ACT Onco® + Report

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Name: 丁鼎		Patient ID: 157368
Date of Birth: May 16, 1939		Gender: Male
Diagnosis: Prostate adenocarcinoma		
ORDERING PHYSICIAN		
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SPECIMEN		
Specimen ID: S11102978	Collection site: Pleural	Type: FFPE tissue
Date received: Mar 09, 2022	Lab ID: AA-22-01129	D/ID: NA

ABOUT ACTOnco®+

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

SUMMARY FOR ACTIONABLE VARIANTS

VARIANTS/BIOMARKERS WITH EVIDENCE OF CLINICAL SIGNIFICANCE

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

VARIANTS/BIOMARKERS WITH POTENTIAL CLINICAL SIGNIFICANCE

Genomic Alterations/Biomarkers	Possibly Sensitive	Possibly Resistant
FLCN Splice acceptor	Everolimus	-
MSH2 R680*	Olaparib	-

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
FLCN	Splice acceptor	21.6%
MSH2	R680*	20.8%
TP53	C124*	57.5%

- Copy Number Alterations

Chromosome	Gene	Variation	Copy Number
Chr10	*PTEN*	Heterozygous deletion	1
Chr13	*BRCA2, RB1*	Heterozygous deletion	1
Chr17	*TP53*	Heterozygous deletion	1
Chr5	*RICTOR, TERT*	Amplification	6¥
Chr11	*CCND1, FGF3*	Amplification	7¥
Chr20	*AURKA, GNAS*	Amplification	8
Chr8	*MYC*	Amplification	8
Chrx	*AR*	Amplification	41

¥ Increased gene copy number was observed.

- Fusions

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

- Immune Checkpoint Inhibitor (ICI) Related Biomarkers

Biomarker	Results
Tumor Mutational Burden (TMB)	1.9 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 53% tumor purity.
- For more therapeutic agents which are possibly respond to heterozygous deletion of genes listed above, please refer to APPENDIX for more information.
- TMB was calculated by using the sequenced regions of ACTOnco®+ to estimate the number of somatic nonsynonymous mutations per megabase of all protein-coding genes (whole exome). The threshold for high mutation load is set at ≥ 7.5 mutations per megabase. TMB, microsatellite status and gene copy number deletion cannot be determined if calculated tumor purity is < 30%.

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THERAPEUTIC IMPLICATIONS

TARGETED THERAPIES

Genomic Alterations	Therapies	Effect
Level 3B		
FLCN Splice acceptor	Everolimus	**sensitive**
MSH2 R680*	Olaparib	**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

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

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
MYC Amplification	FAC CMF and P-FEC regimens	**Sensitive**	Clinical	Breast cancer
	Platinum-based regimens	**Sensitive**	Clinical	Ovarian cancer
AURKA Amplification	Platinum-based regimens	**Less sensitive**	Clinical	Ovarian carcinoma
	Taxane-based regimens	**Less sensitive**	Clinical	Breast cancer

HORMONAL THERAPIES

Genomic Alterations	Therapies	Effect	Level of Evidence	Cancer Type
CCND1 Amplification	Anastrozole	**Less sensitive**	Clinical	Breast cancer
	Tamoxifen	**Less sensitive**	Clinical	Breast cancer
AR Amplification	Abiraterone	**Resistant**	Clinical	Prostate cancer
	Enzalutamide	**Resistant**	Clinical	Prostate cancer
	Tamoxifen	**Resistant**	Clinical	Breast cancer
AURKA Amplification	Tamoxifen	**Resistant**	Clinical	Estrogen-receptor positive breast cancer

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OTHERS

Pharmacogenomic implication

Gene	Detection Site	Genotype	Drug Impact	Level of Evidence*
UGT1A1	rs4148323	AA	Irinotecan-based regimens	Level 1B

Clinical Interpretation:
Patients with the AA 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 AG or GG 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

FLCN Splice acceptor

Biological Impact

The FLCN gene encodes the tumor suppressor, Folliculin, a GTPase activating protein (GAP) for RagC/D GTPase proteins involved in amino acid sensing and signaling to mTORC1[1]. FLCN has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[2][3]. Inactivation of the FLCN gene by mutation or deletion results in the activation of the mTOR pathway and AKT signaling[4][5]. Germline mutation of the FLCN gene causes the Birt-Hogg-Dubé syndrome, a rare disorder that is characterized by benign hamartomatous skin lesions and an increased risk of pneumothorax and renal tumors[6].

FLCN c.619-1G>T is a variant located at the splice acceptor region, which may result in the exon skipping.

Therapeutic and prognostic relevance

In a prospective Phase 2 study, four anaplastic thyroid cancer (ATC)/ poorly differentiated thyroid cancer (PDTC) patients who had PI3K/mTOR/AKT alterations, including TSC2, FLCN or NF1, showed impressive progression-free survival (PFS) of 15.2 months after receiving everolimus[7]. mTOR inhibition via rapamycin also demonstrated potential in inhibiting the growth of renal cells deficient in FLCN in the preclinical setting[8].

