ACT Onco® + Report

PATIENT	
Name: 廖天宋	Patient ID: 48813010
Date of Birth: Sep 24, 1938	Gender: Male
Diagnosis: Lung adenocarcinoma	
ORDERING PHYSICIAN	
Name: 趙恒勝醫師	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: S11129673A	Collection site: Lung	Type: FFPE tissue
Date received: Aug 09, 2022	Lab ID: AA-22-04640	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	
EML4(7)-ALK(20) (EML4-ALK variant 3b) fusion	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	-	-
EML4(6)-ALK(20) (EML4-ALK variant 3a) fusion	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	-	-

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
FLT4 Amplification	Pazopanib	-

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	Q108*	8.2%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	*CDKN2A*	Heterozygous deletion	1
Chr7	*SMO*	Amplification	6
Chr5	*FLT4*	Amplification	7
Chr20	*GNAS*	Amplification	23

- Fusions

Fusion Gene & Exon	Transcript ID
EML4(6)-ALK(20) (EML4-ALK variant 3a) fusion	EML4(NM_019063.4), ALK(NM_004304.4)
EML4(7)-ALK(20) (EML4-ALK variant 3b) fusion	EML4(XM_005264267.1), ALK(NM_004304.4)

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.3 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 78% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- The fusion gene reported above is confirmed to be in-frame and includes the kinase/functional domain. Such alteration may indicate potential benefits from kinase inhibitors. However, for a novel fusion, its functional significance and response to kinase inhibitors are undetermined.
- 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 1		
EML4(6)-ALK(20) ***(EML4-ALK variant 3a)*** fusion	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	**sensitive**
EML4(7)-ALK(20) ***(EML4-ALK variant 3b)*** fusion	Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib	**sensitive**
Level 4		
FLT4 Amplification	Pazopanib	**sensitive**

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
ALK-positive	Likely associated with WORSE response to ICIs

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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
SMO Amplification	Paclitaxel	**Resistant**	Clinical	Stomach cancer

HORMONAL THERAPIES

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

OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AG	Irinotecan-based regimens	Level 1B
Clinical Interpretation: Patients with the AG genotype and cancer who are treated with irinotecan-based regimens may have an increased risk of diarrhea and neutropenia as compared to patients with the GG genotype, or a decreased risk of diarrhea and neutropenia compared to patients with the AA genotype. Other genetic and clinical factors may also influence a patient's risk of diarrhea and neutropenia.				

* Level of evidence was defined by PharmGKB (https://www.pharmgkb.org/page/clinAnnLevels)

Level 1A: Clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation.
Level 1B: Clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label.
Level 2A: Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely.

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

EML4(6)-ALK(20) (EML4-ALK variant 3a) fusion, *EML4(7)-ALK(20) (EML4-ALK variant 3b)* fusion

Biological Impact

Anaplastic lymphoma kinase (ALK) gene encodes a receptor tyrosine kinase that belongs to the insulin receptor superfamily which was first described as a fusion partner in the t(2;5) chromosomal translocation in anaplastic large cell lymphoma in 1994[1]. ALK activating mutations and gene fusions with a variety of translocation partners are commonly found in cancers, leading to the enhanced mitogenic and anti-apoptotic signaling pathways, including STAT3, MAPK, and PI3K pathways[2][3][4]. Cancer types with ALK alterations include non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma, inflammatory myofibroblastic tumor (IMT), neuroblastoma, and rhabdomyosarcoma[5].

In ALK-positive non-small cell lung cancer (NSCLC), the predominant molecular event leading to ALK activation is juxtaposition of the N-terminal portion of the protein encoded by the echinoderm microtubule-associated protein like 4 (EML4) gene with the intracellular domain of the ALK tyrosine kinase, resulting in the constitutive activation of downstream pathways[6].

Therapeutic and prognostic relevance

Crizotinib, a tyrosine kinase inhibitor (TKI), is the first-generation ALK inhibitor, which was approved by the U.S. FDA for the first-line treatment of patients with ALK-positive advanced NSCLC in 2011[7]. Later, second-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib were granted approval by the U.S. FDA for the treatment of patients with ALK-positive metastatic NSCLC who has progressed on or are intolerant to crizotinib[8][9][10]. Of note, both ceritinib and alectinib showed better treatment effect in ALK-positive metastatic NSCLC with brain metastasis[11][8]. Furthermore, lorlatinib, the third-generation ALK inhibitor, was approved by the U.S. FDA in 2018 for the treatment of patients with refractory ALK-positive, and previously treated with one or more ALK inhibitors[12][13]. In NCCN guidelines for NSCLC, alectinib, brigatinib, and lorlatinib are the preferred therapies for both first -line and complete planned systemic therapy.

