INVITAE

INVITAE PROACTIVE TESTING RESULTS

Patient name:	Jane Doe	**Sample type:**	Blood	**Report date:**	
DOB:		**Sample collection date:**		**Invitae #:**	
Sex:	Female	**Sample accession date:**		**Clincial team:**	
MRN:					

Test performed

Sequence analysis and deletion/duplication testing of the 61 genes listed in the results section below.

- Invitae Cancer Screen

RESULT: POSITIVE

A clinically significant genetic change was found in the BRCA1 gene, which is associated with hereditary cancer.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
BRCA1	c.1961dupA (p.Tyr655Valfs*18)	Heterozygous	Pathogenic

About this test

This test evaluates 61 genes for variants (genetic changes) that indicate a significantly increased risk of developing certain types of cancer. 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 www.nccn.org for management guidelines regarding BRCA1-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.
- 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.

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Clinical summary

A Pathogenic variant, c.1961dupA (p.Tyr655Valfs*18), was identified in BRCA1.

- Certain genetic changes in the BRCA1 gene significantly increase the risk for a condition called hereditary breast and ovarian cancer (HBOC) syndrome.
- The specific genetic change identified is a clinically significant change that increases the risk to develop BRCA1-related condition/s.
- Individuals with HBOC are more likely to develop one or more cancers involving the breasts (in both females and males), ovaries/fallopian tubes/peritoneum, prostate, and less frequently, the pancreas and possibly the skin (melanoma) when compared to individuals in the general population. Screening and management guidelines exist to help prevent 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 that not all individuals with a genetic change in BRCA1 will develop cancer.
- Clinically significant genetic changes in the BRCA1 gene are inherited in an autosomal dominant fashion. This means that an individual only needs to inherit one clinically significant genetic change to be at risk for the BRCA1-related condition/s. Close family members have up to a 50% chance of also carrying this genetic change and being at risk.

Variant details

BRCA1, Exon 10, c.1961dupA (p.Tyr655Valfs*18), heterozygous, Pathogenic

- This sequence change creates a premature translational stop signal (p.Tyr655Valfs*18) in the BRCA1 gene. It is expected to result in an absent or disrupted protein product.
- This variant is present in population databases (rs80357853, ExAC 0.01%).
- This variant has been observed in individuals with breast, ovarian, and prostate cancer (PMID: 7837387, 21324516, 22516946, 22970155, 21559243). This variant is also known as 2080insA in the literature. ClinVar contains an entry for this variant (Variation ID: 54417).
- Loss-of-function variants in BRCA1 are known to be pathogenic (PMID: 20104584).
- For these reasons, this variant has been classified as Pathogenic.

Genes analyzed

No reportable variants were identified in the remaining tested genes. Variants of Uncertain Significance, Benign, Likely Benign, and silent and intronic variants with no evidence towards pathogenicity are not included in this report. Results are negative unless otherwise indicated.

Cancer-related genes

GENE(S)	TRANSCRIPT	ASSOCIATED CONDITION
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
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

Genes listed in this table may also have additional reported associations outside of the conditions listed. Additional information about gene-condition associations can be found at http://www.omim.org/

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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 Sanger 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 Sanger sequenced 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) 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/.

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 IDs: 05D2040778). This test is used for clinical purposes. It should not be regarded as investigational or for research.

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, (circulating hematolymphoid neoplasm, bone marrow transplant, recent blood transfusion) the analyzed DNA may not represent the patient's constitutional genome.

- SDHA: Analysis does not include deletion/duplication testing. RB1: Deletion/duplication analysis is not offered for exons 14-16. EPCAM: Deletion/duplication testing only. GREM1: Promoter region deletion/duplication testing only. HOXB13: c.251G>A, p.Gly84Glu variant only. NBN: Deletion/duplication analysis is not offered for exons 15-16. PTEN: Deletion/duplication analysis is not offered for exons 3-4. MITF: c.952G>A, p.Glu318Lys variant only.

- Regions of the following genes had sub-optimal levels of sequence coverage, and sensitivity to detect variants in these regions is expected to be reduced. If the clinical presentation in this patient is highly consistent with mutations in these genes, follow up testing may be indicated: SMAD4: 18:48556993-48556993.

This report has been reviewed and approved by:

INVITAE

GENERAL GUIDELINES

POSITIVE RESULTS GUIDE: BRCA1

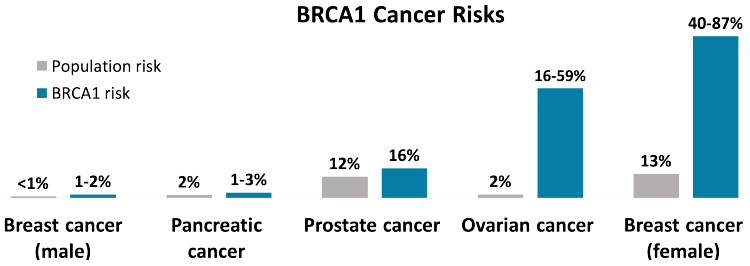
This document is not part of Invitae's clinical report and does not represent medical advice. These are general guidelines that are not specific to your result. You can use this guide to talk to your healthcare provider about your test results, clinical history, and the most current guidelines.

What is a positive BRCA1 result?

A positive test result means that you have a genetic change, called a pathogenic or likely pathogenic variant ("mutation"), in your BRCA1 gene. This variant can cause hereditary breast and ovarian cancer (HBOC) syndrome.

