Test performed
Sequence analysis and deletion/duplication testing of the 147 genes listed in the Genes Analyzed section.

- Invitae Genetic Health Screen

RESULT: POSITIVE

A clinically significant genetic change was found in the BRIP1 gene, which is associated with hereditary cancer.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRIP1	c.1343G>A (p.Trp448*)	heterozygous	PATHOGENIC

About this test
This test evaluates 147 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain types of cancer, heart-related conditions, or other types of actionable medical genetic conditions. These are disorders for which effective medical interventions and preventive measures are known and available. Genetic changes of uncertain significance are not included in this report; however, if additional evidence becomes available to indicate that a previously uncertain genetic change is clinically significant, Invitae will update this report and provide notification.

Next Steps

- This is a medically important result that should be discussed with an appropriate healthcare provider. Genetic counseling is recommended to discuss the implications of this result and potential next steps.
- Please see NCCN (www.nccn.org) for management guidelines regarding BRIP1-related condition(s).
- Consider sharing this result with relatives as they may also be at risk. Details on our Family Variant Testing program can be found at www.invitae.com/family.
- Register your test at www.invitae.com/patients to download a digital copy of your results. You can also access educational resources about how your results can help inform your health.

Laboratory Director Tina Hambuch, Ph.D., FACMG
NY Laboratory Director Swaroop Aradhya, Ph.D., FACMG
Invitae 1400 16th Street, San Francisco, CA 94103
E: clientservices@invitae.com P: 415.374.7782 or 800.436.3037

Clinical Summary

A Pathogenic variant, c.1343G>A (p.Trp448*), was identified in BRIP1.

- Certain genetic changes in one copy of the BRIP1 gene significantly increase the risk for autosomal dominant forms of ovarian cancer and possibly breast cancer. If a person carries two clinically significant genetic changes, one in each copy of the BRIP1 gene, this may result in an autosomal recessive condition known as Fanconi anemia.
- This is a clinically significant result that increases the risk to develop autosomal dominant BRIP1-related conditions and is associated with being a carrier of autosomal recessive BRIP1-related conditions.
- Individuals with clinically significant changes in BRIP1 are more likely to develop ovarian cancer when compared to individuals in the general population. Studies are still underway to determine if these individuals are also more likely to develop breast cancer. Screening and management guidelines exist to help prevent some of these cancers and/or identify them at an earlier stage. It is important to recognize that this result is not a diagnosis of cancer and not all individuals with a genetic change in BRIP1 will develop cancer.
  Fanconi anemia is a rare condition that affects many parts of the body. Affected individuals may have bone marrow failure, physical abnormalities, and a significantly higher than normal chance to develop certain cancers such as leukemia early in life.
- Since genetic changes are often shared within families, there is a chance that biological relatives may be at risk for the autosomal dominant BRIP1-related conditions. Additionally, being a carrier for the autosomal recessive BRIP1-related conditions means there is a chance of having children with autosomal recessive BRIP1-related conditions.

Variant Details

BRIP1, Exon 10, c.1343G>A (p.Trp448*), heterozygous, PATHOGENIC

- This sequence change creates a premature translational stop signal (p.Trp448*) in the BRIP1 gene. It is expected to result in an absent or disrupted protein product.
- This variant is present in population databases (rs775171520, ExAC 0.05%).
- This variant has been reported in an individual with a personal or familial history of breast cancer (PMID: 26824983). ClinVar contains an entry for this variant (Variation ID: 216129).
- Loss-of-function variants in BRIP1 are known to be pathogenic (PMID: 16116423, 17033622, 21964575).
- For these reasons, this variant has been classified as Pathogenic.

Genes Analyzed

This table represents a complete list of genes analyzed for this individual. Genes listed in this table may also have additional reported clinical associations outside of the conditions listed. Additional information about gene-condition associations can be found at http://www.omim.org. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