Previous clinical studies showed different clinical outcomes on ALK TKIs or pemetrexed treatment according to ALK fusion variant in lung adenocarcinoma. Variant 1 showed significantly longer PFS on pemetrexed or crizotinib treatment than other variants[14][15]. First- or second-generation ALK TKI pretreated patients with variant 3a/b was associated with a significantly longer PFS than variant 1 under lorlatinib treatment[16]. The variants of EML4-ALK also influence the spectrum of developed ALK resistance mutations under ALK inhibitor treatment. For example, ALK G1202R was more common in patients with variant 3a/b than in variant 1[16].

For patients with co-occurrence of EML4-ALK rearrangement and EGFR mutations, EML4-ALK fusion has been associated with resistance to EGFR-TKIs[17][18]. However, there are accumulated clinical evidence suggest that patients carrying such mutation could benefit from EGFR-TKIs[19][20].

Notably, there is a case report revealed that an NSCLC patient with coexisting EGFR mutation and EML4-ALK fusion had developed a stable disease after combined EGFR-TKIs and ALK inhibitor treatment[21].

GNAS Q108*, Amplification

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[22]. 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[23][24][22]. GNAS activation may affect downstream MAPK and Wnt signaling pathway, suggesting activating mutation of GNAS can modify cell growth and may be oncogenic[24].

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Amplification of GNAS is commonly observed in ER-positive breast cancers[25], which is associated with increased MAPK/ERK signaling and tumor pathogenesis[25].

Q108* mutation results in a premature truncation of the GNAS protein at amino acid 108 (UniProtKB). This mutation is predicted to lead to a loss of GNAS function, despite not having characterized in the literature.

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[26].

GNAS amplification was significantly associated with poor progression-free survival (PFS) in advanced epithelial ovarian cancer patients receiving standard therapy and poor survival in intrahepatic cholangiocarcinoma[27][28].

CDKN2A Heterozygous 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[29][30][31]. 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[32]. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation[33][34].

Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors[35][36]. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments[37][38][39]. 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[40][41][42]. However, 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).

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[36][43][44].

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[38]. 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[45].

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[46].

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FLT4 Amplification

Biological Impact

The FLT4 (FMS-like tyrosine kinase 4) gene encodes for a vascular endothelial growth factor receptor 3 (VEGFR3), which involves in lymphangiogenesis and the maintenance of lymphatic endothelium[47]. VEGFR3 has been shown to mediate cell proliferation, survival, and chemoresistance in leukemia[48], and to promote invasion and metastasis of human lung adenocarcinoma cells[49]. Mutations in FLT4 cause hereditary Nonne-Milroy disease, an autosomal dominant form of primary lymphedema type IA[50]. In addition to lymphatic endothelial cells, FLT4 is also expressed in lung adenocarcinoma[51], colorectal adenocarcinoma[52], head and neck carcinoma[53], prostate carcinoma[54], leukemia[48], and Kaposi's sarcoma[55]. FLT4 expression levels were also shown to correlate with different stages of cervical carcinogenesis[56].

Therapeutic and prognostic relevance

In a phase II trial of sorafenib in radiation-associated breast angiosarcomas, patients with co-amplification of MYC and FLT4 achieved complete or partial response (DOI: 10.1200/jco.2012.30.15_suppl.10019). In clinical studies, a subset of patients with secondary angiosarcoma, mostly related to radiation-induced breast cancer and postlymphedema, co-harbored MYC and FLT4 amplification. The MYC and FLT4 amplification was associated to poor prognosis[57][58].

A case report showed that angiosarcoma patient with concurrent KDR and FLT4 amplification experienced a potent antitumor response and achieved clinically stable disease for 6 months after receiving pazopanib therapy[59].