MSH2 R680*

Biological Impact

The MSH2 gene encodes the protein MutS protein homolog 2, also known as MSH2. MSH2 forms a heterodimer with MSH6 and MSH3 to make the MutS-alpha and MutS-beta DNA mismatch repair (MMR) complex, respectively[9][10]. Mutations in MSH2 and other MMR genes are associated with microsatellite instability and some cancers, such as hereditary non-polyposis colon cancer(HNPCC), also known as Lynch syndrome[11][12][13][14][15]. MSH2 mutations have also been reported in other cancers and syndromes, including endometrial and uterine cancers, and sebaceous gland tumors[16][17].

R680* mutation results in a premature truncation of the MSH2 protein at amino acid 680 (UniProtKB). This mutation is predicted to lead to a loss of MSH2 function, despite not having characterized in the literature.

Therapeutic and prognostic relevance

Tumors with mismatch-repair defects were associated with a large number of somatic mutations and have been predictive of clinical benefit to certain immune checkpoint blockade therapies[18][19]. The PD-1 antibodies pembrolizumab and nivolumab have been approved by the U.S. FDA for instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors and MSI-H or dMMR colorectal cancer respectively. 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[20].

MSH2 loss or loss of function mutations have been selected as an inclusion criteria for the trial examining olaparib in mCRPC (NCT03434158).

TP53 C124*, Heterozygous deletion

Biological Impact

TP53 encodes the p53 protein, a crucial tumor suppressor that orchestrates essential cellular processes including cell cycle arrest, senescence and apoptosis[21]. TP53 is a proto-typical haploinsufficient gene, such that loss of a single copy of TP53 can result in tumor formation[22].

C124* mutation results in a premature truncation of the p53 protein at amino acid 124 (UniProtKB). This mutation is predicted to lead to a loss of p53 function, despite not having characterized in the literature. Loss of the second wild-type allele resulted in the biallelic inactivation of the gene.

Therapeutic and prognostic relevance

Despite having a high mutation rate in cancers, there are currently no approved targeted therapies for TP53 mutations. A phase II trial demonstrated that Wee1 inhibitor (AZD1775) in combination with carboplatin was well tolerated and showed promising anti-tumor activity in TP53-mutated ovarian cancer refractory or resistant (< 3 months) to standard first-line therapy (NCT01164995)[23].

In a retrospective study (n=19), advanced sarcoma patients with TP53 loss-of-function mutations displayed improved progression-free survival (208 days versus 136 days) relative to patients with wild-type TP53 when treated with pazopanib[24]. Results from another Phase I trial of advanced solid tumors (n=78) demonstrated that TP53 hotspot mutations are associated with better clinical response to the combination of pazopanib and vorinostat[25].

Advanced solid tumor and colorectal cancer patients harboring a TP53 mutation have been shown to be more sensitive to bevacizumab when compared with patients harboring wild-type TP53[26][27][28]. In a pilot trial (n=21), TP53-negative breast cancer patients demonstrated increased survival following treatment with bevacizumab in combination with chemotherapy agents, Adriamycin (doxorubicin) and Taxotere (docetaxel)[29]. TP53 mutations were correlated with poor survival of advanced breast cancer patients receiving tamoxifen or primary chemotherapy[30][31]. In a retrospective study of non-small cell lung cancer (NSCLC), TP53 mutations were associated with high expression of VEGF-A, the primary target of bevacizumab, offering a mechanistic explanation for why patients exhibit improved outcomes after bevacizumab treatment when their tumors harbor mutant TP53 versus wild-type TP53[32].

AR Amplification

Biological Impact

The AR gene encodes for the androgen receptor, a steroid-hormone activated transcription factor which expresses in a wide range of adult tissue[33][34]. In breast cancer, the AR signaling axis activates the HER3 signaling through the Wnt/β-Catenin pathway[35]and followed by c-Myc mediated amplification of AR signaling[36]. But in the ER-negative subtype, AR expression was predominantly observed in HER2-positive class[37][38]. The amplification of HER2 coupled with AR activation enhances PI3K signaling and the oncogenic function of MYC[36]. AR-positive breast cancer tumors have been associated with a high rate of PIK3CA mutations, but the clinical significance of this correlation remains unknown[39]. Genetic alterations of AR are frequently identified in castration-resistant prostate cancer (CRPCs)[40], particularly in the drug-resistant form of CRPC[41][42][43].

Therapeutic and prognostic relevance

In CRPCs, amplification of the AR gene was associated with decreased response to enzalutamide[44] and lack of response to abiraterone[43].

In breast cancer, AR overexpression has been shown to be associated with resistance to tamoxifen[45]. Clinical reports demonstrated that patients with AR-positive metastatic breast cancer experienced clinical benefit with the bicalutamide[46][47].

