

YOUR LAB

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1700 Lincoln Blvd, Suite 20, Redwood City, CA 94063  
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Additional Information

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## Test Performed: Inherited Cancer Panel

Report Date **Jun 22, 2021**  
Status -

**Patient**  
Patient Name  
Date of Birth  
Age  
Sex  
Ethnicity  
Symptoms Not Applicable  
Indication hereditary disorder

**Client**  
Client  
Client ID  
Physician  
Pathologist

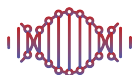
**Specimen**  
Accession ID brca\_int\_vars  
Specimen  
Collection  
Accession Jun 22, 2021

**Result:** **Positive**

**9**  
Pathogenic

## Variant Summary

Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
<b>BRCA1</b> c.5266dupC p.Q1756fs*74 g. 41209079_41209080insG	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA1</b> c.594-2A>C g.41247941T>G	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.4284dupT p.Q1429fs*9 g.32912770_32912771insT	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.4398_4402delACATT p.L1466fs*2 g.32912887_32912891delA TTAC	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.4965C>G p.Y1655* g.32913457C>G	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.5616_5620delAGTAA p.K1872fs*2 g.32914103_32914107delA GTAA	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer



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Accession ID: brca\_int\_vars

Report Date: Jun 22, 2021

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Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
<b>BRCA2</b> c.5621_5624delTTAA p.I1874fs*34 g. 32914110_32914113delTAAT	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.5946delT p.S1982fs*22 g.32914438delT	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.7069_7070delCT p.L2357fs*2 g. 32929058_32929059delTC	Heterozygous	<b>Pathogenic</b>	dominant	Hereditary breast and/or ovarian cancer

## Individual Variant Interpretations

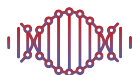
Gene **BRCA1**  
 Exon 19  
 Amino Acid p.Q1756fs\*74  
 Nucleotide NM\_007294.4:  
 g.41209079\_41209080i  
 nsG  
 c.5266dupC  
 Assessment **Pathogenic**  
 Genotype Heterozygous

### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

### Evidence for Pathogenicity

- PA2 - Established common pathogenic founder mutation (Standalone)
- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 106.45; 95% confidence interval = (80.84, 140.17); FET 2-tail p-value < 0.0001; affected individual count = 10706] (Strong)
- PS7 - At least 10 independent somatic observations of the alteration in literature (Strong)
- PP1 - Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease (Supporting)



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- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.231%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)

Gene **BRCA1**  
Exon 9  
Amino Acid  
Nucleotide NM\_007294.4:  
g.41247941T>G  
c.594-2A>C  
Assessment **Pathogenic**  
Genotype Heterozygous

#### Interpretation

BRCA1 is a tumor suppressor responsible for repair of DNA double strand breaks and maintenance of genomic stability [7]. Deletions, loss of heterozygosity, and loss-of-function mutations cause BRCA1 inactivation [19, 18].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 27.2, MaxEntScan] (Supporting)

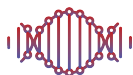
#### Evidence against Pathogenicity

- BP2 - Observed in trans with a pathogenic variant for a dominant disorder (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**  
Exon 11  
Amino Acid p.Q1429fs\*9  
Nucleotide NM\_000059.4:  
g.  
32912770\_32912771insT  
c.4284dupT  
Assessment **Pathogenic**

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline



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Genotype Heterozygous

alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 20.75; 95% confidence interval = (2.86, 150.49); FET 2-tail p-value < 0.0001; affected individual count = 46] (Strong)
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or <= 0.001%] (Moderate)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)

Gene **BRCA2**

Exon 11

Amino Acid p.L1466fs\*2

Nucleotide NM\_000059.4:  
g.32912887\_32912891del  
ATTAC  
c.4398\_4402delACATT

Assessment **Pathogenic**

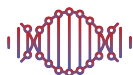
Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 7.28; 95% confidence interval = (0.97, 54.92); FET 2-tail p-value = 3.213E-2; affected individual count = 16] (Strong)



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- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or  $\leq 0.001\%$ ] (Moderate)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)

