

# ACT Onco<sup>®</sup> + Report

PATIENT		
Identifier: 林*賢		Patient ID: ***55502
Date of Birth: Jun **, 1964		Gender: Male
Diagnosis: Gallbladder cancer		
ORDERING PHYSICIAN		
Name: 姜乃榕醫師		Tel: 886-228712121
Facility: 臺北榮總		
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SPECIMEN		
Specimen ID: S11303277	Collection site: Liver	Type: FFPE tissue
Date received: Jan 24, 2024	Lab ID: AA-24-00505	D/ID: NA

## ABOUT ACT Onco<sup>®</sup>+

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) ( $\leq 15$  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	
ATP1B1(2)-NTRK1(10) fusion	Entrectinib, Larotrectinib	-	-

### VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
	Not detected	

#### 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 criteria 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
Not detected		

#### - Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr9	CDKN2A	Homozygous deletion	0
Chr1	ARID1A, CDKN2C	Heterozygous deletion	1
Chr15	RAD51	Heterozygous deletion	1
Chr18	SMAD4	Heterozygous deletion	1
Chr3	BAP1, MLH1, VHL	Heterozygous deletion	1
Chr9	PTCH1, TSC1	Heterozygous deletion	1

#### - Fusions

Fusion Gene & Exon	Transcript ID
ATP1B1(2)-NTRK1(10) fusion	ATP1B1(NM_001677.3), NTRK1(NM_002529.3)

#### - Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	2.6 muts/Mb
Microsatellite Instability (MSI)	Microsatellite stable (MSS)

#### Note:

- Loss of heterozygosity (LOH) information was used to infer tumor cellularity. Copy number alteration in the tumor was determined based on 79% 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<sup>®</sup> 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  $\geq 7.5$  mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is  $< 30\%$ .

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## SUPPLEMENTARY INFORMATION FOR THERAPEUTIC IMPLICATIONS TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 1		
<b>ATP1B1(2)-NTRK1(10)</b> fusion	Entrectinib, Larotrectinib	<b>sensitive</b>

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

### ATP1B1(2)-NTRK1(10) fusion

#### Biological Impact

The NTRK1 gene encodes the TRKA (tropomyosin receptor kinase) receptor which plays an important role in the development and function of the nervous system. Gene fusions of NTRK1 lead to constitutive activation of MAP-kinase, PI3-kinase, and PLC-γ pathways, and represent the main molecular alterations with known oncogenic and transforming potential in various malignancies, including soft tissue sarcoma, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), thyroid carcinoma, and pilocytic astrocytomas<sup>[1][2]</sup>. A pan-cancer study (n=1250) demonstrated that 2.2% of the metastatic cancer patients harbored NTRK amplification and NTRK protein overexpression was observed in 14.8% of NTRK-amplified tumors (doi.org/10.23838/pfm.2017.00142).

ATP1B1-NTRK1 fusion results from a translocation between ATP1B1 and NTRK1, and has been identified in gastric carcinoma<sup>[3]</sup>.

The Neurotrophic Receptor Tyrosine Kinase Genes NTRK1, NTRK2, and NTRK3 encode tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, respectively. Gene fusions involving the 3' tyrosine kinase domain of the TRK proteins and various 5' upstream gene partners often lead to constitutively activated or overexpressed chimeric TRK kinase function and have recently emerged as therapeutic targets in multiple types of adult and pediatric cancer<sup>[4][2]</sup>.

#### Therapeutic and prognostic relevance

Larotrectinib and Entrectinib are FDA-approved for treating patients with solid tumors carrying NTRK gene fusions.

Acquired resistance to TRK tyrosine kinase inhibitors (TKIs) through mutations in drug binding or TRK protein catalytic domains has been reported<sup>[5][6][7]</sup>. Next-generation TRK inhibitors such as LOXO-195, TPX-0005, and ONO-5390556 have shown in vitro activity against TKI-resistant TRK mutants (DOI:10.1158/1538-7445.AM2016-2954A; 10.1158/1538-7445.AM20173161)<sup>[8]</sup>. LOXO-195 and TPX-0005 are currently in phase I/II clinical trials (NCT03215511, NCT03093116) to assess their safety and efficacy.

### ARID1A Heterozygous deletion

#### Biological Impact

The AT-rich interactive domain 1A (ARID1A) gene encodes the BAF250A protein, a component of the SWI/SNF chromatin remodeling complex that plays a role in various cellular functions, including DNA repair, DNA synthesis, and transcription<sup>[9][10]</sup>. Haploinsufficiency of ARID1A is associated with tumor formation in some cancers<sup>[11]</sup>. Inactivation of ARID1A is commonly observed in ovarian, endometrial, uterine, and, gastric cancers<sup>[12][13][14][15][16]</sup>.

#### Therapeutic and prognostic relevance

ARID1A is the most frequently mutated genes in ovarian clear cell carcinoma and several synthetic lethality hypothesis-based therapeutic targets in ARID1A mutated cancer are in development. For examples, 1) EZH2 inhibitor<sup>[17][18]</sup>; 2) AKT-inhibitors MK-2206 and perifosine, as well as PI3K-inhibitor buparlisib<sup>[19]</sup>; 3) multiple kinase inhibitor, dasatinib<sup>[20]</sup>.

Some preclinical evidences suggested that reduced ARID1A expression confers resistance to several HER2/PI3K/mTOR signaling cascade inhibitors such as AZD8055 and trastuzumab, through activation of annexin A1 expression<sup>[21]</sup>. Loss or decreased expression of ARID1A has been reported to associate with resistance to platinum-based chemotherapies, shorter overall survival and lower complete response rate in ovarian cancer patients<sup>[22][23]</sup>.

