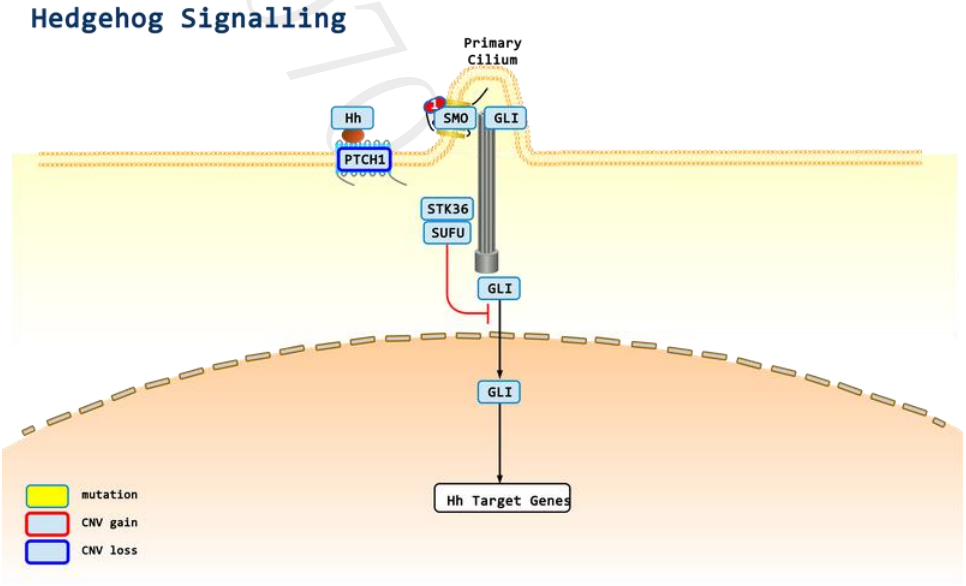
APPENDIX

POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
PTCH1	Sonidegib, Vismodegib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Sonidegib, Vismodegib

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DISCLAIMER

法律聲明

本檢驗報告僅提供專業醫療參考，結果需經專業醫師解釋及判讀。基因突變資訊非必具備藥物或治療有效性指標，反之亦然。本檢驗報告提供之用藥指引不聲明或保證其臨床有效性，反之亦然。本基因檢測方法係由本公司研究開發，已經過有效性測試。
本檢驗報告非經本公司許可，不得私自變造、塗改，或以任何方式作為廣告及其他宣傳之用途。
本公司於提供檢驗報告後，即已完成本次契約義務，後續之報告解釋、判讀及用藥、治療，應自行尋求相關專業醫師協助，若需將報告移件其他醫師，本人應取得該醫師同意並填寫移件申請書，主動告知行動基因，行動基因僅能配合該醫師意願與時間提供醫師解說。

醫療決策需由醫師決定

任何治療與用藥需經由醫師在考慮病患所有健康狀況相關資訊包含健檢、其他檢測報告和病患意願後，依照該地區醫療照護標準由醫師獨立判斷。醫師不應僅依據單一報告結果(例如本檢測或本報告書內容)做決策。

基因突變與用藥資訊並非依照有效性排序

本報告中列出之生物標記變異與藥物資訊並非依照潛在治療有效性排序。

證據等級

藥物潛在臨床效益(或缺乏潛在臨床效益)的實證證據是依據至少一篇臨床療效個案報告或臨床前試驗做為評估。本公司盡力提供適時及準確之資料，但由於醫學科技之發展日新月異，本公司不就本報告提供的資料是否為準確、適宜或最新作保證。

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