Gene **BRCA2**

Exon 11

Amino Acid p.Y1655\*

Nucleotide NM\_000059.4:  
g.32913457C>G  
c.4965C>G

Assessment **Pathogenic**

Genotype Heterozygous

#### Interpretation

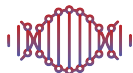
BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical  $\pm 1$  or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 6.01; 95% confidence interval = (1.42, 25.44); FET 2-tail p-value =  $3.321E-3$ ; affected individual count = 24] (Strong)
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or  $\leq 0.001\%$ ] (Moderate)
- PM7 - At least 3 independent somatic observations of the alteration in literature (Moderate)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)



Gene **BRCA2**  
 Exon 11  
 Amino Acid p.K1872fs\*2  
 Nucleotide NM\_000059.4:  
 g.32914103\_32914107del  
 AGTAA  
 c.5616\_5620delAGTAA  
 Assessment **Pathogenic**  
 Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 11.87; 95% confidence interval = (1.61, 87.48); FET 2-tail p-value = 6.896E-4; affected individual count = 26] (Strong)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

**Evidence against Pathogenicity**

- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)

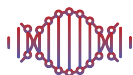
Gene **BRCA2**  
 Exon 11  
 Amino Acid p.I1874fs\*34  
 Nucleotide NM\_000059.4:  
 g.32914110\_32914113delT  
 AAT  
 c.5621\_5624delTTAA  
 Assessment **Pathogenic**  
 Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PM2 - Absent from controls (or at extremely low frequency if recessive) in gnomAD [In these sources of population frequency data, this variant's frequency is 0% or <= 0.001%] (Moderate)



- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 11

Amino Acid p.S1982fs\*22

Nucleotide NM\_000059.4:  
g.32914438delT  
c.5946delTAssessment **Pathogenic**

Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PA2 - Established common pathogenic founder mutation (Standalone)
- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 16.45; 95% confidence interval = (13.13, 20.61); FET 2-tail p-value < 0.0001; affected individual count = 2444] (Strong)
- PS7 - At least 10 independent somatic observations of the alteration in literature (Strong)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

**Evidence against Pathogenicity**

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.589%] (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in trans with a pathogenic variant for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)

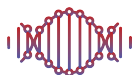
Gene **BRCA2**

Exon 14

Amino Acid p.L2357fs\*2

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by



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Nucleotide NM\_000059.4:  
g.32929058\_32929059d  
eITC  
c.7069\_7070delCT

Assessment **Pathogenic**  
Genotype Heterozygous

binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 6.18; 95% confidence interval = (2.86, 13.37); FET 2-tail p-value < 0.0001; affected individual count = 83] (Strong)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)

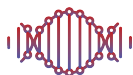
Gene **BRCA1**  
Exon 20  
Amino Acid p.M1775R  
Nucleotide NM\_007294.4:  
g.41203088A>C  
c.5324T>G  
Assessment **Uncertain Significance**  
Genotype Heterozygous

#### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence for Pathogenicity

- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PS4 - The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls [odds ratio = 9.65; 95% confidence interval = (3.53, 26.34); FET 2-tail p-value < 0.0001; affected individual count = 79] (Strong)
- PM1 - Located in a mutational hot spot and in a critical and well-established functional domain (BRCT) without benign variation (Moderate)



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- PM5 - Novel missense change at an amino acid residue where a different missense change (p.M1775K) determined to be pathogenic has been seen before (Moderate)
- PP1 - Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease (Supporting)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 27.3] (Supporting)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.016%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)

Gene **BRCA2**

Exon 13

Amino Acid p.R2318Q

Nucleotide NM\_000059.4:  
g.32920979G>A  
c.6953G>AAssessment **Uncertain Significance**

Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 32.0] (Supporting)

#### Evidence against Pathogenicity

- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

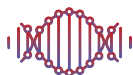
Exon 20

Amino Acid p.Q2858\*

Nucleotide NM\_000059.4:

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2



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g.32945177C>T  
c.8572C>T

Assessment **Uncertain Significance**  
Genotype Heterozygous

can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS1 - Null variant (nonsense, frameshift, canonical +/-1 or 2 splice sites, initiation codon, copy number loss, single or multi exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease (Very Strong)
- PP5 - Reputable source recently reports variant as pathogenic, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.016%] (Strong)