Low expression of ARID1A is a significant and independent prognostic factor for poor disease-free and overall survival in breast cancer patients<sup>[24][25]</sup>. Besides, loss of ARID1A expression was more frequently seen in mismatch repair (MMR)-deficient colorectal cancers, predominantly in tumor with MLH1 promoter hypermethylation<sup>[26]</sup>.

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Positive ARID1A expression could independently predict worse overall survival in stage IV CRC patients compared with negative ARID1A expression<sup>[27]</sup>.

ARID1A mutation has been determined as an inclusion criterion for the trials evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831), and niraparib efficacy in melanoma (NCT03925350), pancreatic cancer (NCT03553004), or any malignancy, except prostate cancer (NCT03207347).

The preclinical study discovered that ARID1A deficiency sensitized some tumors to PARP inhibitor drugs, such as olaparib, rucaparib, talazoparib, and veliparib, which block DNA damage repair pathways<sup>[28]</sup>.

## **BAP1 Heterozygous deletion**

### **Biological Impact**

Breast cancer type 1 susceptibility protein (BRCA1)-associated protein (BAP1) encodes an enzyme with ubiquitin carboxyl hydrolase activity involved in the regulation of cell cycle, transcription, and double-strand DNA repair<sup>[29][30][31]</sup>. BAP1 acts as a tumor suppressor by forming a complex with BRCA1<sup>[32]</sup>. BAP1 is a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is related to renal cell carcinoma (RCC)<sup>[33]</sup>. Inactivating mutations of BAP1 were frequently observed in uveal melanoma with high metastatic risk, malignant mesothelioma and other carcinoma types, including a subtype of renal cell carcinoma and intrahepatic cholangiocarcinoma<sup>[30][34][35][36][37][38][39]</sup>.

### **Therapeutic and prognostic relevance**

In a Phase II trial (MiST1; NCT03654833), rucaparib demonstrated manageable toxicity and clinical activity in patients with relapsed malignant mesothelioma that were negative for BAP1 (n=23), BRCA1 (n=13), or both (n=10), resulting in a 12-week disease control rate (DCR) of 58% (15/26), a 24-week DCR of 23% (6/26), and an objective response rate of 11.5% (3/26)<sup>[40]</sup>. The loss of BAP1 was shown to be associated with increased sensitivity to PARP inhibitor, olaparib, in renal cell carcinoma (RCC)<sup>[36]</sup> and mesothelioma cell lines<sup>[41]</sup>. However, no difference in sensitivity to the PARP inhibitor niraparib (MK4827) was observed between BAP1-mutant and wild-type mesothelioma cell<sup>[30]</sup>. BAP1 deficiency was also linked to a high tumor grade and was correlated with metastasis development in uveal melanoma<sup>[34]</sup>.

An open-label, non-randomized, Phase II study (NCT03207347) has been initiated, aimed at investigating the use of niraparib in mesothelioma, uveal melanoma, renal cell carcinoma, and cholangiocarcinoma patients with tumors known to have mutations in BAP1 and other selected DNA double-strand break repair pathway genes. BAP1 loss of function mutation has been selected as an inclusion criteria for the trial examining olaparib in urothelial cancer (NCT03375307) and malignant mesothelioma (NCT04515836).

## **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<sup>[42][43][44]</sup>. 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<sup>[45]</sup>. Loss of CDKN2A has been frequently found in human tumors that result in uncontrolled cell proliferation<sup>[46][47]</sup>.



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## Therapeutic and prognostic relevance

Intact p16-Cdk4-Rb axis is known to be associated with sensitivity to cyclin-dependent kinase inhibitors<sup>[48][49]</sup>. Several case reports also revealed that patients with CDKN2A-deleted tumors respond to the CDK4/6-specific inhibitor treatments<sup>[50][51][52]</sup>. 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<sup>[53][54][55]</sup>. 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)<sup>[56][57]</sup>.

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<sup>[49][58][59]</sup>.

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<sup>[51]</sup>. 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<sup>[60]</sup>.

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<sup>[61]</sup>.

## CDKN2C Heterozygous deletion

### Biological Impact

CDKN2C gene encodes for cyclin-dependent kinase inhibitor 2C (CDKN2C) or p18 or INK4C, a member of the INK4 family of cyclin-dependent kinase inhibitors. CDKN2C binds to CDK4 or CDK6 and inhibits the activation of cyclin-dependent kinases (CDK) to prevent cell cycle progression at the G1 phase<sup>[62]</sup>. CDKN2C has been implicated as a haploinsufficient tumor suppressor gene<sup>[63]</sup> with one copy loss may promote cell cycle progression and induce proliferation in a variety of cancers<sup>[64][65][66]</sup>. Loss of CDKN2C by gene deletion or inactivating mutation has been reported in multiple cancer types, including myeloma, lymphoma, glioblastoma, meningioma, testicular cancers, melanoma, hepatocellular carcinomas, thyroid, and parathyroid cancer<sup>[67][68][69][70][71][72][73][74][75]</sup>.

## Therapeutic and prognostic relevance

CDKN2C loss has been determined as an inclusion criterion for the trial evaluating abemaciclib and ribociclib efficacies in patients with glioblastoma and myeloma (NCT02981940, NCT04118036, NCT03834740, NCT02933736).

An in vitro study demonstrated that cells expressing CDKN2A/B/C triple deletions activates cyclin-dependent kinases (CDK) and improves the sensitivity to palbociclib in glioblastoma multiforme (GBM) tumor cells<sup>[76]</sup>. Deletion of CDKN2C was associated with poorer prognosis in myeloma, acute lymphoblastic leukemia, hepatocellular carcinomas, and diffuse large B cell lymphoma (DLBCL)<sup>[77][78][74][79]</sup>.