Pre-clinical studies on the effect of bicalutamide and enzalutamide, both anti-androgens, has demonstrated inhibitory activities against both ER-positive and -negative breast cancer cells[35]. Several classes of AR-directed therapies for breast cancer are currently under clinical evaluations[48].

Several studies suggested high expression levels of AR predicts better prognosis in patients with breast cancer[49][50][51][52], while the low expression level of AR was associated with increased risk of cancer-related death in ER-positive breast cancer[53].

AURKA Amplification

Biological Impact

The Aurora kinase A (AURKA) gene encodes a serine/threonine kinase involved in the regulation of cell cycle and maintenance of genomic integrity[54]. AURKA gene amplification is commonly observed in a wide range of human cancers, including breast cancer[55], ovarian cancer[56], gastric cancer[57], colorectal[58], esophageal cancer[59], bladder cancer[60]and leukemia[61].

Therapeutic and prognostic relevance

Small-molecule inhibitors targeting AURKA (and the related Aurora B and C kinases) are currently studied in clinical trials. A Phase II study of the investigational aurora kinase A inhibitor, alisertib, demonstrated activity and safety in patients with breast and small-cell lung cancer (SCLC)[62].

Elevated AURKA activity was associated with taxane resistance in breast cancer patients[63], and platinum resistance in high-grade serous ovarian carcinoma patients[64].

Estrogen receptor positive breast cancer patients with increased AURKA expression were resistant to tamoxifen treatment and had a poorer prognosis[65][66].

BRCA2 Heterozygous deletion

Biological Impact

The BRCA2 gene encodes a tumor suppressor involved in the homologous recombination pathway for double-strand DNA repair[67]. BRCA2 has been implicated as a haploinsufficient gene with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[68]. BRCA2 germline mutations confer an increased lifetime risk of developing breast, ovarian, prostate and pancreatic cancer, limited reports of related gastric cancer, and Fanconi anemia subtype D1-associated risk of brain cancer, medulloblastoma, pharyngeal cancer, chronic lymphocytic leukemia and acute myeloid leukemia[69]. Somatic mutations in BRCA2 are highest in colorectal, non-small cell lung cancer (NSCLC), and ovarian cancers[70].

Therapeutic and prognostic relevance

The U.S. FDA has approved olaparib in advanced ovarian cancer under several settings including (1) first-line maintenance treatment for patients with deleterious or suspected deleterious germline or somatic BRCA mutation who are in complete or partial response to first-line platinum-based chemotherapy[71]; (2) in combination with bevacizumab as first-line maintenance treatment for patients with homologous recombination deficiency (HRD)-positive status[72]; (3) maintenance treatment for patients with germline BRCA-mutated recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy[73][74]; (4) treatment for patients with germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy[75]. In addition, olaparib has also been approved in patients with deleterious or suspected deleterious germline BRCA-mutated, HER2-negative metastatic breast cancer who have been treated with chemotherapy in either neoadjuvant, adjuvant, or metastatic setting[76]and germline BRCA-mutated metastatic pancreatic cancer[77]. Of note, in May 2020, the U.S. FDA approved olaparib for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who carry

mutations in homologous recombination repair (HRR) genes, including BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, and progressed following prior treatment with enzalutamide or abiraterone acetate[78].

Rucaparib has been approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and patients with BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more chemotherapies[79][80]. In May 2020, the U.S. FDA also approved rucaparib to treat adult patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy (TRITON2, NCT02952534).

The U.S. FDA also approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy and patients who have been treated with three or more prior lines of chemotherapy and associated with HRD positive status[81][82][83]. In addition, talazoparib for patients with deleterious or suspected deleterious germline BRCA-mutated, HER2 negative locally advanced or metastatic breast cancer[84].

CCND1 Amplification

Biological Impact

The cyclin D1 (CCND1) gene encodes a protein involved in the control of cell growth, proliferation, transcription, and DNA repair[85]. CCND1 forms a complex with CDK4 and CDK6, leading to G1-S cell-cycle transition by inhibiting the retinoblastoma (RB) protein[85]. Amplification or overexpression of CCND1 could be oncogenic and is associated with carcinogenesis of various cancer types[86].

Therapeutic and prognostic relevance

Several CDK4 inhibitors, including palbociclib (PD0332991), LEE011, and LY2835219 have entered clinical trials for tumors with CCND1 amplification[87][88]. In the Phase II study of palbociclib and letrozole in patients with ER-positive HER2-negative metastatic breast cancer, patient selection based on CCND1 amplification or p16 loss did not further improve patient outcome[89]. Preclinical studies also demonstrated conflicting results regarding the correlation between high-level CCND1 and palbociclib sensitivity[90][91][92].

CCND1 amplification has been implicated in predicting poor clinical outcomes in postmenopausal breast cancer patients treated with either anastrozole or tamoxifen[93]. In lung cancer patients, the increased CCND1 copy number is associated with poorer overall survival[94].

A retrospective study showed that melanoma patients whose tumor harboring CCND1, cRAF or KRAS gene copy number gain had better treatment response with CPS (carboplatin, paclitaxel, and sorafenib)[95].

