# geneType for Breast and Ovarian Cancer

13-gene HBOC panel

Accession ID: PD_test1
Collection Date: 2023-12-16
Received Date: 2023-12-18
Report Date: Not yet approved

## Test Result

**Negative Result** No pathogenic variants were detected.

## Result Summary:

Please refer to attached geneType risk assessment report for patient's absolute risk of developing breast and ovarian cancer over the next 5 years and over her remaining lifetime (to age 90).

**Genes Analyzed (sequencing):** *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53*

## Test Methodology

Genomic DNA is selectively amplified and enriched using a custom Twist Bioscience panel. Sequencing is conducted on Illumina's NovaSeq 6000 Instruments, to an average coverage depth of 20X. The FASTQ files are run through the Dragen pipeline for secondary analysis including alignment to the human reference genome (hg38), and variant calling (SNV/indel). Tertiary analysis including annotations and interpretation are performed using a bioinformatics pipeline available in Fabric Enterprise software. Case interpretation was carried out by qualified scientists at Fabric Clinical (CLIA # 45D2281059 - CAP # 9619501) and at Phenogen Sciences Laboratory. Variant interpretation is performed according to current American College of Medical Genetics and Genomics (ACMG) professional guidelines for the interpretation of germline sequence variants. Variants classified as likely pathogenic or pathogenic are reported for this test. The following quality filters are applied to all variants: allelic balance <0.35, coverage <10x. Fabric is a variant analysis, interpretation and decision support tool analyzing human genetics data. Software includes underlying databases, data reference sets and tools in Fabric Enterprise 3.0.
A PMID is a unique identifier referring to a published, scientific paper. References are included in the selected citations below. Search by PMID at http://www.ncbi.nlm.nih.gov/pubmed. GeneType uses information from individuals undergoing testing to inform variant interpretation. If "GeneType" is cited as a reference in the variant details this may refer to the individual in this requisition and/or historical internal observation.

## Test Limitations

This result is constrained to the list of genes tested and within the limits of variants detectable by targeted sequencing. All clinically significant observations are called in regions of high confidence. For any reported variants, confirmation by orthogonal technology and subsequent consultation with a genetic counselor or qualified healthcare provider can help to establish definitive risk. This result should be considered preliminary until such confirmation has been performed. This test has not been validated on every known pathogenic mutation and may not be able to detect all possible mutations present. Limitations to clinically significant variant calling may exist in regions with known pseudogene interference, homopolymer stretches, other repetitive regions or regions of high GC content.

# geneType for Breast and Ovarian Cancer

13-gene HBOC panel

This assay is designed and validated for detection of germline variants only. It is not designed or validated for the detection of low-level mosaicism or somatic mutations. Additionally, this assay will not detect certain types of genomic aberrations such as translocations, inversions, or repeat expansions (eg. trinucleotide or hexanucleotide repeat expansion). DNA alterations in regulatory regions or deep intronic regions (greater than 10bp from an exon) may not be detected by this test. Certain copy number changes, especially when less than multiple contiguous exons in size, may not be detected due to pseudogene interference or technical limitations for this test. When novel DNA duplications are identified, it is not possible to discern the genomic location or orientation of the duplicated segment, hence the effect of the duplication cannot be predicted. Where deletions are detected, it is not always possible to determine whether or not the predicted product will remain in-frame. The following genomic regions are not reliably covered: CHEK2 chr22:28729310-28729386 (GRCh38). Reads are aligned to a reference sequence (GRCh38), and sequence changes are identified and interpreted in the context of a single clinically relevant transcript. The largest transcript is chosen unless otherwise noted. Enrichment and analysis focus on the coding sequence of the indicated transcripts, 20bp of flanking intronic sequence. The 5'UTR of BRCA1/2 are also included in the sequence analysis, however other gene promoters, untranslated regions, and other non-coding regions are not interrogated. This test analyses the following types of variants: nucleotide substitutions, small deletions (up to 25 bp), small insertions (up to 10 bp), and small indels. The pattern of variant types varies with the genes tested. This test detects a variable percentage of known and unknown variants of the classes stated above. A negative result cannot rule out the possibility that the tested individual carries a variant in the undetectable group. This test is designed and validated to be capable of detecting ~99% of described classes of variants in the genes represented on the panel (analytical sensitivity). The clinical sensitivity of this test may vary widely according to the specific clinical and family history.