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## MLH1 Heterozygous deletion

### Biological Impact

The MutL protein homolog 1 (MLH1) gene encodes a tumor suppressor that dimerizes with PMS2 protein to form a component of the DNA mismatch repair (MMR) system<sup>[80]</sup>. Deletion of one copy of the MLH1 gene resulted in haploinsufficiency in the correction of small insertions/deletions (indels), and could be a driving force in pancreatic and renal carcinogenesis<sup>[81]</sup>. Genetic alterations such as mutation, loss of heterozygosity or epigenetic silencing could lead to inactivation of MLH1 and are associated with a broad spectrum of cancers, including a subset of sporadic colon, gastric and endometrial cancers, as well as the hereditary non-polyposis colon cancer (HNPCC, also known as Lynch syndrome)<sup>[82][83][84]</sup>.

### Therapeutic and prognostic relevance

Talazoparib is FDA-approved for treating mCRPC patients harboring mutations in homologous recombination repair (HRR) genes, including MLH1.

Loss or loss of function mutation of HRR genes, including MLH1, MSH2 and MSH6, have been determined as an inclusion criterion for the trial evaluating olaparib efficacy in mCRPC and bladder cancer (NCT03434158, NCT03375307).

A screening test for microsatellite instability (MSI) is commonly used to identify an MMR-deficient tumor in the clinic<sup>[85][86]</sup>. Pembrolizumab (KEYTRUDA), an inhibitor targeting programmed cell death 1 (PD-1), has been approved by the U.S. FDA for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient cancer. Down-regulation of genes involved in the MMR pathway such as MLH1, MSH2 and MSH6 in high-grade serous epithelial ovarian cancer cell lines rendered cells sensitive to PARP inhibitors<sup>[87]</sup>.

## 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<sup>[88]</sup>. Inactivation of PTCH1 results in hedgehog ligand-independent activation of SMO, causing a downstream activation of the pathway and lead to the neoplastic growth<sup>[89][90]</sup>. Recurrent PTCH1 mutations have been reported in sporadic basal cell carcinoma (BCCs) and medulloblastoma<sup>[91][92][93][94]</sup>. Germline PTCH1 mutations are associated with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), predisposing patients to basal cell carcinoma and medulloblastoma<sup>[92]</sup>. PTCH1 is a haploinsufficient tumor suppressor gene with one copy loss may be sufficient to promote tumor development in mice<sup>[89][95]</sup>.

### 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<sup>[96][97][98][99]</sup>. 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<sup>[100]</sup>. 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<sup>[101]</sup>. In the phase II MyPathway trial, three advanced solid tumors patients harboring PTCH1 loss-of-function mutations had partial responses to vismodegib treatment<sup>[102]</sup>. In a clinical study, two patients with Sonic Hedgehog (SHH) activated medulloblastoma harboring PTCH1 loss-of-function mutations demonstrated partial responses to sonidegib treatment<sup>[103]</sup>.



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## **RAD51 Heterozygous deletion**

### **Biological Impact**

The RAD51 gene encodes a recombinase that is crucial for homologous recombination (HR)-mediated repair of double-strand DNA breaks (DSBs) by forming complexes with known tumor suppressors including BRCA1, BRCA2, and PALB2<sup>[104][105][106]</sup>. RAD51 has been characterized as a haploinsufficient tumor suppressor gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions<sup>[107]</sup>. Overexpression of RAD51 has been observed in many cancer cells, including pancreatic cancer and breast cancer and its hyperexpression is implicated in drug resistance<sup>[108][109][110][111][112][113][114]</sup>. Germline mutations in RAD51 are associated with increased susceptibility to breast cancer<sup>[115][116][117][118]</sup>.

### **Therapeutic and prognostic relevance**

RAD51 loss or loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in ovarian cancer<sup>[119]</sup> and metastatic biliary tract cancer (NCT04042831); rucaparib efficacy in solid tumor (NCT04171700); talazoparib efficacy in lung cancer (NCT03377556); niraparib efficacy in pancreatic cancer (NCT03553004) or any malignancy (except prostate cancer) (NCT03207347).

Preclinical studies showed that decreased RAD51 expression could sensitize cells to olaparib-induced tumor cell cytotoxicity<sup>[120][121]</sup>.

## **SMAD4 Heterozygous deletion**

### **Biological Impact**

The SMAD family member 4 (SMAD4) gene encodes a transcription factor that acts as a downstream effector in the TGF- $\beta$  signaling pathway. Upon phosphorylated and activated by serine-threonine receptor kinase, Smad4 is the Co-Smad which recruits other activated R-Smad proteins to the Smad transcriptional complex and regulate TGF- $\beta$ -targeted genes<sup>[122]</sup>. Smad4 has been identified as a haploinsufficient gene with one copy loss may lead to a weak protein expression and is insufficient to execute its original physiological function<sup>[123]</sup>. SMAD4 germline mutations are associated with juvenile polyposis syndrome (JPS)<sup>[124][125][126][127]</sup>. Somatic mutations of SMAD4 are commonly observed in pancreatic cancer<sup>[128]</sup>, colorectal cancer (CRC)<sup>[126][129][130]</sup>, and less frequently seen in other cancers such as lung adenocarcinoma<sup>[131]</sup>, head and neck cancer<sup>[132][133]</sup>, and cutaneous squamous cell carcinoma<sup>[134]</sup>.

### **Therapeutic and prognostic relevance**

In Chinese patients with metastatic colorectal cancer, SMAD4 or NF1 mutations are suggested as a potential biomarker for poor prognosis to cetuximab-based therapy<sup>[135]</sup>. Preclinical data demonstrated that depletion of SMAD4 by shRNA knockdown increased clonogenic survival and cetuximab resistance in HPV-negative head and neck squamous cell carcinoma cells<sup>[136]</sup>.