Amplification of CCND1 are frequent and contributes to dedifferentiation and cellular proliferative activity of intrahepatic cholangiocarcinoma (ICC), and also indicates a poor prognosis for ICC patients[96].

Of note, CCND1 amplification has been selected as an inclusion criterion for the trial examining CDK4/6 inhibitors in different types of malignant solid tumors (NCT02187783, NCT02896335, NCT03526250, NCT02693535, NCT01037790, NCT03454919, NCT03310879, and NCT03356223).

FGF3 Amplification

Biological Impact

FGF3 (fibroblast growth factor 3, also known as INT2) gene encodes a protein belonging to the fibroblast growth factor family. FGF/FGFR signaling plays essential roles in embryonic development, angiogenesis, cell proliferation, differentiation, migration and survival[97][98][99]. FGF3, FGF4, FGF19, and CCND1 are located at 11q13 and has been reported to co-amplify in multiple cancer types including breast cancer, lung cancer, colon cancer, bladder cancer, advanced medullary thyroid cancer, and hepatocellular carcinoma[100][101][102][103]. Furthermore, recurrent amplification and overexpression of FGF3 and FGF4 are observed in Kaposi's Sarcoma[104].

Therapeutic and prognostic relevance

A retrospective study indicated that FGF3/FGF4 amplification associates with increased response to sorafenib in hepatocellular carcinoma[105]. However, FGF3 and FGF4 locate at chromosome 11 (11q13), the region which also contains FGF19 and CCND1, are frequently reported to exert amplifications in HCC[103]. Further evidence is needed to clarify if FGF3/FGF4 amplification is directly associated with higher response rate to sorafenib[106].

GNAS 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[107]. 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[108][109][107]. GNAS activation may affect downstream MAPK and Wnt signaling pathway, suggesting activating mutation of GNAS can modify cell growth and may be oncogenic[109].

Amplification of GNAS is commonly observed in ER-positive breast cancers[110], which is associated with increased MAPK/ERK signaling and tumor pathogenesis[110].

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[111].

GNAS amplification was significantly associated with poor progression-free survival (PFS) in advanced epithelial ovarian cancer patients receiving standard therapy[112]and poor survival in intrahepatic cholangiocarcinoma[113].

MYC Amplification

Biological Impact

The v-myc avian myelocytomatosis viral oncogene homolog, also known as c-myc (MYC) gene encodes a transcription factor involved in cellular proliferation, inhibiting exit from the cell cycle, stimulating vascularization and enhancing genomic instability[114][115][116]. Dysregulated MYC expression is implicated in a wide range of human cancers[117].

Therapeutic and prognostic relevance

MYC amplification was associated with better clinical outcome in breast cancer patients treated with FAC (5-fluorouracil, doxorubicin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate and 5-fluorouracil) and P-FEC (paclitaxel followed by 5-fluorouracil, epirubicin and cyclophosphamide) and higher expression of MYC was also associated with a better response rate in platinum-treated ovarian cancer patients[118][119][120].

CDK inhibition using the dinaciclib, a CDK1, 2, 5 and 9 inhibitors, exerted antitumor activity in triple-negative breast

cancer (TNBC) tumor xenograft and cell lines with increased activity of the MYC pathway[121][122].

Overexpression of MYC has been reported as a favorable prognostic biomarker in colorectal carcinoma (CRC)[123][124]. However, the favorable prognostic value of MYC in CRC is abrogated by the TP53 mutation[124].

MYC amplification with the loss of tumor suppressor pathways such as p53 and RB has been shown to be associated with poor outcomes and was correlated with shortened disease-free survival in breast cancer with BRCA1 deficiency in TNBC[121][125].

PTEN Heterozygous deletion

Biological Impact

The phosphatase and tensin homolog deleted on chromosome ten (PTEN) gene encodes a lipid/protein phosphatase that is important for the regulation of cell proliferation, survival, homologous recombination and maintenance of genomic integrity[126][127]. PTEN acts as an essential tumor suppressor by antagonizing the PI3K/AKT/mTOR signaling pathway[128]. PTEN is a haploinsufficient tumor suppressor gene, in which having only one copy of the wild-type allele does not produce enough protein product to execute wild-type functions[22][129][130]. Germline loss-of-function PTEN mutations are found in approximately 80% of patients with Cowden syndrome, a disorder that is associated with high-penetrance breast and thyroid cancer[131][132][133]. Somatic mutations or monoallelic loss of PTEN is regularly observed in a significant fraction of human cancers, including sporadic breast cancer, colon cancer, endometrial cancer, prostate cancer, and glioblastoma[134][135][136][137][138].