## Exceptions

Although uncommon, diagnostic errors may occur due to sample mix-up, DNA contamination, or other laboratory operational errors (including, without limitation, equipment or reagent failure, or upstream supplier errors). Additionally, poor sample DNA quality and certain characteristics inherent to specific regions of an adult's genomic DNA may limit the accuracy of results. All classifications are based on review, interpretation, and/or analysis of evidence available at the time of reporting. Medical literature and scientific databases may change as new evidence becomes available. In the absence of an identified pathogenic or likely pathogenic mutation, standard risk models may still be employed to determine risk estimates and subsequent guidelines. All risk estimation is approximate. "Increased risk" is not a diagnosis and does not guarantee that a person will develop the disease.

## Regulatory Disclosures

This test was developed and its performance characteristics determined by Gene By Gene (CLIA#45D1102202 | CAP#7212851, 1445 N Loop W STE 820 Houston, TX, sample receipt, accessioning, processing) and Phenogen Sciences Laboratory (CLIA#99D2023356, 60-66 Hanover Street Fitzroy, Victoria, 3065, Australia, sample accessioning, data interpretation and final report). It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research. Since genetic variation, as well as systematic and technical factors, can affect the accuracy of testing, the results of testing should always be interpreted in the context of clinical and familial data. It is recommended that patients receive appropriate genetic counseling to explain the implications of the test result, including its residual risks, uncertainties and reproductive or medical options.

**Signature will be placed here once report is approved**

Risk Assessment Test Report Summary
Negative Reflex 13-gene HBOC

# geneType Multi-Suite Comprehensive

## This patient received 2 disease risk prediction results and is at increased risk for 1 disease.



| Disease | Result Summary | Clinical Action Available |
|---|---|---|
| Breast Cancer | Increased | see supplemental screening and risk reduction options |
| Ovarian Cancer | Average | average risk screening |

## Interpretation Summary

This patient tested negative for the presence of a pathogenic variant in a 13-gene hereditary breast and ovarian cancer panel *(ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53)*.
As a negative reflex, the additional geneType report provides the patient's absolute risk of developing breast and/or ovarian cancer due to a combination of clinical and polygenic factors.

This patient has an increased risk of developing Breast Cancer. Please read the appended report for specific details.

This patient is considered within the average range of risk for an adult of the same age, sex and ethnicity for the remaining disease listed above.

The risk scores are patient-specific and cannot be used to estimate risk in relatives. Furthermore, the following results should be interpreted in the context of the patient's full clinical history, particularly for patients close to a threshold risk value.

Report continued on next page

Breast Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

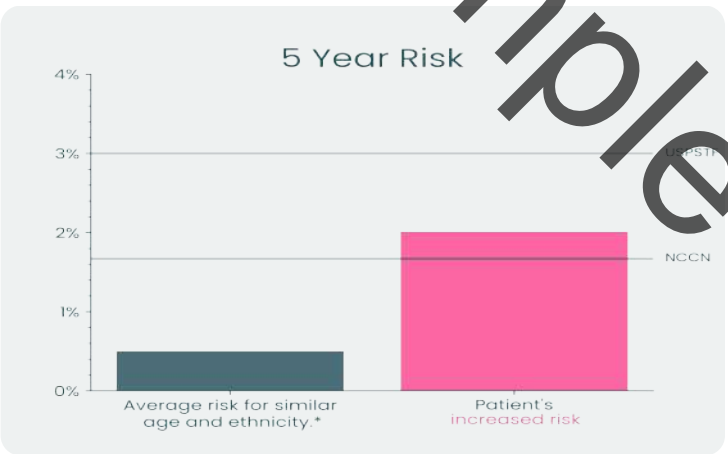
# geneType for Breast Cancer Comprehensive

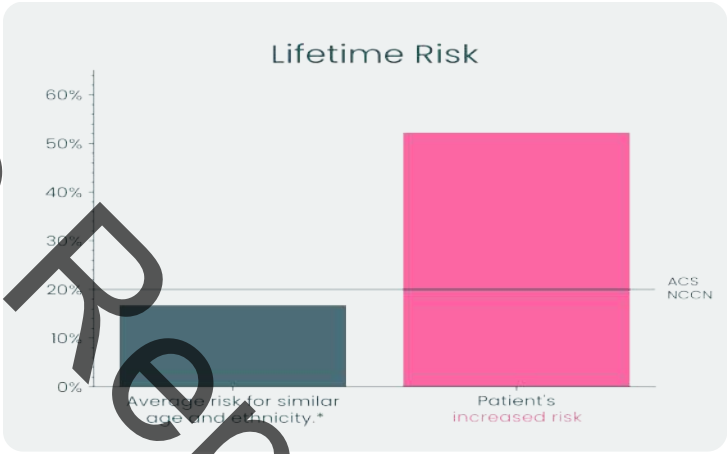


This patient is at an
INCREASED
risk of breast cancer

**2.01%**
Patient's
5 year risk

**52.26%**
Patient's
Lifetime risk




**The average risk is based on the same age, biological gender and race/ethnicity as the patient from the general population.*

## Interpretation

This patient has a 52.26% chance of developing breast cancer within her remaining lifetime up to age 90 years. This is considered an increased risk because it is above the 20% threshold defined by the American Cancer Society and other medical associations.