SMAD4 is also suggested as a predictive marker for 5-fluorouracil-based chemotherapy in colorectal cancer (CRC)<sup>[137][138]</sup>. CRC patients with normal SMAD4 diploidy exhibited three-fold higher benefit of 5-FU/mitomycin-based adjuvant therapy when compared with those with SMAD4 deletion<sup>[139]</sup>.

Results from clinical and meta-analyses showed that loss of SMAD4 in CRC, pancreatic cancer was correlated with poor prognosis<sup>[140][141][142][143][144][145][146][147]</sup>. In cervical cancer patients, weak cytoplasmic SMAD4 expression and absent nuclear SMAD4 expression were shown to be significantly associated with poor disease-free and overall 5-year survival<sup>[148]</sup>.

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## TSC1 Heterozygous deletion

### Biological Impact

The tuberous sclerosis complex 1 (TSC1) gene encodes a tumor suppressor, hamartin, a key negative regulator of the mammalian target of rapamycin (mTOR) pathway<sup>[149][150]</sup>. Mutations in TSC1/TSC2 tumor suppressor genes that result in inactivation of the complex are commonly found in patients with tuberous sclerosis<sup>[151][152][153]</sup>, while LOH in TSC1/TSC2 has been identified in head and neck squamous cell carcinoma (HNSCC)<sup>[154]</sup> and endometrial cancer<sup>[155]</sup>. Loss of single TSC1 allele (haploinsufficiency) may provide a growth advantage to bladder epithelial cells, contributing to bladder cancer development<sup>[156]</sup>. Both TSC1 and TSC2 mutations cause the autosomal dominant genetic disorder tuberous sclerosis complex (TSC), in which individuals develop a variety of benign but often progressive neoplasms<sup>[157]</sup>.

### Therapeutic and prognostic relevance

Everolimus is FDA-approved for treating Tuberous Sclerosis Complex (TSC)-associated renal angiomyolipoma and Tuberous Sclerosis Complex (TSC)-associated subependymal giant cell astrocytoma (SEGA).

TSC1/2 mutation/loss has been selected as an inclusion criteria for the trials examining temsirolimus efficacy in multiple cancer types (NCT02693535, NCT03297606).

TSC1/TSC2 genomic alterations activate the mTOR signaling pathway and confer sensitivity to mTOR inhibitors, including everolimus, sirolimus, and temsirolimus. Everolimus is effective in multiple cancers, such as bladder tumors, gastric, sarcoma, thyroid cancer, and HNSCC<sup>[158][159]</sup>. Sirolimus is effective in treating malignant uterine PEComa with TSC1/TSC2 mutations/deletions<sup>[160][161][162]</sup>, while temsirolimus is effective in those with hyperactivated mTOR pathway<sup>[163]</sup>. In advanced endometrial cancer, TSC1, and TSC2 mutations may predict clinical benefits from Temsirolimus with or without megestrol acetate and tamoxifen<sup>[164]</sup>.

## VHL Heterozygous deletion

### Biological Impact

VHL encodes the von Hippel-Lindau protein, a tumor suppressor that function is the substrate-binding subunit of an E3 ubiquitin ligase that targets the degradation of the  $\alpha$ -subunit of hypoxia-inducible factor (HIF- $\alpha$ ) in normal physiological condition<sup>[165]</sup>. VHL is a haploinsufficient tumor suppressor gene considering the etiology of VHL disease since all VHL patients are VHL heterozygotes<sup>[166]</sup>.

### Therapeutic and prognostic relevance

Belzutifan is FDA-approved for treating adult patients with von Hippel-Lindau (VHL) disease associated RCC, CNS hemangioblastomas who require therapy, or patients with pNET not requiring immediate surgery.

VHL mutation has been determined as an inclusion criterion for the trials evaluating sunitinib efficacy in solid tumors (NCT02693535).

Sunitinib has shown partial response in 33% of VHL disease associated RCC patients in a phase I trial<sup>[167]</sup>. However, a meta-analysis of six clinical studies suggests that VHL alteration has no prognostic or predictive value in ccRCC patients<sup>[168]</sup>. Belzutifan showed anti-tumor activity against VHL-mutant RCC xenografts in a preclinical study<sup>[169]</sup>. The combination of sunitinib and trametinib demonstrated a stronger anti-tumor effect in a PDX model of VHL-mutant RCC, while sunitinib alone suppressed tumor growth<sup>[170]</sup>.

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## US FDA-APPROVED DRUG(S)

### Belzutifan (WELIREG)

Belzutifan is a hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor.

#### - FDA Approval Summary of Belzutifan (WELIREG)

Study 004 NCT03401788	Renal cell carcinoma (Approved on 2021/08/13)
	VHL
	Belzutifan [ORR(%): 49.0]
Study 004 NCT03401788	Brain cancer (Approved on 2021/08/13)
	VHL
	Belzutifan [ORR(%): 63.0]
Study 004 NCT03401788	Neuroendocrine tumor (Approved on 2021/08/13)
	VHL
	Belzutifan [ORR(%): 83.0]

### Dasatinib (SPRYCEL)

Dasatinib is an oral Bcr-Abl tyrosine kinase inhibitor (inhibits the "Philadelphia chromosome") and Src family tyrosine kinase inhibitor. Dasatinib is produced by Bristol-Myers Squibb and sold under the trade name SPRYCEL.