Therapeutic and prognostic relevance

Somatic loss of PTEN results in aberrant activation of PI3K/AKT/mTOR signaling pathway and provides a mechanistic rationale for PI3K pathway inhibitors treatment[139][140]. Preclinical studies demonstrated that PTEN deficiency was associated with increased sensitivity to PI3K pathway inhibitors in selected cancer subtypes[141][142][143][144][145][146]. Moreover, early clinical data also indicated that PTEN loss was associated with improved response and longer PFS in patients with advanced breast cancer[147], advanced pancreatic neuroendocrine tumors[148], and metastatic castration-resistant prostate cancer treated with mTORC1 inhibitor, everolimus[149].

Several groups found that PTEN loss was generally associated with poor response to trastuzumab therapy, whether this agent was administered in the neoadjuvant, adjuvant, or metastatic settings[150][151][152][153][154].

Loss of PTEN expression in advanced colorectal cancer (CRC) has been linked with resistance to anti-EGFR mAbs like cetuximab and panitumumab[155][156][157][158][159][160]. However, encouraging anti-tumor activity of the combination of an EGFR antibody and a mTORC1 inhibitor (everolimus or temsirolimus) have been reported in early-phase clinical studies (J Clin Oncol. 2011;29 (suppl): abstr 3587; J Clin Oncol. 2013;31 (suppl): abstr 608). Ongoing phase I/II studies testing combinations of EGFR antibodies and PI3K/AKT/mTOR pathway inhibitors (e.g., NCT01816984, NCT01252628, NCT01719380) will provide larger numbers of patients to assess the role of PTEN status in therapeutic response.

Preclinical studies showed that loss of PTEN expression in EGFR mutant cells was associated with decreased sensitivity to EGFR TKIs, erlotinib and gefitinib[161][162]. Inhibition of the PI3K/AKT/mTOR signal pathway has been shown to be an effective strategy to radiosensitize NSCLC cells harboring the EGFR activating mutation that acquires resistance to both TKIs due to PTEN loss or inactivation mutations[163].

Loss or biallelic inactivation of PTEN is associated with resistance to anti-PD-1 checkpoint blockade therapies, including pembrolizumab and nivolumab in melanoma and leiomyosarcoma patients[164][165][166].

PTEN loss of function mutation has been determined as an inclusion criterion for the trial evaluating olaparib efficacy in metastatic biliary tract cancer (NCT04042831); talazoparib efficacy in HER2-negative breast cancer (NCT02401347),

and niraparib efficacy in breast cancer (NCT04508803) or any malignancy (except prostate) cancer (NCT03207347). Clinical data also suggested that PTEN deficient cancers may be sensitive to olaparib[167].

RB1 Heterozygous deletion

Biological Impact

The Retinoblastoma (RB1) gene encodes a tumor suppressor that negatively regulates the cell cycle, cell division, and DNA replication[168]. Loss-of-function RB1 could lead to unregulated cell division and growth, abrogation of multiple mechanisms that safeguard against cellular transformation, and tumorigenesis[169]. RB1 has also been implicated as a haploinsufficient tumor suppressor with one copy loss may lead to weak protein expression and is insufficient to execute its original physiological functions[170][171][172]. Deletion or inactivating mutation of RB1 is found in a number of tumors, including lung, prostate, bladder, breast cancers and sarcomas. RB1 mutations are found in approximately half of all retinoblastoma cases[173].

Therapeutic and prognostic relevance

A deleterious mutation in one or more of the three DNA repair genes ATM, RB1, and FANCC predicted pathologic response and better overall survival to cisplatin-based chemotherapy for muscle-invasive bladder cancer patients[174]. High RB loss was found to be associated with improved pathologic clinical response in breast cancer patients treated with 5-fluorouracil/adriamycin/cytoxan (FAC), T/FAC, and Taxane/Adriamycin neoadjuvant therapy[175].

Clinical and experimental data suggested that a non-functional retinoblastoma pathway is associated with resistance to tamoxifen in breast cancer[176][177].

Acquired RB1 mutations were found in hormone receptor positive breast cancer patients who developed resistance to palbociclib or ribociclib treatment[178]. Preclinical data also showed that knockdown of RB1 would impair antitumor activity of CDK4/6 inhibitor, abemaciclib[179].

Two large-scale genome-sequencing projects have identified a high prevalence of mutations in TP53 and RB1 in small cell lung cancer (SCLC)[180][181]. Analyses of repeat biopsy samples from patients with EGFR-mutant adenocarcinoma that had transformed to the SCLC subtype have revealed that 100% of these patients have loss of RB1 and may be the alteration that induces this non-small-cell to small-cell transformation[177][182].

RICTOR Amplification

Biological Impact

The RICTOR (rapamycin-insensitive companion of mTOR) gene encodes a core component of the mTOR complex-2 (mTOR2) which phosphorylated downstream kinases such as AKT and regulated cell proliferation and survival[183][184][185]. Amplification of the RICTOR locus is observed in melanoma[186]and lung cancer[187].