Cancer-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
APC	NM_000038.5	Colorectal, Endocrine, Gastric, Nervous System/ Brain and Pancreatic Cancer, Sarcoma
ATM	NM_000051.3	Breast, Pancreatic and Prostate Cancer
AXIN2	NM_004655.3	Colorectal Cancer
BAP1	NM_004656.3	Renal/Urinary Tract Cancer, Melanoma
BARD1	NM_000465.3	Breast Cancer
BMPR1A	NM_004329.2	Colorectal, Gastric and Pancreatic Cancer
BRCA1	NM_007294.3	Breast, Gynecologic, Pancreatic and Prostate Cancer
BRCA2	NM_000059.3	Breast, Gynecologic, Pancreatic and Prostate Cancer, Melanoma
BRIP1	NM_032043.2	Breast and Gynecologic Cancer
CDC73	NM_024529.4	Endocrine and Renal/Urinary Tract Cancer
CDH1	NM_004360.3	Breast, Colorectal and Gastric Cancer
CDK4	NM_000075.3	Melanoma
CDKN2A (p14ARF)	NM_058195.3	Nervous System/Brain Cancer, Melanoma
CDKN2A (p16INK4a)	NM_000077.4	Pancreatic Cancer, Melanoma
CHEK2	NM_007194.3	Breast, Colorectal, Endocrine, Gynecologic and Prostate Cancer
DICER1	NM_177438.2	Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract Cancer, Sarcoma
EPCAM*	NM_002354.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
FH	NM_000143.3	Renal/Urinary Tract Cancer, Sarcoma
FLCN	NM_144997.5	Renal/Urinary Tract Cancer
GREM1*	NM_013372.6	Colorectal Cancer
HOXB13	NM_006361.5	Prostate Cancer
KIT	NM_000222.2	Gastric Cancer, Sarcoma
MAX	NM_002382.4	Endocrine Cancer
MEN1	NM_130799.2	Endocrine, Nervous System/Brain and Pancreatic Cancer
MET	NM_001127500.1	Renal/Urinary Tract Cancer
MITF*	NM_000248.3	Melanoma
MLH1	NM_000249.3	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH2	NM_000251.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MSH3	NM_002439.4	Colorectal Cancer, Includes Reporting of Carrier Status
MSH6	NM_000179.2	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
MUTYH*	NM_001128425.1	Colorectal Cancer
NBN*	NM_002485.4	Breast and Prostate Cancer
NF1	NM_000267.3	Breast, Endocrine, Gastric and Nervous System/ Brain Cancer
NF2	NM_000268.3	Nervous System/Brain Cancer
NTHL1	NM_002528.6	Colorectal Cancer, Includes Reporting of Carrier Status
PALB2	NM_024675.3	Breast and Pancreatic Cancer
PDGFRA	NM_006206.4	Gastric Cancer, Sarcoma
PMS2	NM_000535.5	Colorectal, Gastric, Gynecologic, Nervous System/ Brain, Pancreatic, Prostate and Renal/Urinary Tract Cancer
POLD1	NM_002691.3	Colorectal Cancer
POLE	NM_006231.3	Colorectal Cancer
PRKAR1A	NM_002734.4	Endocrine and Nervous System/Brain Cancer, Sarcoma
PTCH1	NM_000264.3	Nervous System/Brain and Skin Cancer, Sarcoma
PTEN*	NM_000314.4	Breast, Colorectal, Endocrine, Gynecologic, Nervous System/Brain and Renal/Urinary Tract Cancer, Melanoma
RAD51C	NM_058216.2	Breast, and Gynecologic Cancer
RAD51D	NM_002878.3	Breast, and Gynecologic Cancer
RB1*	NM_000321.2	Melanoma, Retinoblastoma, Sarcoma
RET	NM_020975.4	Endocrine Cancer
SDHA*	NM_004168.3	Endocrine and Gastric Cancer, Sarcoma
SDHAF2	NM_017841.2	Endocrine Cancer

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
SDHB	NM_003000.2	Endocrine, Gastric and Renal/Urinary Tract Cancer, Sarcoma
SDHC	NM_003001.3	Endocrine, Gastric and Renal/Urinary Tract Cancer, Sarcoma
SDHD	NM_003002.3	Endocrine, Gastric and Renal/Urinary Tract Cancer, Sarcoma
SMAD4	NM_005359.5	Colorectal, Gastric and Pancreatic Cancer
SMARCA4	NM_001128849.1	Gynecologic Cancer
SMARCB1	NM_003073.3	Nervous System/Brain and Renal/Urinary Tract Cancer
STK11	NM_000455.4	Breast, Colorectal, Gastric, Gynecologic and Pancreatic Cancer
TMEM127	NM_017849.3	Endocrine Cancer
TP53	NM_000546.5	Breast, Endocrine, Gastrointestinal, Genitourinary, Gynecologic, Hematologic, Nervous System/Brain and Skin Cancer, Sarcoma
TSC1	NM_000368.4	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
TSC2	NM_000548.3	Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
VHL	NM_000551.3	Endocrine, Nervous System/Brain, Pancreatic and Renal/Urinary Tract Cancer
WT1	NM_024426.4	Renal/Urinary Tract Cancer