This patient has a 2.01% chance of developing breast cancer over the next 5 years which is considered an increased risk. This is higher than the actionable threshold of 1.67% as defined by NCCN and lower than 3% as defined by USPSTF.

The patient should continue following general population breast screening protocols at a minimum, regardless of their estimated risk score. Also note that the risk scores are patient-specific and cannot be used to estimate risk in relatives. Furthermore, these results should be interpreted by a healthcare professional in the context of the patient's full clinical history, particularly for patients close to a threshold risk value.

Report continued on next page

Breast Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

# geneType for Breast Cancer Comprehensive

**This comprehensive risk assessment included a 13-gene HBOC panel; the patient tested negative for a pathogenic variant in the following genes:**
***ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53***

## Clinical Responses

*as provided on the requisition form*

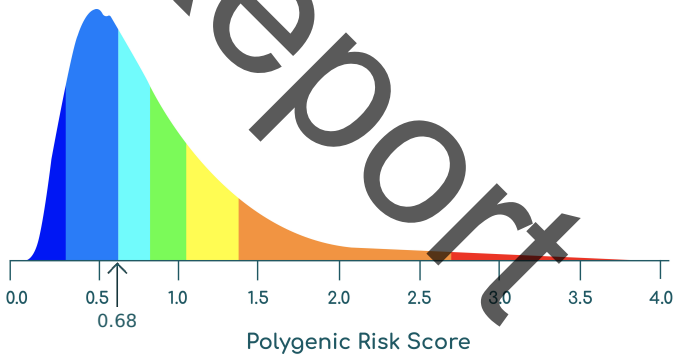
| | |
|---|---|
| Does the patient have a medical history of any breast cancer or ductal carcinoma *in situ* (DCIS)?* | **No** |
| What is the patient's age? | **36** |
| What is the patient's race/ethnicity? | **White non-Hispanic** |
| What is the patient's height? | **5'8"** |
| What is the patient's weight? | **155 lbs** |
| How many first-degree relatives does the patient have who have had breast cancer? (mother, sister, daughter) | **1** |
| What was the age of the youngest first-degree relative when they were diagnosed with breast cancer? | **38** |
| How many second-degree relatives does this patient have who have had breast cancer? (aunts, nieces, grandparents, grandchildren, half-siblings, and double cousins) | **0** |
| What is the patient's menopausal status? | **pre-menopausal** |
| Has the patient ever had a breast mammogram? | **Yes** |
| What is the patient's reported mammographic breast density? | **Bi-Rads d** |

**please note, this risk assessment does not incorporate risk from high penetrance variants in genes associated with hereditary breast cancer.*



## Polygenic Risk Score

**0.68**
Patient's Polygenic Risk Score




The Polygenic Risk Score (PRS) is the genetic contribution to risk. It is a relative risk calculated as the multiplicative product of the patient's risk alleles weighted according to ethnicity-specific allele frequencies and odds ratios. This graph represents the breast cancer PRS range in the general population. The arrow represents where the patient falls compared to the general population. Note that PRS alone is not clinically actionable – it is just one of the factors integrated into the patient's breast cancer risk scores. Please refer to the 5 year and remaining lifetime for the absolute breast cancer risk scores.

Report continued on next page

Breast Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

# geneType for Breast Cancer Comprehensive

## The Test

GeneType for Breast Cancer incorporates clinical responses with an analysis of the genetic markers known to be associated with breast cancer. The test is intended to help patients and their healthcare professional make informed decisions regarding breast cancer screening and prevention options. The risk scores are patient-specific and cannot be used to estimate risk in relatives. These results should be interpreted by a healthcare professional in the context of the patient's full clinical history.