#### - FDA Approval Summary of Dasatinib (SPRYCEL)

DASISION <sup>[171]</sup> NCT00481247	Chronic myeloid leukemia (Approved on 2010/10/28)
	-
	Dasatinib vs. Imatinib [ORR(%): 76.8 vs. 66.2]
[172] NCT00123474	Chronic myeloid leukemia (Approved on 2007/11/08)
	-
	Dasatinib [ORR(%): 63.0]
[173] NCT00123487	Acute lymphocytic leukemia (Approved on 2006/06/28)
	-
	Dasatinib [ORR(%): 38.0]

### Entrectinib (ROZLYTREK)

Entrectinib is an inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2, and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK) with IC50 values of 0.1 to 2 nM. Entrectinib is developed and marketed by Genentech under the tradename ROZLYTREK.

#### - FDA Approval Summary of Entrectinib (ROZLYTREK)

ALKA, STARTRK-1, STARTRK-2 <sup>[174]</sup> NCT02097810, NCT02568267	Cancer (Approved on 2019/08/15)
	NTRK fusion
	Entrectinib [ORR(%): 57.0]

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ALKA, STARTRK-1, STARTRK-2 <sup>[175]</sup> NCT02097810, NCT02568267	Non-small cell lung carcinoma (Approved on 2019/08/15)
	ROS1+
	Entrectinib [ORR(%): 78.0]

## Everolimus (AFINITOR)

Everolimus, a derivative of sirolimus, works as an inhibitor of mammalian target of rapamycin complex 1 (mTORC1) and blocks mTORC1-mediated downstream signals for cell growth, proliferation, and survival. Everolimus is developed and marketed by Novartis under the trade name AFINITOR.

### - FDA Approval Summary of Everolimus (AFINITOR)

RADIANT-4 <sup>[176]</sup> NCT01524783	Lung or gastrointestinal neuroendocrine tumor (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2 <sup>[177]</sup> NCT00863655	Breast cancer (Approved on 2012/07/20)
	ER+/HER2-
	Everolimus + exemestane vs. Placebo + exemestane [PFS(M): 7.8 vs. 3.2]
EXIST-2 NCT00790400	Tuberous sclerosis complex (tsc)-associated renal angiomyolipoma (Approved on 2012/04/26)
	-
	Everolimus vs. Placebo [ORR(%): 41.8 vs. 0]
RADIANT-3 <sup>[178]</sup> NCT00510068	Pancreatic neuroendocrine tumor (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1 <sup>[179]</sup> NCT00789828	Subependymal giant cell astrocytoma (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1 <sup>[180]</sup> NCT00410124	Renal cell carcinoma (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

## Larotrectinib (VITRAKVI)

Larotrectinib is an inhibitor of the tropomyosin receptor kinases (TRK), TRKA, TRKB, and TRKC. Larotrectinib is developed and marketed by Loxo Oncology under the trade name VITRAKVI.

### - FDA Approval Summary of Larotrectinib (VITRAKVI)

LOXO-TRK-14001, SCOUT, NAVIGATE <sup>[181]</sup> NCT02122913, NCT02637687, NCT02576431	Cancer (Approved on 2018/11/26)
	NTRK fusion
	Larotrectinib [ORR(%): 75.0, DOR(M): NR]

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## Niraparib (ZEJULA)

Niraparib is an oral, small molecule inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1 and -2 (PARP-1, -2). Niraparib is developed and marketed by Tesaro under the trade name ZEJULA.

### - FDA Approval Summary of Niraparib (ZEJULA)

<b>MAGNITUDE</b> NCT03748641	<b>Prostate cancer</b> (Approved on 2023/08/11)
	<b>BRCA mutation</b> Niraparib and abiraterone acetate plus prednisone vs. placebo and abiraterone acetate plus prednisone [rPFS(M): 16.6 vs. 10.9]
<b>PRIMA</b> NCT02655016	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2020/04/29)
	- Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
<b>NOVA<sup>[182]</sup></b> NCT01847274	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/03/27)
	- Niraparib vs. Placebo [PFS (overall population)(M): 11.3 vs. 4.7]

## Olaparib (LYNPARZA)

Olaparib is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase-1, -2, and -3 (PARP-1, -2, -3). Olaparib is developed by KuDOS Pharmaceuticals and marketed by AstraZeneca under the trade name LYNPARZA.

### - FDA Approval Summary of Olaparib (LYNPARZA)

<b>PROpel</b> NCT03732820	<b>Prostate cancer</b> (Approved on 2023/05/31)
	<b>BRCA mutation</b> Olaparib + abiraterone + prednisone vs. Placebo + abiraterone + prednisone [rPFS(M): not reached vs. 8]
<b>OlympiA</b> NCT02032823	<b>HER2-negative high-risk early breast cancer</b> (Approved on 2022/03/11)
	<b>HER2-/gBRCA mutation</b> Olaparib vs. Placebo [invasive disease-free survival (IDFS)(M): ]
<b>PROfound<sup>[183]</sup></b> NCT02987543	<b>Prostate cancer</b> (Approved on 2020/05/19)
	<b>HRR genes mutation</b> Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
<b>PAOLA-1<sup>[184]</sup></b> NCT02477644	<b>Ovarian cancer</b> (Approved on 2020/05/08)
	<b>HRD+</b> Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
<b>POLO<sup>[185]</sup></b> NCT02184195	<b>Pancreatic adenocarcinoma</b> (Approved on 2019/12/27)
	<b>gBRCA mutation</b> Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
<b>SOLO-1<sup>[186]</sup></b> NCT01844986	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/12/19)
	<b>gBRCA mutation or sBRCA mutation</b> Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
<b>OlympiAD<sup>[187]</sup></b> NCT02000622	<b>Breast cancer</b> (Approved on 2018/02/06)
	<b>HER2-/gBRCA mutation</b> Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]



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<b>SOLO-2/ENGOT-Ov21</b> <sup>[188]</sup> NCT01874353	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/08/17)
	<b>gBRCA mutation</b>
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
<b>Study19</b> <sup>[189]</sup> NCT00753545	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]

## Rucaparib (RUBRACA)

Rucaparib is an inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase-1, -2 and -3 (PARP-1, -2, -3). Rucaparib is developed and marketed by Clovis Oncology under the trade name RUBRACA.