Cardiovascular-related genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ACTA2	NM_001613.2	Aortopathy
ACTC1	NM_005159.4	Cardiomyopathy, Congenital Heart Disease
ACTN2	NM_001103.3	Arrhythmia, Cardiomyopathy
ACVRL1	NM_000020.2	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
APOB	NM_000384.2	Familial Hypercholesterolemia, Familial Hypobetalipoproteinemia
BAG3	NM_004281.3	Cardiomyopathy, Neuromuscular Condition
BMPR2	NM_001204.6	Pulmonary Arterial Hypertension
CACNA1C	NM_000719.6;NM_001129840.1	Arrhythmia, Cardiomyopathy, Congenital Heart Disease
CACNB2	NM_201590.2	Arrhythmia
CALM1	NM_006888.4	Arrhythmia
CALM2	NM_001743.4	Arrhythmia
CALM3	NM_005184.2	Arrhythmia
CASQ2	NM_001232.3	Arrhythmia, Includes Reporting of Carrier Status
CAV1	NM_001753.4	Pulmonary Arterial Hypertension
CAV3	NM_033337.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
COL3A1	NM_000090.3	Aortopathy
CRYAB	NM_001885.2	Cardiomyopathy, Neuromuscular Condition
CSRP3	NM_003476.4	Cardiomyopathy
DES	NM_001927.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
DMD	NM_004006.2	Cardiomyopathy, Neuromuscular Condition
DSC2	NM_024422.4	Arrhythmia, Cardiomyopathy
DSG2	NM_001943.3	Arrhythmia, Cardiomyopathy
DSP	NM_004415.2	Arrhythmia, Cardiomyopathy
EMD	NM_000117.2	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
ENG	NM_000118.3	Hereditary Hemorrhagic Telangiectasia, Pulmonary Arterial Hypertension
F2*	NM_000506.3	Hereditary Thrombophilia
F5*	NM_000130.4	Hereditary Thrombophilia
F9	NM_000133.3	Hemophilia, Hereditary Thrombophilia
FBN1	NM_000138.4	Aortopathy
FHL1	NM_001449.4	Cardiomyopathy, Neuromuscular Condition
FLNC*	NM_001458.4	Cardiomyopathy, Neuromuscular Condition

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
GDF2	NM_016204.2	Hereditary Hemorrhagic Telangiectasia
GLA	NM_000169.2	Cardiomyopathy, Lysosomal Storage Disease
GPD1L	NM_015141.3	Arrhythmia
HCN4	NM_005477.2	Arrhythmia, Cardiomyopathy
JUP	NM_002230.2	Arrhythmia, Cardiomyopathy
KCNE1	NM_000219.5	Arrhythmia
KCNE2	NM_172201.1	Arrhythmia
KCNH2	NM_000238.3	Arrhythmia
KCNJ2	NM_000891.2	Arrhythmia
KCNQ1	NM_000218.2	Arrhythmia
LAMP2	NM_002294.2	Cardiomyopathy, Glycogen Storage Disease
LDLR	NM_000527.4	Familial Hypercholesterolemia
LDLRAP1	NM_015627.2	Familial Hypercholesterolemia, Includes Reporting of Carrier Status
LMNA	NM_170707.3	Arrhythmia, Cardiomyopathy, Neuromuscular Condition
MYBPC3	NM_000256.3	Cardiomyopathy
MYH11	NM_001040113.1	Aortopathy
MYH7	NM_000257.3	Cardiomyopathy, Neuromuscular Condition
MYL2	NM_000432.3	Cardiomyopathy
MYL3	NM_000258.2	Cardiomyopathy
MYLK	NM_053025.3	Aortopathy
NKX2-5	NM_004387.3	Arrhythmia, Congenital Heart Disease
PCSK9	NM_174936.3	Familial Hypercholesterolemia
PKP2*	NM_004572.3	Arrhythmia, Cardiomyopathy
PLN	NM_002667.3	Arrhythmia, Cardiomyopathy
PRKAG2*	NM_016203.3	Arrhythmia, Cardiomyopathy
PRKG1	NM_006258.3	Aortopathy
PROC	NM_000312.3	Hereditary Thrombophilia
PROS1*	NM_000313.3	Hereditary Thrombophilia
RBM20	NM_001134363.2	Arrhythmia, Cardiomyopathy
RYR2	NM_001035.2	Arrhythmia, Cardiomyopathy
SCN5A	NM_198056.2	Arrhythmia, Cardiomyopathy
SERPINC1	NM_000488.3	Hereditary Thrombophilia
SGCD	NM_000337.5	Cardiomyopathy, Neuromuscular Condition
SMAD3	NM_005902.3	Aortopathy
SMAD4	NM_005359.5	Hereditary Hemorrhagic Telangiectasia

