Dwayne Holder

Diagnosis
Pancreatic Ductal Adenocarcinoma

Accession No.
ABC-12345678

xT

Date of Birth
8/8/1971

Sex
Male

Physician
Dr. David Patel

Institution
Northwestern University Medical Center
NW-12345-DH6

TEMPUS | xT 595 Genes

Tumor specimen:
Core Needle Biopsy
Case #ABC 123, B1
Collected on 12/29/2017
Received on 1/2/2018
Tumor percentage: **40%**

Normal specimen:
Blood
Collected on 1/23/2018
Received on 1/24/2018

Notes
The tumor shows loss of heterozygosity in BRCA2.

This patient has a pathogenic germline BRCA2 mutation combined with somatic loss of heterozygosity, indicating that this is a BRCA2 driven tumor, therefore, PARP inhibitor therapy is suggested. Genetic counseling is recommended for this patient and potentially affected family members.

RNA analysis is being performed and will be reported in the Tempus online portal when complete.

GENOMIC VARIANTS

Somatic - Potentially Actionable

		Variant Allele Fraction
CDKN2A	p.A76fs Frameshift - LOF	40.7%
KRAS	p.G12V Point mutation - GOF	22.0%
BRCA2	Copy number loss - LOF	

Germline

		Clinical Significance
BRCA2	p.S611* chr13:32907447	Pathogenic Hereditary breast and ovarian cancer
TPMT	p.A80P chr6: 18143724	Pharmacogenetic Variant

No reportable single nucleotide variants, indels, or copy number changes found in:

TP53 SMAD4

IMMUNOTHERAPY MARKERS

Tumor Mutational Burden

4.7 m/MB 79th percentile

Microsatellite Instability Status

Stable | Equivocal | High

TREATMENT IMPLICATIONS

Olaparib (PARP inhibitor) FDA approved, other diagnoses	BRCA2 Copy Number Loss, Loss-of-Function Clinical research, breast cancer: PMID 20609467
Palbociclib (CDK4/6 inhibitor) FDA approved, other diagnoses	CDKN2A p. A76fs Loss-of-Function Clinical research, breast cancer: PMID 26715889
YAP inhibitor + Pan-RAF inhibitor Investigational drug	KRAS p. G12V Gain-of-Function Preclinical, pancreatic cancer: PMID 28576749
Gemcitabine + Erlotinib Resistance	KRAS Exon 2 Gain-of-Function Clinical research, pancreatic cancer: PMID 21862683

VARIANTS OF UNKNOWN SIGNIFICANCE

Somatic variant	Mutation effect	Variant allele fraction
ARHGAP5	c.1441G>T p.E481*	18.6%
ARHGAP5	c.1465G>A p.E489K	22.1%
CCT6A	c.725+1G>A Splice-Donor	21%

LOW COVERAGE REGIONS

CDKN1C	GFRA2	NOTCH1	PDPK1	RECQL4
FLT4	MTAP	NOTCH2	PIK3R2	ZNRF3

CLINICAL TRIALS

Gemcitabine hydrochloride and cisplatin with or without veliparib or veliparib alone in treating patients with locally advanced or metastatic pancreatic cancer (NCT01585805)	**Phase II** University of Chicago - 6 miles ✓ **BRCA2 mutation**
Genetic analysis-guided dosing of FOLFIRABAX in treating patients with advanced gastrointestinal cancer (NCT02333188)	**Phase I/II** University of Chicago - 6 miles
Study of PD1 Blockade by Pembrolizumab With Stereotactic Body Radiotherapy in Advanced Solid Tumors (NCT02608385)	**Phase I** University of Chicago - 6 miles

Includes matched trials for which the patient fits inclusion criteria, regardless of distance or presence of biomarker match.

SOMATIC VARIANT DETAILS - POTENTIALLY ACTIONABLE

CDKN2A c.225delC p.A76fs Frameshift - Loss-of-Function — Variant Allele Fraction: 40.7%

CDKN2A encodes two proteins, p16(INK4A) and p14(ARF) which function in regulating cell growth. The p16(INK4A) protein regulates the cell cycle through the inhibition of CDK4 and CDK6, preventing them from stimulating cell proliferation. The p14(ARF) protein binds to MDM2 to keep p53 intact and stimulate the p53-dependent cell cycle arrest and apoptosis. Deleterious single nucleotide variants, copy number loss and underexpression of CDKN2A are associated with cancer progression.

KRAS c.35G>T p.G12V Point mutation - Gain-of-Function — Variant Allele Fraction: 22.0%

KRAS encodes a GDP/GTP binding protein that acts as an intracellular signal transducer. KRAS is involved in several pathways involved in cellular proliferation and survival, including the PI3K-AKT-mTOR pathway and the MAPK cascade. Activating mutations in KRAS are associated with cancer progression.

BRCA2 Copy Number Loss, Loss-of-Function

BRCA2 encodes a nuclear phosphoprotein which helps maintain DNA stability through homologous recombination based DNA double stranded break repair and involvement in DNA damage checkpoint control. Deleterious mutations and copy number loss in BRCA2 are associated with cancer progression.