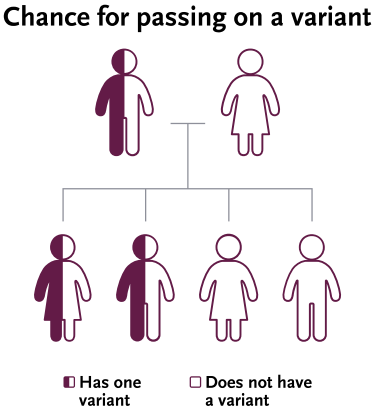
What does this mean?

It's possible for anyone to get cancer at some point in their life, however, people with HBOC are more likely to get breast, ovarian, prostate, and pancreatic cancers than the average person. See the table later in this guide for ways to find and manage HBOC.



What does this mean for family members?

Genes and variants are passed from generation to generation. Your relatives may also have this variant in BRCA1. Both men and women can inherit and pass on this variant.



Who should be tested next?
Your close relatives have a 50% chance of also having the same positive variant. This means your parents, siblings, and children. Your other relatives may also have this BRCA1 variant.

Inheriting this BRCA1 variant does not mean that a person will definitely develop cancer. This variant affects everyone differently. Members of the same family with the same variant may develop different features of the condition or at a different age. Features of this condition usually do not affect children. Genetic testing for this variant is not recommended until the age of 18.

Genetic testing is a personal choice and your family members may choose not to have genetic testing. It is recommended that they talk with their own healthcare provider about a plan for screening.

Create a plan with your healthcare provider

These options are a guide for you and your healthcare provider. They are meant to be used along with your genetic test results and other health information. Each option may or may not be right for you. Your positive test result on its own can not predict how this condition may affect you. Please talk with your healthcare provider to make a plan that's right for you.

Options you and your healthcare provider might consider

CONDITION	RISK FOR GENERAL POPULATION	RISK FOR BRCA1	OPTION	MORE INFORMATION
Breast cancer (female)	13%	40-87%	• Periodic breast self exam starting at age 18 (1)	• Helps find cancer so you can seek treatment as soon as possible.
			• Clinical breast exam every 6-12 months, starting at age 25 (1)	• Helps find cancer so you can seek treatment as soon as possible. • If you have a family history of breast cancer, screening may be started earlier than age 25.
			• Breast MRI with contrast once per year from ages 25–29 (1)	• Helps find cancer so you can seek treatment as soon as possible. • If a breast MRI is not available, consider a mammogram or a 3D mammogram. • If you have a family history of breast cancer, screening may be started earlier than age 25.
			• Mammogram or 3D mammogram and a breast MRI with contrast once per year from ages 30-75 (1)	• Helps find cancer so you can seek treatment as soon as possible. • If you have a family history of breast cancer, screening may be started earlier than age 30. • Your personal and family health history will help determine if this screening is appropriate over age 75.
			• Consider risk-reducing mastectomy (surgery to remove the breasts) based on personal and family history (1)	• May help lower the chance for cancer.
Breast cancer (male)	<1%	1-2%	• Breast self exam starting at age 35 (1)	• Helps find cancer so you can seek treatment as soon as possible.
			• Clinical breast exam once per year starting at age 35 (1)	• Helps find cancer so you can seek treatment as soon as possible. • If you have a family history of breast cancer, screening may be started earlier than age 35.
Ovarian cancer	2%	16-59%	• Transvaginal ultrasound with CA-125 blood testing once per year starting at age 35 may be considered for those that do not yet have their ovaries removed (1)	• Helps find cancer so you can seek treatment as soon as possible. • The benefit of these tests is unknown.
			• Consider risk-reducing salpingo-oophorectomy (RRSO) (surgery to remove the ovaries and fallopian tubes) from ages 35-40, after child bearing is complete (1)	• Helps find cancer so you can seek treatment as soon as possible. • Your personal and family health history will help determine if and when to consider this option.
Prostate cancer	12%	16%	• Consider prostate specific antigen (PSA) blood screening starting at age 40 (1)	• Helps find cancer so you can seek treatment as soon as possible.
Pancreatic cancer	2%	1-3%	• Consider pancreatic imaging (MRI with contrast or endoscopic ultrasound) if there is additional family history of pancreatic cancer (1)	• Helps find cancer so you can seek treatment as soon as possible. • Specific recommendations have not yet been determined; you may consider screening

CONDITION	RISK FOR GENERAL POPULATION	RISK FOR BRCA1	OPTION	MORE INFORMATION
				through clinical trials or if you have a close relative with pancreatic cancer. • Results of this test will help determine if and when you will need more testing.

These options outline recommendations from NCCN. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.1.2020. (1) © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed December 19, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. We are always learning more about genetics and disease, so please always refer to the current guidelines and recommendations when considering surveillance and treatment options. Information in this document may not include all relevant international recommendations and acts as a supplement to the Invitae result report. This information is not meant to replace a discussion with your healthcare provider and should not be considered or interpreted as medical advice.

We (and others) are here to help

Genetic counseling is recommended to help you clearly and accurately understand your results so it's important to talk to your genetic counselor or other healthcare provider about your test results. Invitae also has board-certified genetic counselors who are available to answer questions about your test results or these options. Log in to your patient portal (invitae.com) to view your results, search for a local or Invitae genetic counselor, or join Invitae's Patient Insight Network (PIN), a community where you can connect with other patients and share your experience.

Notes for personalized assessment