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
TCAP	NM_003673.3	Cardiomyopathy, Neuromuscular Condition
TGFB2	NM_003238.3	Aortopathy
TGFB3	NM_003239.3	Aortopathy, Arrhythmia, Cardiomyopathy
TGFBR1	NM_004612.2	Aortopathy, Multiple Self-Healing Squamous Epithelioma
TGFBR2	NM_003242.5	Aortopathy
TMEM43	NM_024334.2	Arrhythmia, Cardiomyopathy
TNNC1	NM_003280.2	Cardiomyopathy
TNNI3	NM_000363.4	Arrhythmia, Cardiomyopathy
TNNT2	NM_001001430.2	Arrhythmia, Cardiomyopathy
TPM1	NM_001018005.1	Cardiomyopathy
VCL	NM_014000.2	Cardiomyopathy

Other genes

GENE	TRANSCRIPT	ASSOCIATED CONDITION(S)
ATP7B	NM_000053.3	Wilson Disease, Includes Reporting of Carrier Status
CACNA1S	NM_000069.2	Hypokalemic Periodic Paralysis, Malignant Hyperthermia Susceptibility
HAMP	NM_021175.2	Hereditary Hemochromatosis, Includes Reporting of Carrier Status
HFE	NM_000410.3	Hereditary Hemochromatosis, Includes Reporting of Carrier Status
HJV	NM_213653.3	Hereditary Hemochromatosis, Includes Reporting of Carrier Status
OTC	NM_000531.5	Ornithine Transcarbamylase Deficiency
RYR1*	NM_000540.2	Malignant Hyperthermia Susceptibility, Neuromuscular Condition
SERPINA1	NM_000295.4	Alpha-1-Antitrypsin Deficiency, Includes Reporting of Carrier Status
SLC40A1	NM_014585.5	Hereditary Hemochromatosis
TFR2	NM_003227.3	Hereditary Hemochromatosis, Includes Reporting of Carrier Status

Laboratory Director Tina Hambuch, Ph.D., FACMG
NY Laboratory Director Swaroop Aradhya, Ph.D., FACMG
Invitae 1400 16th Street, San Francisco, CA 94103
E: clientservices@invitae.com P: 415.374.7782 or 800.436.3037