BRCA2 chr13:32907447 c.1832C>A p.S611*

Clinical Significance: ● Pathogenic

The patient has a pathogenic germline BRCA2 mutation. Genetic counseling and appropriate cancer screening is recommended for this patient and potentially affected family members.

TPMT chr6:18143955 c.238G>C p.A80P

Pharmacogenetic Variant: ● Adverse Event

This patient has a pharmacogenomic variant in the TPMT gene which leads to reduced enzyme activity. People with this variant are at an increased risk for an adverse drug event when treated with azathioprine or other purine analogs.

CLINICAL HISTORY

2018

- **Release from Northwestern ICU**
  1/6/2018

2017

- **Biopsy: Lung**
  MRI: Abdomen
  12/29/2017
- **Admitted to Northwestern ICU**
  12/27/2017
- **Started Palbociclib**
  Ended Gemcitabine
  9/10/2017
- **CT: Chest**
  9/2/2017
- **Cardiac arrhythmia**
  8/24/2017
- **Started Gemcitabine**
  6/23/2017
- **Diagnosis: Pancreatic ductal adenocarcinoma T2 N0 M0**
  CT: Chest
  Pancreaticoduodenectomy
  Northwestern University Medical Center
  Comorbidity: Diabetes
  6/19/2017

Assay Description

“Alterations Detected” is the total number of somatic alterations detected in the tumor sample. Potentially Actionable are protein-altering variants with an associated therapy. “Biologically Relevant” are protein-altering variants that may have functional significance or have been observed in the medical literature, but are not associated with a specific therapy. “Unknown Significance” are protein-altering variants exhibiting an unclear effect on function and/or not identified in the literature. The clinical summary of the report shows pathogenic and actionable with the highest levels of evidence when they are present in the patient’s sequencing results.

Tumor mutational burden (TMB) measures the quantity of mutations carried in a tumor as the number of protein-altering somatic mutations per million base pairs. Studies have shown that tumors with higher TMB have an increased likelihood of response to immunotherapy.

MSI-H tumors have changes in microsatellite repeat lengths due to defective DNA mismatch repair activity.

MSS tumors have no functional defects in DNA mismatch repair.

MSE tumors have an intermediate phenotype that cannot be clearly classified as MSI-H or MSS based on the statistical cutoff used to define those categories. If MSI status will affect clinical management, immunohistochemical staining for DNA mismatch repair proteins is recommended.

Tempus Disclaimer

The analysis of sequence-specific alterations can be affected in many ways, related and unrelated to the tumor DNA. First, the quality of tumor DNA obtained from formalin-fixed samples is generally poor and can result in degraded and damaged DNA. Second, the quantity of DNA obtained can be very low, limiting the amount of DNA that can be successfully analyzed by next generation sequencing. Third, the purity of tumor DNA can be a factor, as a significant portion of the DNA analyzed in the tumor sample may be derived from contaminated normal tissues. These three aspects can reduce the chance of detecting somatic sequence alterations. Additionally, next generation sequencing approaches may provide incorrect sequence or mutational data due to insufficient coverage in specific regions of the genome an inability to distinguish highly related human sequences, and sequencing errors.

Sequence mutations, including single base and small insertions/deletions, are evaluated where the allele frequency is > 5.0%, and amplifications are evaluated when change is 4 fold or greater. These numbers are subject to change based on the depth and quality of the sequencing.

Genetic alterations are defined as clinically significant based on study results in peer-reviewed published literature and other authoritative sources. These references are not comprehensive, therefore clinically unknown findings may occur.

The results of the Tempus Test are intended for use solely by the patient’s clinical care team. In making any diagnosis, counseling, or treatment decisions, qualified health professionals should evaluate these results in the context of other individual patient health information, including clinical presentation and other test reports.

As requested by the ordering physician/institution, and in accordance with the recommendations of the ACMG, [1] Tempus has also included as secondary findings in this report sequencing results for variants in 59 genes that are associated with serious conditions unrelated the the patient’s current cancer diagnosis and that are considered medically actionable. The clinical significance of specific variants is based on germline classification criteria created by the ACMG [2].

Results of germline genetic testing may have implications for both the patient and family members. Tempus does not provide genetic counseling. If genetic counseling is desired, the ordering physician or the patient is responsible for contacting a genetic counselor to discuss test results.

These test results and Information contained within the report is current as of the report date. Tempus will not update reports or send notification regarding reclassification of genomic alterations.

This test was developed and its performance characteristics determined by Tempus. It has not been cleared or approved by the FDA. The laboratory is CLIA certified to perform high-complexity testing. Tempus is not liable for medical judgment with regards to diagnosis, prognosis or treatment in connection with the test results. The results in this report should be interpreted in the context of the patient's clinical profile and family history.

1. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT., Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2016 Nov 17. doi: 10.1038/gim.2016.190

2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. ACMG Laboratory Quality Assurance Committee. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30.