The patient's genetic information is used to generate a polygenic risk score. The polygenic risk score is calculated using a multiplicative model of breast cancer susceptibility. The risk model incorporates clinical risk factors (see Clinical Responses for a full list) and polygenic risk, combined with incidence and mortality data for breast cancer derived from the US Surveillance, Epidemiology, and End Results (SEER) database, in a proprietary algorithm to provide an absolute estimate of the 5 year and remaining lifetime risk of developing breast cancer.



**Indication:** GeneType for Breast Cancer is a breast cancer risk assessment test for women aged 30-85, but the recommended age to begin risk assessment for sporadic breast cancer is 35 years or older. The test is intended to better inform decision- making for breast cancer screening and risk-reduction. It is applicable to women who have not already been shown to carry a (likely) pathogenic variant in a hereditary breast and ovarian cancer (HBOC) associated genes, such as *BRCA1* or *BRCA2*.

**Population Risk:** The average lifetime risk of developing breast cancer is 1 in 9 for women (or 12%).

**Validation:** GeneType for Breast Cancer is currently validated in women 35 years or older of Non-Hispanic White descent and relies on the patient correctly reporting their ethnicity. The risk model incorporates ethnicity-specific population incidence data derived from the Surveillance, Epidemiology, and End Results (SEER) Program, For patients without ethnic-specific polygenic risk scores (PRS), the non-Hispanic white-derived PRS will be utilized until ethnic-specific PRS can be derived and cross-validated. Peer reviewed publications suggest the performance of the non-Hispanic white-derived-PRS in women of Asian and African descent is suitable for stratification in these ethnicities. The clinical risk factors are applicable across ethnicities, however the model has not been validated in these populations as yet.

**Limitations:** GeneType for Breast Cancer is a breast cancer risk prediction test only. An increased risk score does not mean that a patient will definitely develop breast cancer. Conversely, a low risk score does not mean that a patient will definitely not develop breast cancer.

GeneType for Breast Cancer provides an estimate of the likelihood that a woman will develop disease at some stage in the future. Cancer is a multifactorial disease and it is not possible to incorporate all potential risk factors into a risk prediction model. Test results should be interpreted by a healthcare professional in the context of the patient's full clinical and family history. Medical management and decision-making for breast cancer screening and prevention practices should not rely solely on a patient's geneType for Breast Cancer results.

The reliability of results for this test are dependent on the accuracy of the information provided in the clinical responses. If the responses to clinical questions change (e.g. number of first- degree relatives), the patient's risk percentages and risk category may also change.

Although the current test incorporates ethnic-specific incidence data, not all risk factors, such as PRS, have been optimized for ethnic-specific stratification improvements. While geneType improves risk stratification compared to current standards, ethnic-specific-improvements can still be made. Work is ongoing for ethnic-specific expansions that will further improve the calibration and discrimination of the assay across more genetic ancestries. This test is not applicable to women who have a personal history of breast cancer or who have already been shown to have an HBOC mutation, for example in the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of breast cancer. In this case, the patient should be referred to a specialist for genetic counselling.

**Test Methodology:** GeneType for Breast Cancer uses next generation sequencing (NGS) to determine the genotype of 313 polymorphic breast cancer susceptibility loci; Genomic DNA is extracted from the Oragene Dx saliva kit, or GBG buccal swab kit using standard DNA extraction methods. Genomic DNA is selectively amplified and enriched using a custom Twist Bioscience panel. Sequencing is conducted on Illumina's NovaSeq 6000 Instruments, to an average coverage depth of 500X. The FASTQ files are run through the Dragen pipeline for alignment to the human reference genome (hg38), and variant calling. The polygenic risk score is calculated using a multiplicative model of breast cancer susceptibility combined with US Surveillance, Epidemiology, and End Results (SEER) incidence and mortality data for breast cancer in a proprietary algorithm to provide an absolute estimate of the 5-year and remaining lifetime risk of developing breast cancer.

This test was developed and its performance characteristics determined by Gene by Gene (CLIA#45D1102202|CAP#7212851. 1445 N Loop W STE 820, Houston, TX, sample receipt, accessioning, processing) and Phenogen Sciences Laboratory (CLIA#99D2023356, sample accessioning, data interpretation and final report). It has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through pre-market FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Report continued on next page

Breast Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

# geneType for Breast Cancer Comprehensive

Your risk of developing breast cancer is considered INCREASED for a woman your age.

Many women in this risk category will never develop breast cancer, but some will.

Your risk of developing breast cancer over the rest of your life is 52.26% . This is greater than 20%, which puts you at increased risk.

The risk for an average woman your age developing breast cancer over their life is 16.79%.

Your risk of developing breast cancer over the next 5 years is 2.01%. This is greater than 1.67%, which puts you at increased risk.