Methods

- Genomic DNA obtained from the submitted sample is enriched for targeted regions using a hybridization-based protocol, and sequenced using Illumina technology. Unless otherwise indicated, all targeted regions are sequenced with ≥50x depth or are supplemented with additional analysis. Reads are aligned to a reference sequence (GRCh37), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript, indicated below. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 10bp of flanking intronic sequence (20bp for BRCA1/2), and other specific genomic regions demonstrated to be causative of disease at the time of assay design. Promoters, untranslated regions, and other non-coding regions are not otherwise interrogated. For some genes only targeted loci are analyzed (indicated in the table above). Exonic deletions and duplications are called using an in-house algorithm that determines copy number at each target by comparing the read depth for each target in the proband sequence with both mean read-depth and read-depth distribution, obtained from a set of clinical samples. All clinically significant observations are confirmed by orthogonal technologies, except individually validated variants and variants previously confirmed in a first-degree relative. Confirmation technologies include any of the following: Sanger sequencing, Pacific Biosciences SMRT sequencing, MLPA, MLPA-seq, Array CGH. Array CGH confirmation of NGS CNV calling performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778). The following analyses are performed if relevant to the requisition. For PMS2 exons 12-15, the reference genome has been modified to force all sequence reads derived from PMS2 and the PMS2CL pseudogene to align to PMS2, and variant calling algorithms are modified to support an expectation of 4 alleles. If a rare SNP or indel variant is identified by this method, both PMS2 and the PMS2CL pseudogene are amplified by long-range PCR and the location of the variant is determined by Pacific Biosciences (PacBio) SMRT sequencing of the relevant exon in both long-range amplicons. If a CNV is identified, MLPA or MLPA-seq is run to confirm the variant. If confirmed, both PMS2 and PMS2CL are amplified by long-range PCR, and the identity of the fixed differences between PMS2 and PMS2CL are sequenced by PacBio from the long-range amplicon to disambiguate the location of the CNV. Technical component of confirmatory sequencing is performed by Invitae Corporation (1400 16th Street, San Francisco, CA 94103, #05D2040778).
- A PMID is a unique identifier referring to a published, scientific paper. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed.
- An rsID is a unique identifier referring to a single genomic position, and is used to associate population frequency information with sequence changes at that position. Reported population frequencies are derived from a number of public sites that aggregate data from large-scale population sequencing projects, including ExAC (http://exac.broadinstitute.org), gnomAD (http://gnomad.broadinstitute.org), and dbSNP (http://ncbi.nlm.nih.gov/SNP).
- A MedGen ID is a unique identifier referring to an article in MedGen, NCBI's centralized database of information about genetic disorders and phenotypes. Search by MedGen ID at http://www.ncbi.nlm.nih.gov/medgen. An OMIM number is a unique identifier referring to a comprehensive entry in Online Mendelian Inheritance of Man (OMIM). Search by OMIM number at http://omim.org/.
- Invitae uses information from individuals undergoing testing to inform variant interpretation. If "Invitae" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observations.

Limitations

Based on validation study results, this assay achieves >99% analytical sensitivity and specificity for single nucleotide variants, insertions and deletions <15bp in length, and exon-level deletions and duplications. Invitae's methods also detect insertions and deletions larger than 15bp but smaller than a full exon but sensitivity for these may be marginally reduced. Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single-exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (e.g. inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (e.g. short tandem repeats or segmental duplications), may not be detected. Additionally, it may not be possible to fully resolve certain details about variants, such as mosaicism, phasing, or mapping ambiguity. Unless explicitly guaranteed, sequence changes in the promoter, non-coding exons, and other non-coding regions are not covered by this assay. Please consult the test definition on our website for details regarding regions or types of variants that are covered or excluded for this test. This report reflects the analysis of an extracted genomic DNA sample. In very rare cases (such as circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion, or maternal cell contamination), the analyzed DNA may not represent the patient's constitutional genome.

PTEN: Deletion/duplication analysis is not offered for exons 3-4. NBN: Deletion/duplication analysis is not offered for exons 15-16. RB1: Deletion/duplication analysis is not offered for exons 14-16. SDHA: Deletion/duplication analysis is not offered for this gene. RYR1: Deletion/duplication analysis is not offered for exons 48-49. FLNC: Deletion/duplication analysis is not offered for exon 47. GREM1: Promoter region deletion/duplication testing only. PKP2: Deletion/duplication analysis is not offered for exons 13-14. MITF: c.952G>A, p.Glu318Lys variant only. PROS1: Deletion/duplication analysis is not offered for exons 3-4. F2: Prothrombin G20210A (c.*97G>A) variant only. PRKAG2: Deletion/duplication analysis is not offered for exons 9-10. MUTYH: Deletion/duplication analysis is not offered for exon 1. F5: Factor V Leiden variant only. EPCAM: Sequencing analysis is not offered for this gene.

Disclaimer

DNA studies do not constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it is not a diagnosis itself. This test was developed and its performance characteristics determined by Invitae. It has not been cleared or approved by the FDA. The laboratory is regulated under the Clinical Laboratory Improvement Act (CLIA) as qualified to perform high-complexity clinical tests (CLIA ID: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

This report has been reviewed and approved by:

Ian Wilson, Ph.D., FACMG
Clinical Molecular Geneticist