Therapeutic and prognostic relevance

A non-small cell lung cancer (NSCLC) patient harboring RICTOR-amplified tumor achieved stable disease for more than 18 months from the treatment with dual mTOR1/2 inhibitors CC-223 and MLN0128[187]. Preclinical data showed that a RICTOR-amplified patient-derived cancer cell line is sensitive to mTORC1/2 inhibitor (AZD2014)[188]. RICTOR amplification and mutation have been determined as an inclusion criterion for the trial examining everolimus efficacy in patients with prostate cancer (NCT03580239).

Several studies have demonstrated that patients with a RICTOR-amplified tumor have lower overall survival in small cell lung cancer, colorectal cancer, and esophageal squamous cell carcinoma[189][190][191][192]. Overexpression of RICTOR is positively associated with tumor progression and poor survival in hepatocellular carcinoma, gastric cancer, pituitary adenoma, and endometrial carcinoma[193][194][195][196].

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TERT Amplification

Biological Impact

The TERT gene encodes the catalytic subunit of telomerase, an enzyme that maintains telomere length and genomic integrity[197]. Upregulation of TERT promotes cancer development and progression via modulation of Wnt-catenin and nuclear factor kappa B signaling[198][199], and mitochondrial RNA processing[200]. Activating mutations in the TERT promoter have been identified in a number of cancer types including melanoma, hepatocellular carcinoma, urothelial carcinoma, medulloblastoma, and glioma whereas TERT gene amplification is implicated in lung cancer, cervical cancer, breast cancer, Merkel cell carcinoma, neuroblastoma and adrenocortical carcinoma[201][202][203][204][205].

Therapeutic and prognostic relevance

Imetelstat (GRN163L), a telomere inhibitor which has been shown to inhibit cell proliferation in various cancer cell lines and tumor xenografts is currently in clinical trials[197].

TERT gene amplification is an independent poor prognostic marker for disease-free survival in non-small cell lung cancer (NSCLC) and breast cancer[206][207][208].

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US FDA-APPROVED DRUG(S)

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[209] NCT01524783	**Lung or gastrointestinal neuroendocrine tumor** (Approved on 2016/02/26)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 3.9]
BOLERO-2[210] 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[148] NCT00510068	**Pancreatic neuroendocrine tumor** (Approved on 2011/05/05)
	-
	Everolimus vs. Placebo [PFS(M): 11 vs. 4.6]
EXIST-1[211] NCT00789828	**Subependymal giant cell astrocytoma** (Approved on 2010/10/29)
	-
	Everolimus vs. Placebo [ORR(%): 35.0]
RECORD-1[212] NCT00410124	**Renal cell carcinoma** (Approved on 2009/05/30)
	-
	Everolimus vs. Placebo [PFS(M): 4.9 vs. 1.9]

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)

PRIMA NCT02655016	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2020/04/29)
	-
	Niraparib vs. Placebo [PFS (overall population)(M): 13.8 vs. 8.2]
QUADRA[83] NCT02354586	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2019/10/23)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Niraparib [ORR(%): 24.0, DOR(M): 8.3]
NOVA[82] NCT01847274	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (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)

PROfound[78] NCT02987543	**Prostate cancer** (Approved on 2020/05/19)
	ATMm, BRCA1m, BRCA2m, BARD1m, BRIP1m, CDK12m, CHEK1m, CHEK2m, FANCLm, PALB2m, RAD51Bm, RAD51Cm, RAD51Dm, RAD54Lm
	Olaparib vs. Enzalutamide or abiraterone acetate [PFS(M): 5.8 vs. 3.5]
PAOLA-1[72] NCT02477644	**Ovarian cancer** (Approved on 2020/05/08)
	HRD-positive (defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability)
	Olaparib + bevacizumab vs. Placebo + bevacizumab [PFS(M): 37.2 vs. 17.7]
POLO[77] NCT02184195	**Pancreatic adenocarcinoma** (Approved on 2019/12/27)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib vs. Placebo [ORR(%): 23.0 vs. 12.0, PFS(M): 7.4 vs. 3.8]
SOLO-1[71] NCT01844986	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/12/19)
	Germline or somatic BRCA-mutated (gBRCAm or sBRCAm)
	Olaparib vs. Placebo [PFS(M): NR vs. 13.8]
OlympiAD[76] NCT02000622	**Breast cancer** (Approved on 2018/02/06)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	Olaparib vs. Chemotherapy [PFS(M): 7 vs. 4.2]
SOLO-2/ENGOT-Ov21[213] NCT01874353	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	gBRCA+
	Olaparib vs. Placebo [PFS(M): 19.1 vs. 5.5]
Study19[214] NCT00753545	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2017/08/17)
	-
	Olaparib vs. Placebo [PFS(M): 8.4 vs. 4.8]
Study 42[215] NCT01078662	**Ovarian cancer** (Approved on 2014/12/19)
	Germline BRCA mutation (deleterious/suspected deleterious)
	Olaparib [ORR(%): 34.0, DOR(M): 7.9]

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)