SMO Amplification

Biological Impact

Smoothened, frizzled family receptor (SMO) is a G-protein coupled receptor and member of the sonic hedgehog signaling pathway, which is involved in embryonic development, cell differentiation, proliferation, and survival[60]. Activating mutation and overexpression of SMO have been reported in various types of cancers, such as basal cell carcinoma, medulloblastoma, colorectal cancer, and gastric cancer[61][62][63][64][65].

Therapeutic and prognostic relevance

High SMO expression was associated with paclitaxel drug resistance in patients with gastric cancer[65].

In a preclinical study, SMO amplification and MET phosphorylation were observed in human NSCLC cell line which is resistant to EGFR tyrosine kinase inhibitors like gefitinib[66].

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US FDA-APPROVED DRUG(S)

Abemaciclib (VERZENIO)

Abemaciclib is a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor. Abemaciclib is developed and marketed by Eli Lilly under the trade name VERZENIO.

- FDA Approval Summary of Abemaciclib (VERZENIO)

monarchE NCT03155997	**Breast cancer** (Approved on 2021/10/12)
	HR-positive, HER2-negative
	Abemaciclib + tamoxifen/aromatase inhibitor vs. Tamoxifen/aromatase inhibitor [IDFS at 36 months(%): 86.1 vs. 79.0]
MONARCH 3[67] NCT02246621	**Breast cancer** (Approved on 2018/02/26)
	HR-positive, HER2-negative
	Abemaciclib + anastrozole/letrozole vs. Placebo + anastrozole/letrozole [PFS(M): 28.2 vs. 14.8]
MONARCH 2[44] NCT02107703	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 16.4 vs. 9.3]
MONARCH 1[68] NCT02102490	**Breast cancer** (Approved on 2017/09/28)
	HR-positive, HER2-negative
	Abemaciclib [ORR(%): 19.7 vs. 17.4]

Alectinib (ALECENSA)

Alectinib is a small molecule tyrosine kinase receptor inhibitor with potent activity against anaplastic lymphoma kinase (ALK) that is rearranged and mutated in selective cancer. Alectinib is developed and marketed by Genentech under the trade name ALECENSA.

- FDA Approval Summary of Alectinib (ALECENSA)

NP28673[69] NCT01801111	**Non-small cell lung carcinoma** (Approved on 2015/12/11)
	ALK-positive
	Alectinib [ORR(%): 44.0]
NP28761[70] NCT01871805	**Non-small cell lung carcinoma** (Approved on 2015/12/11)
	ALK-positive
	Alectinib [ORR(%): 38.0]

Brigatinib (ALUNBRIG)

Brigatinib is a potent dual inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). Brigatinib is developed and marketed by Takeda under the trade name ALUNBRIG.

- FDA Approval Summary of Brigatinib (ALUNBRIG)

ALTA 1L NCT02737501	**Non-small cell lung carcinoma** (Approved on 2020/05/22)
	ALK Fusion
	Brigatinib vs. Crizotinib [PFS(M): 24 vs. 11]
ALTA NCT02094573	**Non-small cell lung carcinoma** (Approved on 2017/04/28)
	ALK-positive
	Brigatinib [ORR (90mg)(%): 48.0, ORR (90→180mg)(%): 53.0]

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Ceritinib (ZYKADIA)

Ceritinib is a small molecule inhibitor of anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase which, after genetic rearrangement, acts as an oncogenic driver. Ceritinib is developed and marketed by Novartis under the trade name ZYKADIA.

- FDA Approval Summary of Ceritinib (ZYKADIA)

ASCEND-4[8] NCT01828099	**Non-small cell lung carcinoma** (Approved on 2017/05/26)
	ALK-positive
	Ceritinib vs. Pemetrexed + cisplatin| pemetrexed + carboplatin [ORR(%): 73.0 vs. 27.0]
ASCEND-1[71] NCT01685060	**Non-small cell lung carcinoma** (Approved on 2014/04/29)
	ALK-positive
	Ceritinib [ORR(%): 43.6]

Crizotinib (XALKORI)

Crizotinib is an inhibitor of the tyrosine kinases anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), by competitively binding with the ATP-binding pocket. Crizotinib is developed and marketed by Pfizer under the trade name XALKORI.