Gene **BRCA2**

Exon 11

Amino Acid p.G2274V

Nucleotide NM\_000059.4:  
g.32915313G>T  
c.6821G>T

Assessment **Likely Benign**  
Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

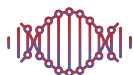
#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 23.1] (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.285%] (Strong)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**



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Exon 20

Amino Acid p.R2842H

Nucleotide NM\_000059.4:  
g.32945130G>A  
c.8525G>A

Assessment **Likely Benign**

Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PM1 - Located in a mutational hot spot and in a critical and well-established functional domain (RPA\_2b-aaRSs\_OBF\_like) without benign variation (Moderate)
- PM5 - Novel missense change at an amino acid residue where a different missense change (p.R2842C) determined to be pathogenic has been seen before (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 31.0] (Supporting)

**Evidence against Pathogenicity**

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.049%] (Strong)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 20

Amino Acid p.E2856A

Nucleotide NM\_000059.4:  
g.32945172A>C  
c.8567A>C

Assessment **Likely Benign**

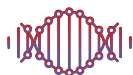
Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PM7 - At least 3 independent somatic observations of the alteration in literature (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 25.6] (Supporting)



### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.192%] (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

Exon 15

Amino Acid p.M1652I

Nucleotide NM\_007294.4:  
g.41222975C>T  
c.4956G>A

Assessment **Benign**

Genotype Heterozygous

### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

### Evidence for Pathogenicity

- PS3 - Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product (Strong)
- PM7 - At least 3 independent somatic observations of the alteration in literature (Moderate)

### Evidence against Pathogenicity

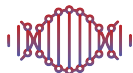
- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 3.799%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis with a pathogenic variant in any inheritance pattern (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

Exon 10

### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of



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Amino Acid p.R1347G  
 Nucleotide NM\_007294.4:  
 g.41243509T>C  
 c.4039A>G  
 Assessment **Benign**  
 Genotype Heterozygous

genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence for Pathogenicity

- PS7 - At least 10 independent somatic observations of the alteration in literature (Strong)
- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 21.4] (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.606%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

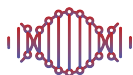
Gene **BRCA1**  
 Exon 10  
 Amino Acid p.E1038G  
 Nucleotide NM\_007294.4:  
 g.41244435T>C  
 c.3113A>G  
 Assessment **Benign**  
 Genotype Heterozygous

#### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot (Moderate)
- PM7 - At least 3 independent somatic observations of the alteration in literature (Moderate)



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**Evidence against Pathogenicity**

- BA1 - Allele frequency is >5% in gnomAD: [50.35%] (Standalone)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

Exon 10

Amino Acid p.P871L

Nucleotide NM\_007294.4:  
g.41244936G>A  
c.2612C>TAssessment **Benign**

Genotype Heterozygous

**Interpretation**

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

**Evidence for Pathogenicity**

- PVS7 - At least 20 independent somatic observations of the alteration in literature (Very Strong)
- PM1 - Located in a mutational hot spot (Moderate)

**Evidence against Pathogenicity**

- BA1 - Allele frequency is >5% in gnomAD: [81.94%] (Standalone)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in trans with a pathogenic variant for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

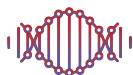
Exon 10

Amino Acid p.Y856H

Nucleotide NM\_007294.4:

**Interpretation**

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead



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g.41244982A>G  
c.2566T>C

Assessment **Benign**  
Genotype Heterozygous

to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 23.0] (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 2.230%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

Exon 10

Amino Acid p.R841W

Nucleotide NM\_007294.4:  
g.41245027G>A  
c.2521C>T

Assessment **Benign**  
Genotype Heterozygous

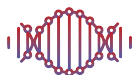
#### Interpretation

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence for Pathogenicity

- PS7 - At least 10 independent somatic observations of the alteration in literature (Strong)
- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 21.5] (Supporting)

#### Evidence against Pathogenicity



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- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.212%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA1**

Exon 10

Amino Acid p.D693N

Nucleotide NM\_007294.4:  
g.41245471C>T  
c.2077G>AAssessment **Benign**

Genotype Heterozygous

**Interpretation**

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1 lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