### - FDA Approval Summary of Rucaparib (RUBRACA)

<b>TRITON2</b> NCT02952534	<b>Prostate cancer</b> (Approved on 2020/05/15)
	<b>gBRCA mutation or sBRCA mutation</b>
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
<b>ARIEL3</b> <sup>[190]</sup> NCT01968213	<b>Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma</b> (Approved on 2018/04/06)
	-
	Rucaparib vs. Placebo [PFS (All)(M): 10.8 vs. 5.4, PFS (HRD)(M): 13.6 vs. 5.4, PFS (tBRCA)(M): 16.6 vs. 5.4]

## 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)

<b>BOLT</b> <sup>[98]</sup> NCT01327053	<b>Basal cell carcinoma</b> (Approved on 2015/07/24)
	-
	Sonidegib [ORR(%): 58.0]

## Sunitinib (SUTENT)

Sunitinib is an oral, small molecule, multi-kinase inhibitor that targets receptor tyrosine kinase including platelet-derived growth factor receptor- $\alpha$ , - $\beta$  (PDGFR- $\alpha$ , - $\beta$ ), vascular endothelial growth factor receptors-1, -2, -3 (VEGFR-1, -2, -3), c-kit, Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET), thereby inhibiting angiogenesis. Sunitinib is developed and marketed by Pfizer under the trade name SUTENT.

### - FDA Approval Summary of Sunitinib (SUTENT)

<sup>[191][192][193]</sup> NCT00428597	<b>Pancreatic cancer</b> (Approved on 2011/05/20)
	-
	Sunitinib vs. Placebo [PFS(M): 10.2 vs. 5.4]
<sup>[194][195]</sup> NCT00083889	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib vs. Ifn- $\alpha$ [PFS(W): 47.3 vs. 22]



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[196][197][195] NCT00077974	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 34.0]
[197][195] NCT00054886	<b>Renal cell carcinoma</b> (Approved on 2007/02/02)
	-
	Sunitinib [ORR(%): 36.5]
[198] NCT00075218	<b>Gastrointestinal stromal tumor</b> (Approved on 2006/01/26)
	-
	Sunitinib vs. Placebo [TTP(W): 27.3 vs. 6.4]

## Talazoparib (TALZENNA)

Talazoparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1 and PARP2. Talazoparib is developed and marketed by Pfizer under the trade name TALZENNA.

### - FDA Approval Summary of Talazoparib (TALZENNA)

TALAPRO-2 NCT03395197	<b>Prostate cancer</b> (Approved on 2023/06/20)
	<b>HRR genes mutation</b>
	Talazoparib + enzalutamide vs. Placebo + enzalutamide [rPFS(M): Not reached vs. 13.8]
EMBRACA <sup>[199]</sup> NCT01945775	<b>Breast cancer</b> (Approved on 2018/10/16)
	<b>HER2-/gBRCA mutation</b>
	Talazoparib vs. Chemotherapy [PFS(M): 8.6 vs. 5.6]

## Temsirolimus (TORISEL)

Temsirolimus is a soluble ester of sirolimus (rapamycin, brand-name drug Rapamune) and functions as an inhibitor of mammalian target of rapamycin complex (mTORC). The inhibitory molecular mechanism is similar to Everolimus. Temsirolimus is developed by Wyeth Pharmaceuticals and marketed by Pfizer under the trade name TORISEL.

### - FDA Approval Summary of Temsirolimus (TORISEL)

[200] NCT00065468	<b>Renal cell carcinoma</b> (Approved on 2007/05/30)
	-
	Temsirolimus vs. Ifn-α [OS(M): 10.9 vs. 7.3]

## 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 <sup>[96]</sup> NCT00833417	<b>Basal cell carcinoma</b> (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.

### Entrectinib

(NCT04589845, Phase 2)

TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or who are tumor mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay. Participants with solid tumors will be treated with a drug or drug regimen tailored to their NGS assay results at screening. Participants will be assigned to the appropriate cohort based on their genetic alteration(s). Treatment will be assigned on the basis of relevant oncogenotype, will have cohort-specific inclusion/exclusion criteria, and, unless otherwise specified, will continue until disease progression, loss of clinical benefit, unacceptable toxicity, participant or physician decision to discontinue, or death, whichever occurs first.

### - Contact

Name: Reference Study ID Number: BO41932 <https://forpatients.roche.com/>

Phone: 888-662-6728 (U.S. and Canada)

Email: [Global-Roche-Genentech-Trials@gene.com](mailto:Global-Roche-Genentech-Trials@gene.com)

### - Location

Status: Recruiting Country: Taiwan City: Tainan Name: National Cheng Kung University Hospital; Oncology	Status: Recruiting Country: Taiwan City: Taipei City Name: Taipei Veterans General Hospital; Department of Oncology
Status: Recruiting Country: Taiwan City: Taoyuan County Name: Chang Gung Memorial Hospital-Linkou; Dept of Oncology	Status: Active, not recruiting Country: Taiwan City: Zhongzheng Dist. Name: National Taiwan University Hospital; Oncology