TRITON2 NCT02952534	**Prostate cancer** (Approved on 2020/05/15)
	gBRCA+, sBRCA
	Rucaparib [ORR(%): 44.0, DOR(M): NE]
ARIEL3[79] NCT01968213	**Ovarian cancer, Fallopian tube cancer, Peritoneal carcinoma** (Approved on 2018/04/06)
	All|HRD|tBRCA
	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]

ARIEL2[216] NCT01482715, NCT01891344	**Ovarian cancer** (Approved on 2016/12/19)
	Germline and/or somatic BRCA mutation
	Rucaparib [ORR(%): 54.0]

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)

EMBRACA[84] NCT01945775	**Breast cancer** (Approved on 2018/10/16)
	Germline BRCA mutation (deleterious/suspected deleterious) HER2-negative
	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)

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

D=day; W=week; M=month

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ONGOING CLINICAL TRIALS

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

No trial has been found.

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SUPPLEMENTARY INFORMATION OF TESTING RESULTS

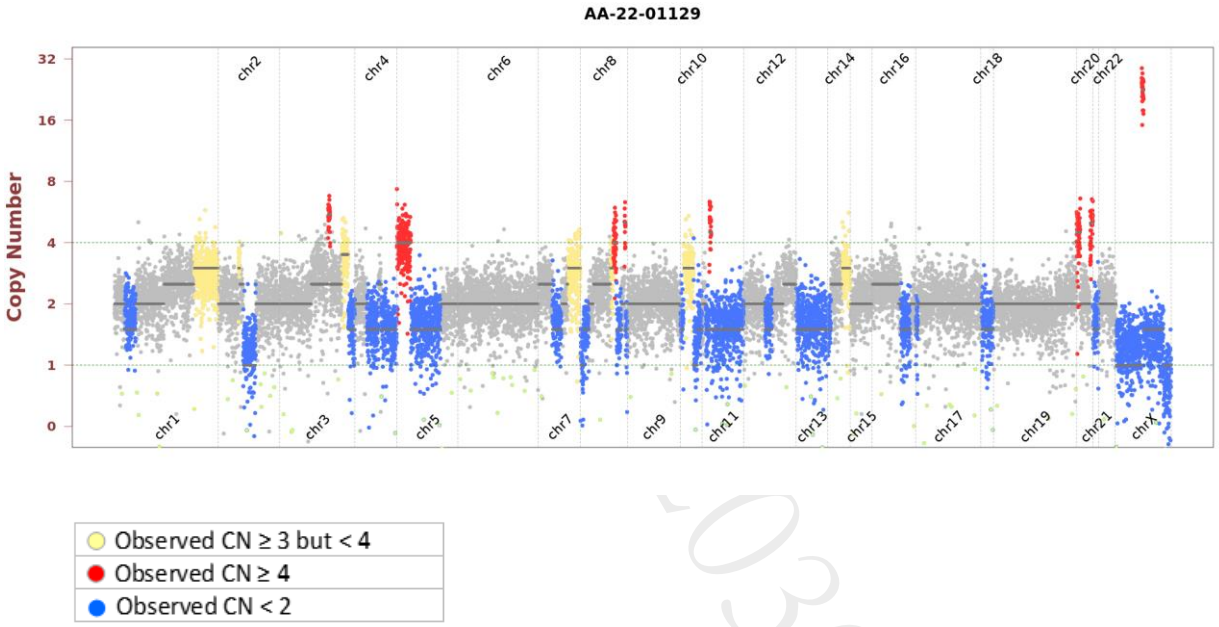
DETAILED INFORMATION OF VARIANTS WITH CLINICAL RELEVANCE

- Single Nucleotide and Small InDel Variants

Gene	Amino Acid Change	Exon	cDNA Change	Accession Number	COSMIC ID	Allele Frequency	Coverage
FLCN	Splice acceptor	-	c.619-1G>T	NM_144997	COSM7912221	21.6%	694
MSH2	R680*	13	c.2038C>T	NM_000251	COSM27628	20.8%	563
TP53	C124*	4	c.372C>A	NM_000546	COSM326716	57.5%	449

- 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
BARD1	P12L	1	c.35C>T	NM_000465	-	58.0%	433
BRCA2	C315S	10	c.943T>A	NM_000059	-	75.0%	256
GRIN2A	V363A	5	c.1088T>C	NM_000833	-	31.4%	1074
JAK2	V392M	9	c.1174G>A	NM_004972	COSM5979661	39.4%	680
KDR	Splice region	-	c.3404+4dup	NM_002253	-	60.2%	113
MSH6	R1095C	5	c.3283C>T	NM_000179	-	15.3%	594
NOTCH2	D1042E	19	c.3126T>A	NM_024408	-	49.4%	1487
STK11	P373L	9	c.1118C>T	NM_000455	-	46.7%	152

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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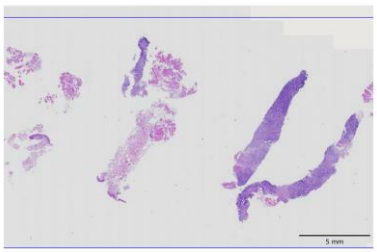
TEST DETAILS