**Evidence for Pathogenicity**

- PM1 - Located in a mutational hot spot (Moderate)
- PM7 - At least 3 independent somatic observations of the alteration in literature (Moderate)

**Evidence against Pathogenicity**

- BA1 - Allele frequency is >5% in gnomAD: [9.37%] (Standalone)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

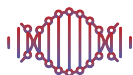
Gene **BRCA1**

Intron 7

Amino Acid

Nucleotide NM\_007294.4:  
g.41249364delA  
c.548-58delT**Interpretation**

BRCA1 encodes the protein Brca1, which is involved in the maintenance of genomic stability, including DNA repair, cell cycle checkpoint, and chromosome segregation [15]. Inactivating mutations of BRCA1 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [17, 11]. Germline mutations in BRCA1



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Assessment **Benign**  
Genotype Heterozygous

lead to an increased risk of breast, ovarian, gastric, and pancreatic cancers [8, 1, 16]. The risk of developing breast and ovarian cancer in BRCA1 mutation carriers has been reported to be approximately 72% and 40%, respectively [4].

#### Evidence against Pathogenicity

- BA1 - Allele frequency is >5% in gnomAD: [36.77%] (Standalone)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**  
Exon 10  
Amino Acid p.N372H  
Nucleotide NM\_000059.4:  
g.32906729A>C  
c.11114A>C  
Assessment **Benign**  
Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PVS7 - At least 20 independent somatic observations of the alteration in literature (Very Strong)
- PM1 - Located in a mutational hot spot (Moderate)

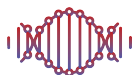
#### Evidence against Pathogenicity

- BA1 - Allele frequency is >5% in gnomAD: [35.66%] (Standalone)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in trans with a pathogenic variant for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**  
Intron 10  
Amino Acid  
Nucleotide NM\_000059.4:  
g.32910328T>C

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle



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c.1910-74T>C

Assessment **Benign**

Genotype Heterozygous

checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence against Pathogenicity

- BA1 - Allele frequency is >5% in gnomAD: [21.87%] (Standalone)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 11

Amino Acid p.R2034C

Nucleotide NM\_000059.4:

g.32914592C>T

c.6100C>T

Assessment **Benign**

Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 20.2] (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.426%] (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 12

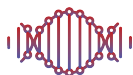
Amino Acid p.D2312V

Nucleotide NM\_000059.4:

g.32918788A>T

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle



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c.6935A&gt;T

Assessment **Benign**

Genotype Heterozygous

checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 33.0, MaxEntScan] (Supporting)

**Evidence against Pathogenicity**

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.190%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 14

Amino Acid p.V2466A

Nucleotide NM\_000059.4:  
g.32929387T>C  
c.7397T>CAssessment **Benign**

Genotype Heterozygous

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PM1 - Located in a mutational hot spot (Moderate)

**Evidence against Pathogenicity**

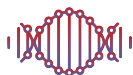
- BA1 - Allele frequency is >5% in gnomAD: [100.00%] (Standalone)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 22

**Interpretation**

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-



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Amino Acid p.I2944F  
 Nucleotide NM\_000059.4:  
 g.32953529A>T  
 c.8830A>T  
 Assessment **Benign**  
 Genotype Heterozygous

strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot and in a critical and well-established functional domain (RPA\_2b-aaRSs\_OBF\_like) without benign variation (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 24.0] (Supporting)

#### Evidence against Pathogenicity

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 4.070%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

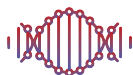
Gene **BRCA2**  
 Exon 22  
 Amino Acid p.A2951T  
 Nucleotide NM\_000059.4:  
 g.32953550G>A  
 c.8851G>A  
 Assessment **Benign**  
 Genotype Heterozygous

#### Interpretation

BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

#### Evidence for Pathogenicity

- PM1 - Located in a mutational hot spot and in a critical and well-established functional domain (RPA\_2b-aaRSs\_OBF\_like) without benign variation (Moderate)
- PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product [CADD = 25.8] (Supporting)



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**Evidence against Pathogenicity**

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 3.784%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in cis or trans with a pathogenic variant (phase unknown) for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)