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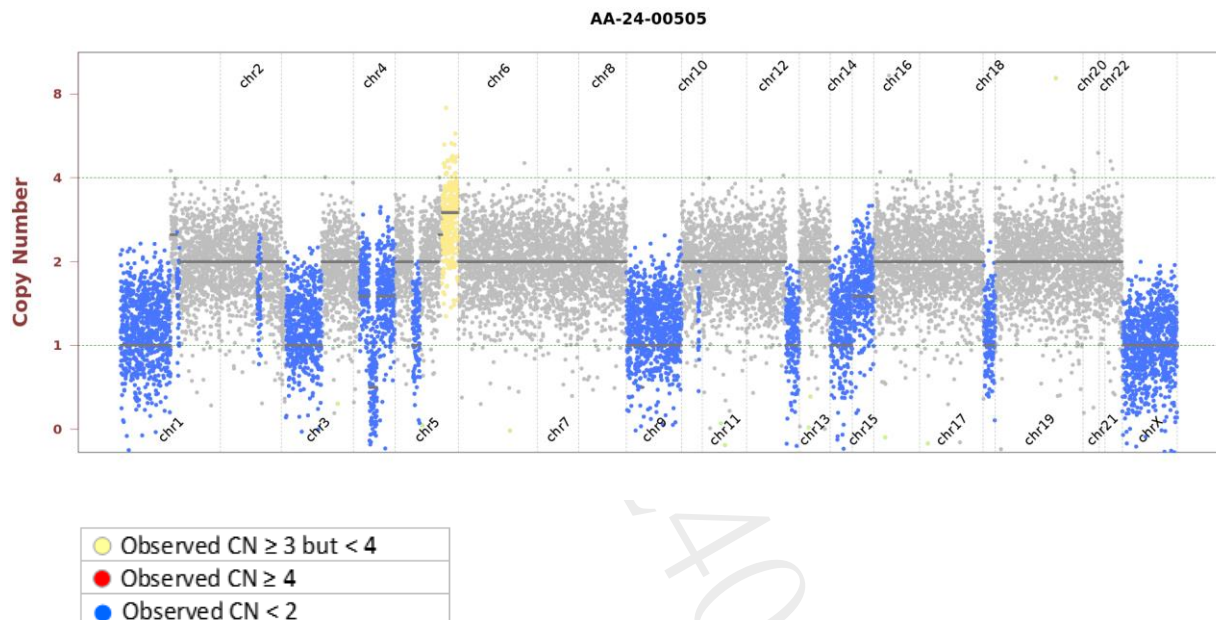
## SUPPLEMENTARY INFORMATION OF TESTING RESULTS DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

### - Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
Not Detected							

### - 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
ADGRA2	R662H	13	c.1985G>A	NM_032777	COSM3374906	51.0%	725
CCNB2	Splice donor	-	c.24+2T>G	NM_004701	-	62.3%	870
E2F3	G243C	4	c.727G>T	NM_001949	-	43.7%	1450
HR	R927H	13	c.2780G>A	NM_005144	-	48.2%	591
LRP1B	L3289P	62	c.9866T>C	NM_018557	-	41.2%	699
MEF2B	G178R	7	c.532G>A	NM_005919	-	51.7%	621
MUC16	T5195N	3	c.15584C>A	NM_024690	-	52.9%	918
MUC4	A864S	2	c.2590G>T	NM_018406	-	52.1%	906
ZNF217	P823L	3	c.2468C>T	NM_006526	-	51.5%	1329

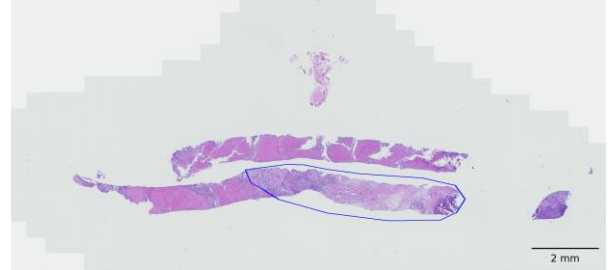
Note:

- 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: Jan 17, 2024
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11303277
- Collection site: Liver
- Examined by: Dr. Chien-Ta Chiang
- 1. The percentage of viable tumor cells in total cells in the whole slide (%): 15%
- 2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 40%
- 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: 912x
- Target Base Coverage at 100x: 95%

### RNA test

- Average unique RNA Start Sites per control GSP2: 145



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## 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.

## 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  $\geq 20$ , allele frequency  $\geq 5\%$  and actionable variants with allele frequency  $\geq 2\%$  were retained. This test provides uniform coverage of the targeted regions, enabling target base coverage at  $100\times \geq 85\%$  with a mean coverage  $\geq 500\times$ .

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  $\geq 0.3$  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<sup>®</sup>+ 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  $\geq 7.5$  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).



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## 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  $\geq 10$ .

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  $\geq 3$ ; (2) Number of supporting reads spanning the fusion junction  $\geq 5$ ; (3) Percentage of supporting reads spanning the fusion junction  $\geq 10\%$ ; (4) Fusions annotated in Quiver Gene Fusion Database.

## 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:

醫檢師黃靖婷 博士  
Ching-Ting Huang Ph.D.  
檢字第 016511 號

CT Huang

## Sign Off

解剖病理專科醫師朱旆億  
Pei-Yi Chu M.D.  
病解字第 000357 號

Pei-Yi Chu



行動基因是美國病理學會認證實驗室，認證實驗室號碼: 9028096.