- FDA Approval Summary of Crizotinib (XALKORI)

ADVL0912, A8081013 NCT00939770, NCT01121588	**Inflammatory myofibroblastic tumor** (Approved on 2022/08/05)
	ALK-positive
	Crizotinib [ORR(pediatric patients)(%): 86.0, ORR(adult patients)(%): 71.0]
ADVL0912 NCT00939770	**Alk fusion-positive anaplastic large cell lymphoma (alcl)** (Approved on 2021/01/14)
	ALK fusion
	Crizotinib [ORR(%): 88.0, DOR(M): 39 (maintained response for at least 6 months) vs. 22 (maintained response for at least 12 months)]
PROFILE 1001[72] NCT00585195	**Non-small cell lung carcinoma** (Approved on 2016/03/11)
	ROS1-positive
	Crizotinib [ORR(%): 66.0]
PROFILE 1014[73] NCT01154140	**Non-small cell lung carcinoma** (Approved on 2015/03/20)
	ALK-positive
	Crizotinib vs. Pemetrexed + cisplatin or pemetrexed + carboplatin [PFS(M): 10.9 vs. 7]
PROFILE 1007[7] NCT00932893	**Non-small cell lung carcinoma** (Approved on 2013/11/20)
	ALK-positive
	Crizotinib vs. Pemetrexed or docetaxel [PFS(M): 7.7 vs. 3]

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Lorlatinib (LORBRENA)

Lorlatinib is a kinase inhibitor with in vitro activity against ALK and ROS1 as well as TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. Lorlatinib demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors. Lorlatinib is developed and marketed by Pfizer under the trade name LORBRENA.

- FDA Approval Summary of Lorlatinib (LORBRENA)

Study B7461006 (CROWN) NCT03052608	**Non-small cell lung carcinoma** (Approved on 2021/03/03)
	ALK fusion
	Lorlatinib vs. Crizotinib [PFS(M): NR vs. 9.3]
Study B7461001[12] NCT01970865	**Non-small cell lung carcinoma** (Approved on 2018/11/02)
	ALK-positive
	Lorlatinib [ORR(%): 48, ORR (intracranial)(%): 60]

Palbociclib (IBRANCE)

Palbociclib is an oral, cyclin-dependent kinase (CDK) inhibitor specifically targeting CDK4 and CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Palbociclib is developed and marketed by Pfizer under the trade name IBRANCE.

- FDA Approval Summary of Palbociclib (IBRANCE)

PALOMA-2[74] NCT01740427	**Breast cancer** (Approved on 2017/03/31)
	ER+, HER2-
	Palbociclib + letrozole vs. Placebo + letrozole [PFS(M): 24.8 vs. 14.5]
PALOMA-3[75] NCT01942135	**Breast cancer** (Approved on 2016/02/19)
	ER+, HER2-
	Palbociclib + fulvestrant vs. Placebo + fulvestrant [PFS(M): 9.5 vs. 4.6]

Pazopanib (VOTRIENT)

Pazopanib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including vascular endothelial growth factor receptor-1, -2, -3 (VEGFR-1, -2, -3), platelet-derived growth factor receptor-α, -β (PDGFR-α, -β), c-kit, fibroblast growth factor-1 and -3 (FGFR-1, -3), thereby inhibiting angiogenesis. Pazopanib is developed and marketed by GlaxoSmithKline under the trade name VOTRIENT.

- FDA Approval Summary of Pazopanib (VOTRIENT)

PALETTE[76] NCT00753688	**Sarcoma** (Approved on 2016/04/26)
	-
	Pazopanib vs. Placebo [PFS(M): 4.6 vs. 1.6]
VEG105192[77] NCT00334282	**Renal cell carcinoma** (Approved on 2009/10/19)
	-
	Pazopanib vs. Placebo [PFS(M): 9.2 vs. 4.2]

Ribociclib (KISQALI)

Ribociclib is a cyclin-dependent kinase (CDK) inhibitor specifically targeting cyclin D1/CDK4 and cyclin D3/CDK6, thereby inhibiting retinoblastoma (Rb) protein phosphorylation. Ribociclib is developed by Novartis and Astex Pharmaceuticals and marketed by Novartis under the trade name KISQALI.