The risk for an average woman your age developing breast cancer over the next 5 years is 0.50%.

**The average risk is based on the same age, biological gender and race/ethnicity as the patient from the general population.*



## Understanding Breast Cancer Risk Factors

A risk factor is anything that may increase your chance of developing a disease. Some risk factors are strong and significantly increase your personal risk of the disease while others are weaker and only have a small impact on overall risk. Some risk factors can be modified by making changes to your lifestyle, while others are beyond your control.

**Age:** Increasing age is one of the strongest risk factors for breast cancer. Most breast cancers occur in women over the age of 50 years. This is why it is important to maintain regular wellness visits as you get older.

**Weight:** Being overweight, particularly post-menopause, has been shown to increase the risk of breast cancer.

**Genetics:** You are born with a set of genetic markers called Single Nucleotide Polymorphisms (SNPs). GeneType for Breast Cancer looks at your SNPs to help determine your risk of developing breast cancer.

**Family History:** If you have relatives who have been diagnosed with breast cancer, this will impact your risk of developing the disease. The more relatives with breast cancer you have, the more your risk increases.

**Breast Density:** Breast density often changes with age, hormonal fluctuation and weight. Women with dense breasts are at increased risk of developing breast cancer.

**Oestrogen:** Oestrogen is a female sex hormone that helps regulate a woman's reproductive system. Levels of oestrogen fluctuate from adolescence through adulthood as a woman goes through changes such as menarche, childbirth and menopause. Oestrogen is associated with the development of some types of breast cancer.

**Hormone Replacement Therapy:** Use of hormone replacement therapy (HRT), especially for long periods, has been associated with a modest increase in risk of breast cancer. However, it is important to note that the benefits of these medicines may outweigh the risks for many women. If you are taking combined HRT, review your needs every six to twelve months with your healthcare professional.

**Smoking:** Smoking increases your risk of breast cancer.

**Alcohol:** Alcohol consumption has been associated with an increased risk of breast cancer in both pre- and post-menopausal women.

**Physical Activity:** If you're not physically active, you have a greater chance of developing breast cancer. Being more active can help lower your risk.

## What You Can Do

Together with your healthcare provider, you will discuss options for breast cancer risk reduction, including screening. Below we briefly outline some of the clinical recommendations that your healthcare provider may discuss with you in greater detail.

## Risk Reduction

A woman can develop breast cancer at any age, regardless of her level of risk. As a result, it is important to know the normal look and feel of your breasts and to perform regular self- examinations. Make sure you visit your healthcare provider if you detect any change in your breasts.

Maintaining a healthy lifestyle is a simple way to reduce your risk of breast cancer. This includes maintaining a healthy weight, not smoking and limiting your alcohol intake. In order to reduce your risk of breast cancer, it is best not to drink alcohol or, if you drink, limit consumption to 1 standard drink or less per day. Moderate physical activity of between 1.5 to 4 hours per week has also been shown to reduce risk for breast cancer.

Report continued on next page

For women at potentially high risk of developing breast cancer or risk-reducing medications may also be discussed with a specialist.

Women with a 5 year risk of ≥1.67% should be offered risk reduction counselling. Furthermore, the United States Preventive Services Taskforce (USPSTF) guidelines state that women with an estimated 5 year risk of 3% or greater are more likely to benefit from tamoxifen or raloxifene to prevent invasive breast cancer. The American Society of Clinical Oncology (ASCO) also recommend the option of aromatase inhibitors for post- menopausal women and suggest at risk above 3% the risk reducing benefits outweigh harms. Discuss your breast cancer prevention options, including the risks and benefits of risk- reducing medication, with your healthcare provider.

## Screening

Regardless of risk score, we recommend that all women undergo routine mammography as recommended by her healthcare provider. Women at average risk of developing breast cancer have the option to begin annual mammogram screening between the ages of 40 and 50. Your screening may be tailored to your risk, within the context of your full medical history, following an informed decision-making discussion between you and your healthcare provider.

Women who have a lifetime risk of ≥20% as defined by models that are dependent on family history are recommended to consider an annual breast MRI. Discuss your screening options with your healthcare provider.

You may be referred to a high-risk center or a healthcare provider who specializes in breast cancer prevention to discuss your risk and the potential risk-reducing options that may be available to you.

## References

Allman R, Mu Y, Dite GS, et al. Validation of a breast cancer risk prediction model based on the key risk factors: family history, mammographic density and polygenic risk. Breast Cancer Res Treat. 2023 Apr;198(2):335-347. 8.