行動基因僅提供技術檢測服務及檢測報告，檢測結果之臨床解釋及相關醫療處置，請諮詢專業醫師。報告結果僅對此試驗件有效。

行動基因臨床分子醫學實驗室 台北市內湖區新湖二路345號3F

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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*	BTB	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*	SLC1B1*
SLC1B3*	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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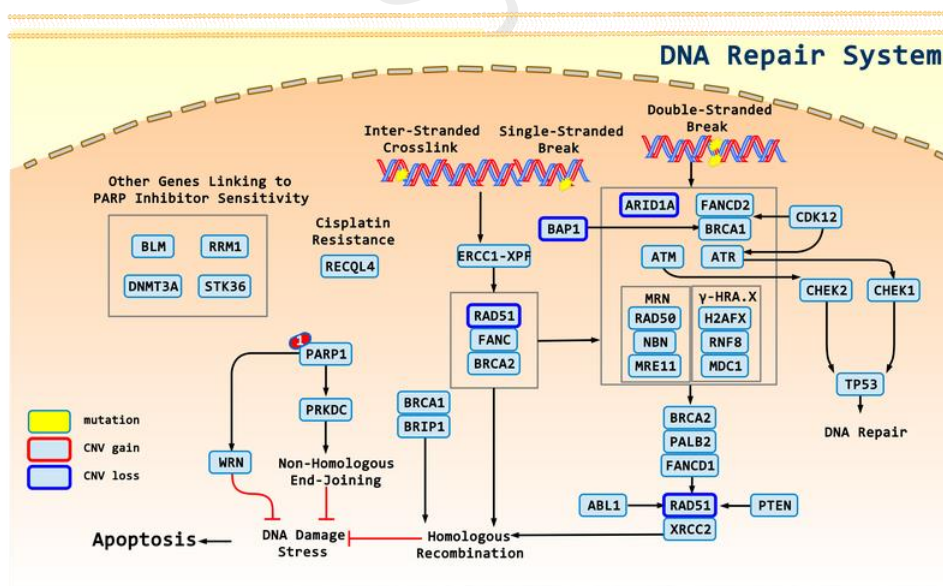
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## APPENDIX

### POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
VHL	Belzutifan, Sunitinib	sensitive
ARID1A	Dasatinib, Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
TSC1	Everolimus, Temsirolimus	sensitive
BAP1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
MLH1	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
RAD51	Niraparib, Olaparib, Rucaparib, Talazoparib	sensitive
PTCH1	Sonidegib, Vismodegib	sensitive
SMAD4	Cetuximab	resistant

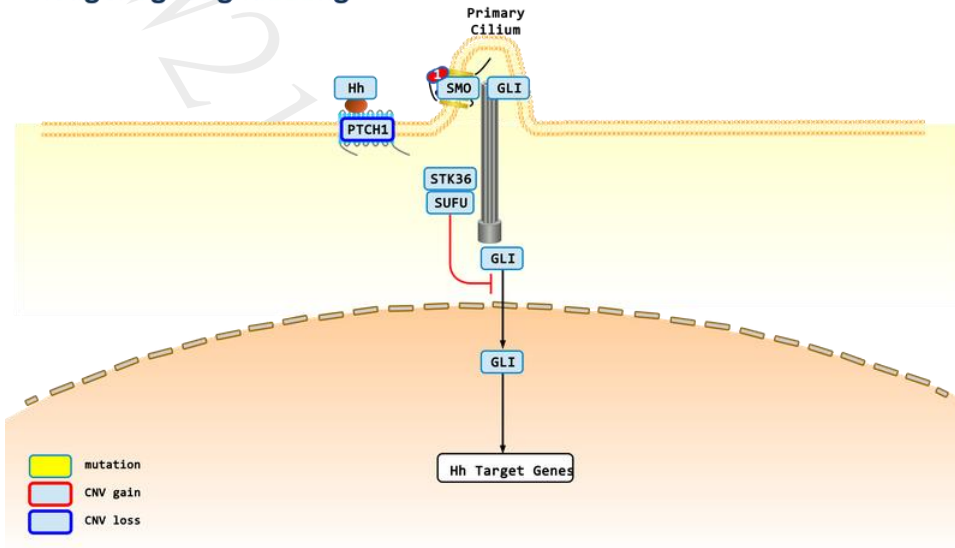
### SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib

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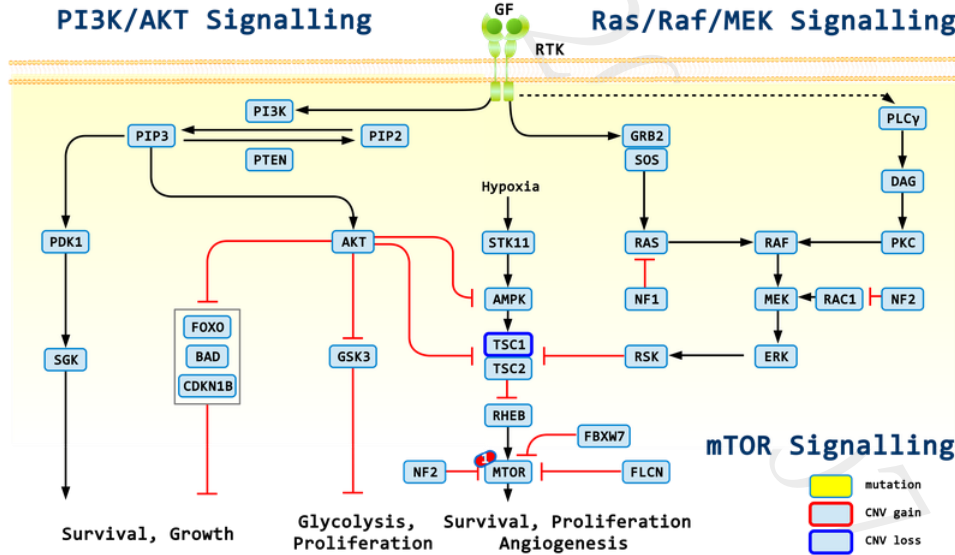
## Hedgehog Signalling



1: Sonidegib, Vismodegib

## PI3K/AKT Signalling

## Ras/Raf/MEK Signalling



1: Everolimus, Temsirolimus

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### 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。

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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。

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