Taipei Veterans General Hospital

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Sample Information

Patient Name: 安德萍
Gender: Female
ID No.: C990000677
History No.: 40177228
Age: 62

Ordering Doctor: DOC1242E_劉峻宇
Ordering REQ.: D754J6D
Signing in Date: 2023/04/07

Path No.: M112-00055
MP No.: BR23015
Assay: Oncomine BRCA1/2 Assay
Sample Type: Blood
Date of blood drawing: 2023/03/22

Reporting Doctor: DOC5424G 彭昱璟 (Phone: 8#5424)

Note:

Sample Cancer Type: Breast Cancer

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Relevant Biomarkers

No clinically significant biomarkers found in this sample.

Prevalent cancer biomarkers without relevant evidence based on included data sources
BRCA1 exon 13-15 deletion

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar[1]	Coverage
BRCA2	p.(?)	c.-26G>A	chr13:32890572	52.20%	NM_000059.3	unknown	Benign	3996
BRCA2	p.(K1132=)	c.3396A>G	chr13:32911888	51.20%	NM_000059.3	synonymous	Benign	3998
BRCA2	p.(V1269=)	c.3807T>C	chr13:32912299	48.73%	NM_000059.3	synonymous	Benign	3710
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	99.79%	NM_000059.3	synonymous	Benign	1405

[1] Based on Clinvar version 20200329

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Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar[1]	Coverage
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	99.97%	NM_000059.3	synonymous	Benign	3995
BRCA2	p.(S2414=)	c.7242A>G	chr13:32929232	47.81%	NM_000059.3	synonymous	Benign	2625
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.73%	NM_000059.3	missense	Benign	2205
BRCA1	p.(S1436=)	c.4308T>C	chr17:41234470	50.21%	NM_007294.4	synonymous	Benign	2139
BRCA1	p.(K1183R)	c.3548A>G	chr17:41244000	49.26%	NM_007294.4	missense	Benign	3999
BRCA1	p.(E1038G)	c.3113A>G	chr17:41244435	50.50%	NM_007294.4	missense	Benign	4000
BRCA1	p.(P871L)	c.2612C>T	chr17:41244936	49.00%	NM_007294.4	missense	Benign	3998
BRCA1	p.(L771=)	c.2311T>C	chr17:41245237	51.51%	NM_007294.4	synonymous	Benign	2392
BRCA1	p.(S694=)	c.2082C>T	chr17:41245466	50.23%	NM_007294.4	synonymous	Benign	4000

[1] Based on Clinvar version 20200329

Copy Number Variations

Gene	Locus	Copy Number	ClinVar[1]
BRCA1	chr17:41222904	1	

[1] Based on Clinvar version 20200329

Biomarker Descriptions

BRCA1 (BRCA1 DNA repair associated)

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[1,2]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[1,2]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[3,4,5]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer[6].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer[7,8,9,10,11,12,13]. Somatic alterations in BRCA1 are observed in 2-8% of breast, ovarian, cervical, uterine, diffuse large B-cell lymphoma (DLBCL), melanoma, gastric, bladder, squamous lung, colorectal, and head and neck cancers[14,15].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[16]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[17,18]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[19] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[19] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[20] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[21] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[22] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Despite tolerability and efficacy, acquired resistance to PARP inhibition has

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Biomarker Descriptions (continued)

been clinically reported[23]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[24]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[25], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

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