Spaeth EL, Dite GS, Hopper JL, et al. Validation of an Abridged Breast Cancer Risk Prediction Model for the General Population. Cancer Prev Res (Phila). 2023 May 1;16(5):281-291.

Medication Use to Reduce Risk of Breast Cancer, United States Preventitavie Services Task Force. JAMA. 2019; 322(9):857-867. doi:10 .1001/ jama.2019.11885; Corrected on October 11, 2019

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Breast Cancer Screening and Diagnosis. Version 3.2023. Accessed December 2023

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Breast Cancer Risk Reduction. Version1.2024. Accessed December 2023

Use of Endocrine Therapy for Breast Cancer Risk Reduction. Journal of Clinical Oncology 37, no. 33 (November 20, 2019) 3152-3165.

For a full list of references supporting the GeneType for Breast Cancer risk assessment test, please visit **www.genetype.com**

Ovarian Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

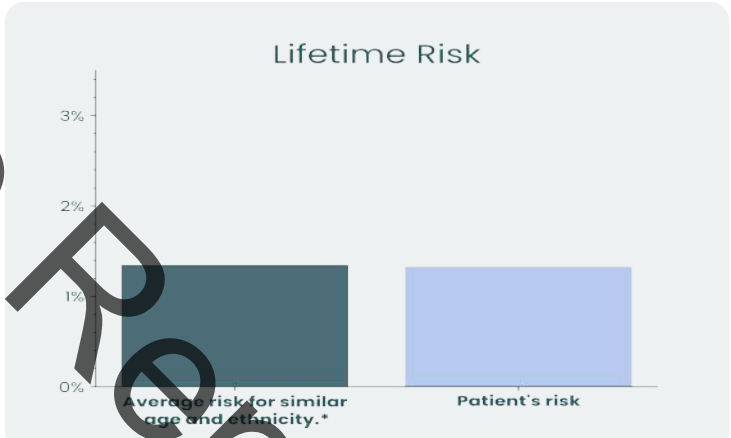
# geneType for Ovarian Cancer Comprehensive



This patient is at an
AVERAGE
risk of ovarian cancer compared
to a woman her age

**0.03%**
Patient's
5 year risk

**1.33%**
Patient's
Lifetime risk


**The average risk is based on the same age, biological gender and race/ethnicity as the patient from the general population.*

## Interpretation

This patient has a 1.33% chance of developing ovarian cancer within her remaining lifetime up to age 90 years which is considered an average risk. This is within the average range of risk for a woman her same age and ethnicity.

The risk scores are patient-specific and cannot be used to estimate risk in relatives. Furthermore, these results should be interpreted by a healthcare provider in the context of the patient's full clinical history, particularly for patients close to a threshold risk value.

Report continued on next page

# geneType for Ovarian Cancer Comprehensive

**This comprehensive risk assessment included a 13-gene HBOC panel; the patient tested negative for a pathogenic variant in the following genes:**
***ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, STK11, TP53***

## Clinical Responses

*as provided on the requisition form*

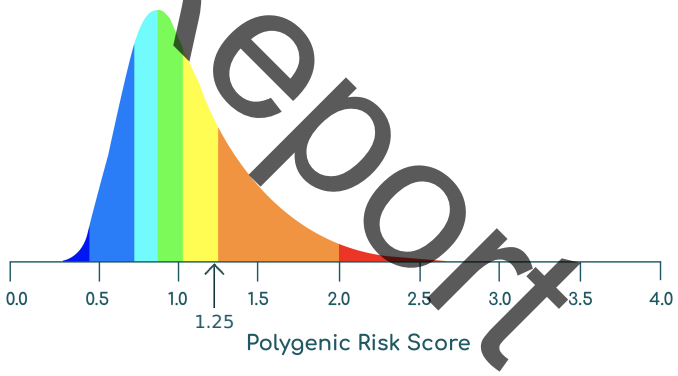
| | |
|---|---|
| What is the patient's age? | **36** |
| What is the patient's race/ethnicity? | **White non-Hispanic** |
| Has the patient had hormone replacement therapy (HRT)? | **No** |
| If so, what was the duration of HRT? | **0** |
| Has the patient had an oopherectomy? | **No** |
| What is the patient's height? | **5'8"** |
| What is the patient's weight? | **155 lbs** |
| What is the patient's menopausal status? | **Pre-menopausal** |
| If the patient is menopausal, what was her menopause age of onset? | **N/A** |
| Has the patient had any live births? | **Yes** |
| If so how many live births? | **2** |
| Has the patient taken hormonal birth control? | **Yes** |
| If so what was the duration of hormonal birth control? | **9 years** |

**please note, this risk assessment does not incorporate risk from high penetrance variants in genes associated with hereditary ovarian cancer.*



## Polygenic Risk Score

**1.25**
**Patient's Polygenic Risk Score**




The Polygenic Risk Score (PRS) is a relative risk calculated as the multiplicative product of the patient's risk alleles weighted according to ethnicity-specific allele frequencies and odds ratios. This graph represents the ovarian cancer PRS range in the general population.