Gene **BRCA2**

Exon 27

Amino Acid p.K3326\*

Nucleotide NM\_000059.4:  
g.32972626A>T  
c.9976A>TAssessment **Benign**

Genotype Heterozygous

**Interpretation**

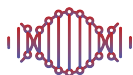
BRCA2 encodes the Brca2 tumor suppressor. Brca2 aids in DNA double-strand break repair in response to chromosomal damage, in part by binding and regulation of Rad51 [20]. Inactivating mutations of BRCA2 can lead to the inability to repair DNA damage and loss of cell cycle checkpoints, which can lead to tumorigenesis [10, 11]. BRCA2 germline alterations predispose patients to familial breast and ovarian cancers, as well as pancreatic cancer, prostate cancer, uveal melanoma, esophageal cancer, and other cancers [3, 9, 12, 21, 5, 14, 6, 13, 2].

**Evidence for Pathogenicity**

- PVS7 - At least 20 independent somatic observations of the alteration in literature (Very Strong)

**Evidence against Pathogenicity**

- BS1 - Allele frequency is greater than expected for disorder [Max Dominant Expected Frequency: 0.013%; gnomAD Frequency: 0.908%] (Strong)
- BS3 - Well-established in vitro or in vivo functional studies show no damaging effect on protein function or splicing (Strong)
- BS4 - Lack of segregation in affected members of a family (Strong)
- BP2 - Observed in trans with a pathogenic variant for a dominant disorder (Supporting)
- BP5 - Variant found in a case with an alternate molecular basis for disease (Supporting)
- BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation (Supporting)



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Accession ID: brca\_int\_vars

Report Date: Jun 22, 2021

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Gene / Variant	Genotype	Assessment	Mode of Inheritance	Phenotype
<b>BRCA1</b> c.5324T>G p.M1775R g.41203088A>C	Heterozygous	<b>Uncertain Significance</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.6953G>A p.R2318Q g.32920979G>A	Heterozygous	<b>Uncertain Significance</b>	dominant	Hereditary breast and/or ovarian cancer
<b>BRCA2</b> c.8572C>T p.Q2858* g.32945177C>T	Heterozygous	<b>Uncertain Significance</b>	dominant	Hereditary breast and/or ovarian cancer

## Genes Tested

Test information such as gene name and hot spot region can be included in this section.

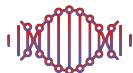
## Methods and Limitations

EXAMPLE Statement including sample type (FFPE, etc), method of extraction, amplification reactions, panel targeted regions, sequencing technology, etc. Additionally, a description of the data analysis software(s), genome of reference and the sensitivity of the methods should be described.

**QIAGEN Clinical Insight (QCI™)** is a variant analysis, interpretation and decision support tool for research and clinical labs analyzing human genetics data and is not intended to be used for diagnostic purposes. QCI Interpret software includes the following underlying databases, data reference sets and tools; QIAGEN Clinical Insight-Interpret (7.1.20210428), Ingenuity Knowledge Base (B-release), CADD (v1.6), Allele Frequency Community (2019-09-25), EVS (ESP6500SI-V2), Refseq Gene Model (2020-04-06), JASPAR (2013-11), Ingenuity Knowledge Base Snapshot Timestamp (2021-06-04 11:24:54.46), Vista Enhancer hg18 (2012-07), Vista Enhancer hg19 (2012-07), Clinical Trials (B-release), MITOMAP: A Human Mitochondrial Genome Database. <http://www.mitomap.org>, 2019 (2020-06-19), PolyPhen-2 (v2.2.2), 1000 Genome Frequency (phase3v5b), ExAC (0.3.1), iva (Apr 29 10:37 ), TargetScan (7.2), phyloP hg18 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), phyloP hg19 (NCBI36 (hg18) 2009-11, GRCh37 (hg19) 2014-02, GRCh38 2015-05), GENCODE (Release 33), CentoMD (5.3), OMIM (July 06, 2020), gnomAD (2.1.1), BSIFT (2016-02-23), TCGA (2013-09-05), Clinvar (2020-09-15), DGV (2016-05-15), COSMIC (v92), HGMD (2021.1), OncoTree (oncotree\_2019\_03\_01), dbSNP (NCBI36 (hg18) 151, GRCh37 (hg19) 153, GRCh38 153), SIFT4G (2016-02-23)

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