SPECIMEN RECEIVED AND PATHOLOGY REVIEW



- Collection date: Jan 2022
- Facility retrieved: 臺北榮總
- H&E-stained section No.: S11102978
- Collection site: Pleural
- Examined by: Dr. Yeh-Han Wang
    1. The percentage of viable tumor cells in total cells in the whole slide (%): 70%
    2. The percentage of viable tumor cells in total cells in the encircled areas in the whole slide (%): 70%
    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: 793x
- Target Base Coverage at 100x: 93%

RNA test

- Average unique RNA Start Sites per control GSP2: 136

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 ≥ 25, 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:
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

Sign Off
醫檢師陳韻仔 博士
Yun-Yu Chen Ph.D.
檢字第 015647 號

Yun Yu Chen

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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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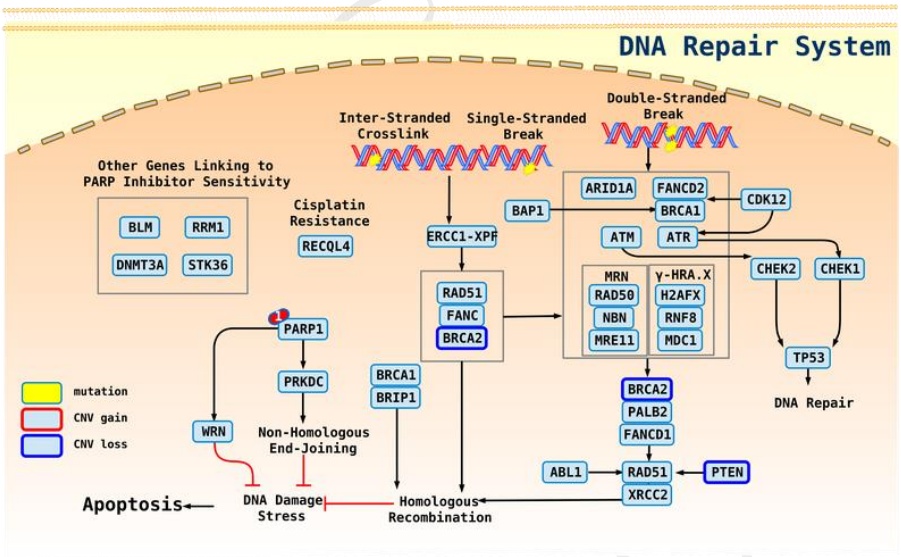
APPENDIX

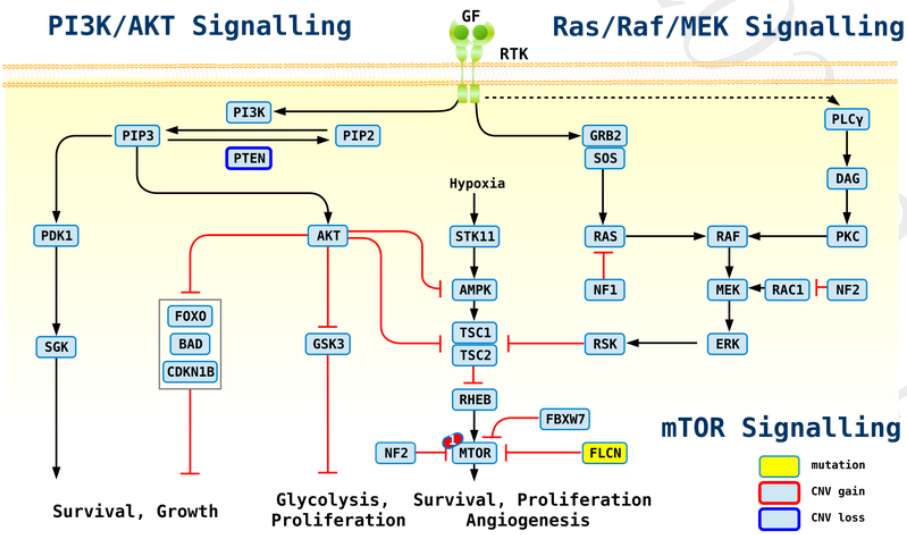
POSSIBLE THERAPEUTIC IMPLICATIONS FOR HETEROZYGOUS DELETION

Gene	Therapies	Possible effect
PTEN	Everolimus, Niraparib, Olaparib, Rucaparib, Talazoparib, Temsirolimus	**sensitive**
BRCA2	Niraparib, Olaparib, Rucaparib, Talazoparib	**sensitive**
RB1	Abemaciclib, Palbociclib, Ribociclib	**resistant**
PTEN	Cetuximab, Erlotinib, Gefitinib, Panitumumab, Trastuzumab	**resistant**

SIGNALING PATHWAYS AND MOLECULAR-TARGETED AGENTS



1: Olaparib, Niraparib, Rucaparib, Talazoparib



1: Everolimus, Temsirolimus

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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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