The arrow represents where the patient falls compared to the general population (not to scale). Note that PRS alone is not clinically actionable – it is just one of the factors integrated into the patient's ovarian cancer risk scores. Please refer to the 5 year and lifetime risk for the absolute ovarian cancer risk scores.

Report continued on next page

Ovarian Cancer Risk Assessment Final Test Report
Negative Reflex 13-gene HBOC

# geneType for Ovarian Cancer Comprehensive

## The Test

GeneType for Ovarian Cancer incorporates clinical responses with an analysis of the genetic markers known to be associated with ovarian cancer. The test is intended to help patients and their healthcare providers make informed decisions regarding ovarian cancer screening and prevention options. The risk scores are patient-specific and cannot be used to estimate risk in relatives. These results should be interpreted by a healthcare provider in the context of the patient's full clinical history.

The patient's genetic information is used to generate a polygenic risk score. The polygenic risk score is calculated using a multiplicative model of ovarian cancer susceptibility. The risk model incorporates clinical risk factors (see Clinical Responses for a full list) and polygenic risk, combined with incidence and mortality data for ovarian cancer derived from the US Surveillance, Epidemiology, and End Results (SEER) database, in a proprietary algorithm to provide an absolute estimate of the 5 year and remaining lifetime risk of developing ovarian cancer. A woman is considered average risk if she is less than 2.1x average risk for a woman of the same age and ethnicity.



**Indication:** GeneType for Ovarian Cancer is an ovarian cancer risk assessment test for women aged 30-85 years or older who have not already been shown to have a hereditary breast and ovarian cancer (HBOC) gene mutation, such as *BRCA1* or *BRCA2*. The recommended age to begin risk assessment is 40 years and is intended to better inform decision-making for ovarian cancer screening and preventative care.

**Population Risk:** The average lifetime risk of developing ovarian cancer is 1 in 79 (or 1.3%).

**Validation:** GeneType for Ovarian Cancer is currently validated in Non-Hispanic White women aged 40 to 69 and relies on the patient correctly reporting their ethnicity. The risk model incorporates ethnicity-specific population incidence data for patients derived from the US Surveillance, Epidemiology, and End Results (SEER) database. For patients without ethnic-specific polygenic risk scores (PRS), the Non-Hispanic White-derived PRS will be utilized until ethnic-specific PRS can be derived and cross-validated. The clinical risk factors are applicable across ethnicities, however the model has not been validated in these populations as yet.

**Limitations:** GeneType for Ovarian Cancer is an ovarian cancer risk prediction test only. An increased risk score does not mean that a patient will definitely develop ovarian cancer. Conversely, a low risk score does not mean that a patient will definitely not develop ovarian cancer.

GeneType for Ovarian Cancer provides an estimate of the likelihood that a woman will develop disease at some stage in the future. Cancer is a multifactorial disease and it is not possible to incorporate all potential risk factors into a risk prediction model. Test results should be interpreted by a healthcare provider in the context of the patient's full clinical history. Medical management and decision-making for ovarian cancer screening and prevention practices should not rely solely on a patient's GeneType for Ovarian Cancer results. The reliability of results for this test are dependent on the accuracy of the information provided in the clinical responses. If the responses to clinical questions change (e.g. age), the patient's risk percentages will change and risk category may also change.

Although the current test incorporates ethnic-specific incidence data, not all risk factors, such as PRS, have been optimized for ethnic-specific stratification improvements. While geneType improves risk stratification compared to current standards, ethnic-specific-improvements can still be made. Work is ongoing for ethnic-specific expansions that will further improve the calibration and discrimination of the assay across more genetic ancestries. This test is not applicable to women who have personal history of ovarian cancer or who have already been shown to have an HBOC mutation, for example in the *BRCA1* or *BRCA2* gene, or a diagnosis of a genetic syndrome that may be associated with elevated risk of ovarian cancer. In this case, the patient should be referred to a specialist for genetic counselling.