- FDA Approval Summary of Ribociclib (KISQALI)

MONALEESA-2[43] NCT01958021	**Breast cancer** (Approved on 2017/03/13)
	HR+, HER2-
	Ribociclib vs. Letrozole [PFS(M): NR vs. 14.7]

D=day; W=week; M=month

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

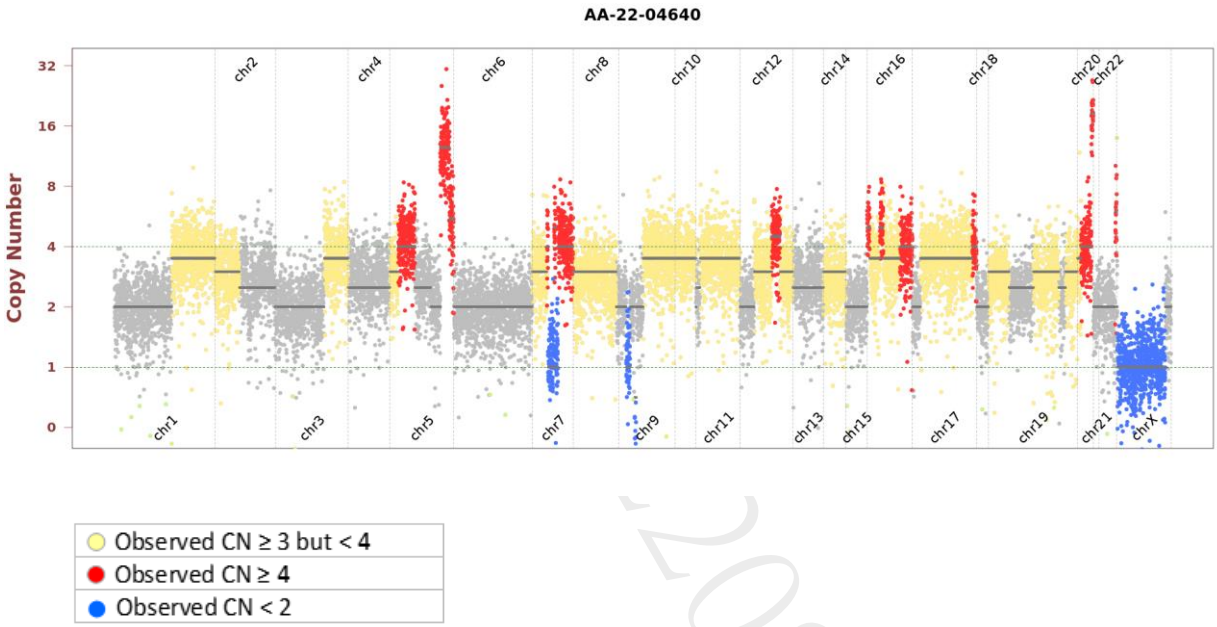
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
GNAS	Q108*	1	c.322C>T	NM_080425	-	8.2%	2523

- 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
ADAMTSL1	A1593T	26	c.4777G>A	NM_001040272	-	11.5%	584
BRCA1	P1856T	23	c.5566C>A	NM_007294	-	45.5%	666
CCND1	L137M	2	c.409C>A	NM_053056	-	26.2%	359
DDR2	I798V	17	c.2392A>G	NM_006182	-	27.1%	1308
FAT1	D4497N	27	c.13489G>A	NM_005245	COSM4525688	29.7%	1785
HR	D178E	2	c.534C>G	NM_005144	-	35.2%	642
IRS2	Q1269P	1	c.3806A>C	NM_003749	COSM5513012	58.1%	160
JAK2	I899T	20	c.2696T>C	NM_004972	COSM4384407	10.1%	527
KMT2C	P2050S	36	c.6148C>T	NM_170606	COSM600213	77.5%	3086
MDM4	H462L	11	c.1385A>T	NM_002393	-	71.6%	573
MUC16	D6322F	3	c.18964_18965delinsTT	NM_024690	-	35.9%	1075
PRKDC	S2050N	47	c.6149G>A	NM_006904	COSM9327167	35.6%	1420
PSMB8	A151T	4	c.451G>A	NM_148919	-	93.5%	825

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: Aug 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11129673A
- Collection site: Lung
- Examined by: Dr. Chien-Ta Chiang
  1. The percentage of viable tumor cells in total cells in the whole slide (%): 45%
  2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 45%
  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: Not performed
- The outline highlights the area of malignant neoplasm annotated by a pathologist.