**Test Methodology:** GeneType for Ovarian Cancer uses next generation sequencing (NGS) to determine the genotype of 36 polymorphic ovarian cancer susceptibility loci. Genomic DNA is extracted from the Oragene Dx saliva kit, or GBG buccal swab kit using standard DNA extraction methods. Genomic DNA is selectively amplified and enriched using a custom Twist Bioscience panel. Sequencing is conducted on Illumina's NovaSeq 6000 Instruments, to an average coverage depth of 500X. The FASTQ files are run through the Dragen pipeline for alignment to the human reference genome (hg38), and variant calling. The polygenic risk score is calculated using a multiplicative model of ovarian cancer susceptibility combined with US Surveillance, Epidemiology, and End Results (SEER) incidence and mortality data for ovarian cancer in the United States in a proprietary algorithm to provide an absolute estimate of the 5-year and lifetime risk of developing ovarian cancer.

This test was developed and its performance characteristics determined by Gene by Gene (CLIA#45D1102202|CAP#7212851. 1445 N Loop W STE 820, Houston, TX, sample receipt, accessioning, processing) and Phenogen Sciences Laboratory (CLIA#99D2023356, sample accessioning, data interpretation and final report). It has not been cleared or approved by the United States Food and Drug Administration (FDA). The FDA does not require this test to go through pre-market FDA review. This test is used for clinical purposes. It should not be regarded as investigational or for research.

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# geneType for Ovarian Cancer Comprehensive

Your risk of developing ovarian cancer is average compared to a woman of your age and ethnicity.

Your risk of developing ovarian cancer over the rest of your life is 1.33% which is within average range of risk.

You are still at some risk of developing ovarian cancer.

There are steps you can take to reduce your risk of developing ovarian cancer. It is important to consider the risk factors you have control over; see below for more information.

**Your lifetime risk is the dominant reported risk score for this disease, although your provider may review your 5-year risk score too.*



## Understanding Ovarian Cancer Risk Factors

A risk factor is anything that may increase your chance of developing a disease. Some risk factors are strong and significantly increase your personal risk of the disease while others are weaker and only have a small impact on overall risk. Some risk factors can be modified by making changes to your lifestyle, while others are beyond your control.

**Age:** Increasing age is a strong risk factor for ovarian cancer. Most ovarian cancers occur in women over the age of 60 years, with the average age at first diagnosis being 64 years.

**Weight:** Being overweight has been shown to increase the risk of ovarian cancer.

**Genetics:** You are born with a set of genetic markers called Single Nucleotide Polymorphisms (SNPs). GeneType for Ovarian Cancer looks at your SNPs to help determine your risk of developing ovarian cancer.

**Family History:** If you have one or more relatives who have been diagnosed with ovarian cancer, this will impact your risk of developing the disease. If you have a relative who has been diagnosed with breast or colon cancer, you may also be at increased risk for ovarian cancer.

**Ethnicity:** In some populations, risk for ovarian cancer is higher.

**Smoking:** Smoking increases your risk of developing ovarian cancer as well as other types of cancer.

**Oral Contraceptives:** Use of birth control has been associated with a lower risk of ovarian cancer.

**Endometriosis:** Women with endometriosis, a chronic disease affecting tissue around the uterus, are at an increased risk for ovarian cancer.

## What You Can Do

A woman can develop ovarian cancer at any age, regardless of her level of risk. That is why it is important to know your body and discuss any unusual and persistent changes with your healthcare provider. You are your own best advocate.

## Risk Reduction

Maintaining a healthy lifestyle is a simple way to reduce your risk of ovarian cancer. For example, you can talk to your healthcare provider about strategies to help you quit smoking or maintain a healthy weight as part of your preventive ovarian cancer health plan. Based on your risk level, you and your healthcare provider can discuss appropriate risk reduction options that may be available to you.

## Screening

There are three available screening options for women at increased risk of ovarian cancer: a pelvic exam, a transvaginal ultrasound and a CA-125 blood test. Your healthcare provider will discuss the risks and benefits of all these screening options to see if one may be an option for you.

## References

The role of the obstetrician–gynecologist in the early detection of epithelial ovarian cancer in women at average risk. Committee Opinion No. 716. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e146–9.

Dite GS, Spaeth E, Murphy NM, Allman R. A combined clinical and genetic model for predicting risk of ovarian cancer. Eur J Cancer Prev 2023; 32: 57-64.

For a full list of references supporting the GeneType for Ovarian Cancer risk assessment test, please visit **www.genetype.com**