RUN QC

- Panel: ACTOnco®+

DNA test

- Mean Depth: 765x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 69

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:
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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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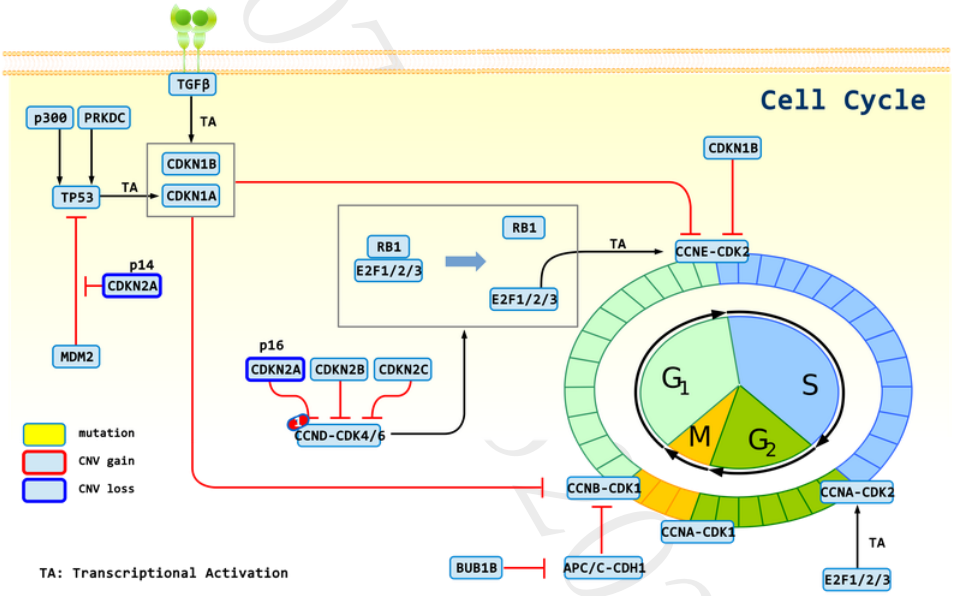
APPENDIX

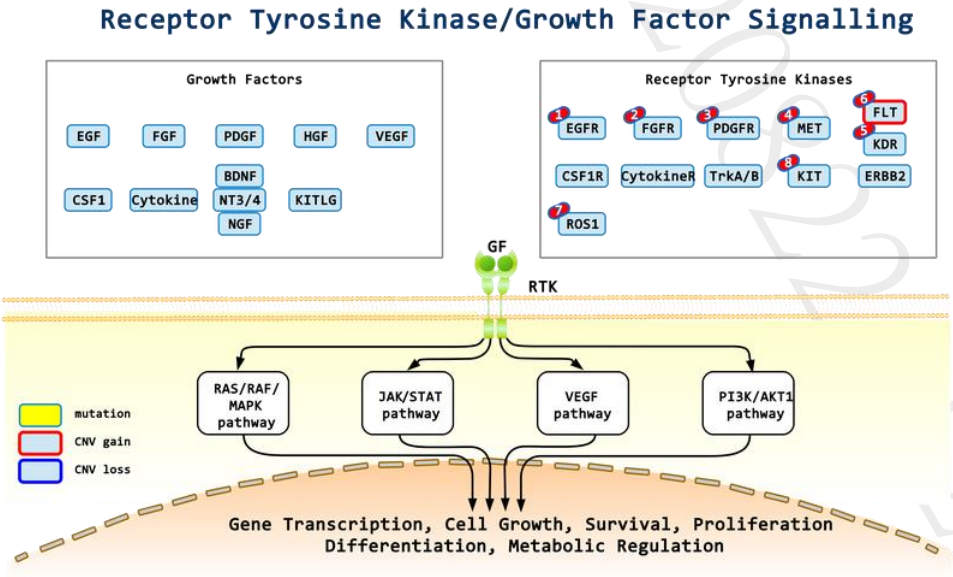
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
CDKN2A	Abemaciclib, Palbociclib, Ribociclib	**sensitive**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Palbociclib, Ribociclib, Abemaciclib



1: Brigatinib; 2: Pazopanib; 3: Pazopanib; 4: Crizotinib; 5: Pazopanib; 6: Pazopanib; 7: Crizotinib, Lorlatinib; 8: Pazopanib

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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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