Eiira

Report on Hereditary Cancer Risk and Related Measures

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Personal data

Name: X
Customer ID: X
Sex: **Female**
Genetic Data: X
Birthday: YYYY.MM.DD
Report date: YYYY.MM.DD
Ordered product: **Eiira Premium**
Genetic test for hereditary cancer based on Whole Genome Sequence (WGS)



Table of content

Executive summary

Purpose of the report

The purpose of our hereditary genetic report is to outline the genetic and familial predispositions to cancer. By analysing genetic variation in your DNA, alongside your family history of cancer, we aim to provide a comprehensive view of your hereditary risks to ten types of cancers. In the case of increased risk, the report will also suggest ways to manage and reduce that risk.

Findings

A **pathogenic** variant was identified in the **BRCA1** gene.

Your **lifetime risk of breast and ovarian cancer** is significantly **increased** compared to the general population.

Executive summary

Measures to manage risk based on the result

Early detection	• Annual mammogram screening for breast cancer is recommended from the ages of 25 to 74, as well as annual MR imaging from the ages of 25 to 55. • Contact with a gynecologist is recommended at the age of 30 for examination of ovaries.

Note

According to Swedish national guidelines, it is recommended that women with a pathogenic variant in BRCA1, which can cause breast and ovarian cancer are included in control programs for these cancer types. The reason for this is that the risk of these cancers is greatly increased.

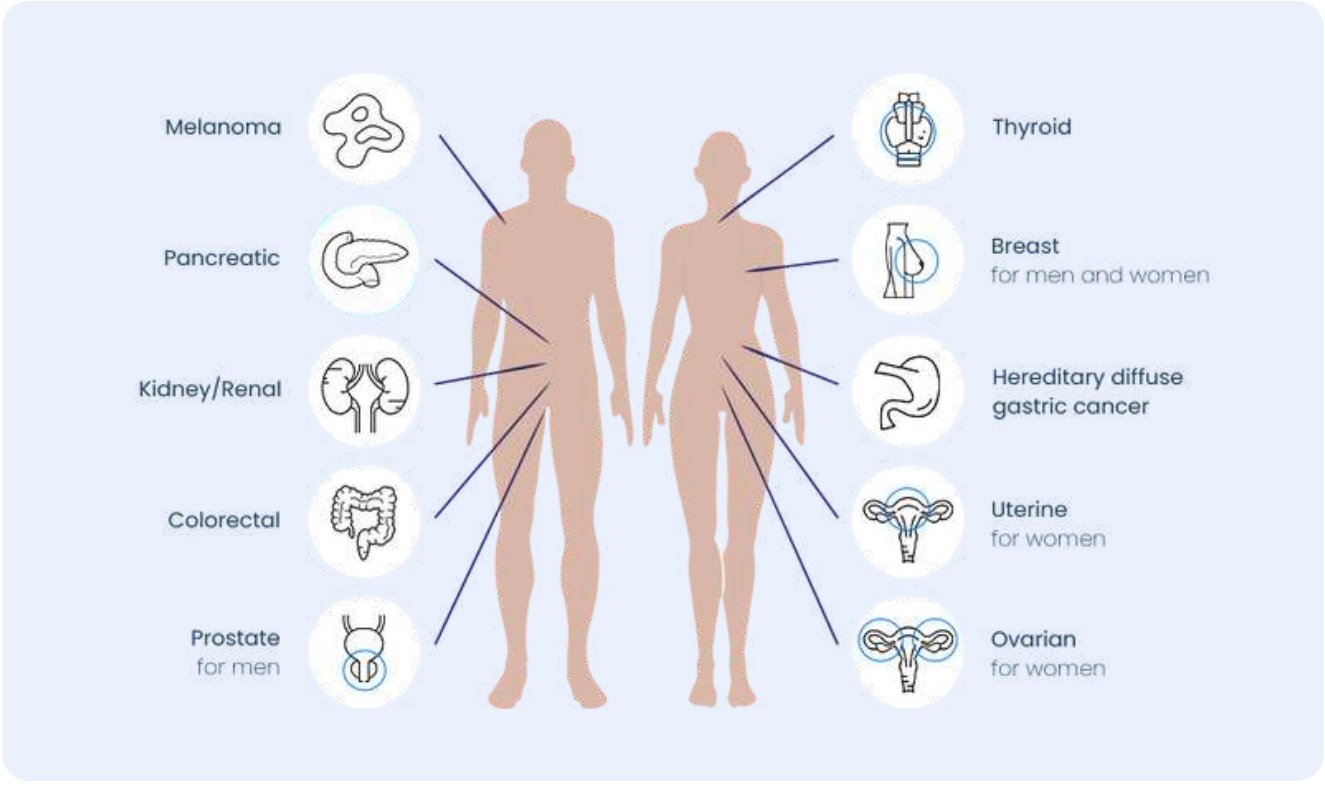
Because pathogenic variants in BRCA1 are inherited in an autosomal dominant manner, your parents, siblings and children have a 50 percent probability of being carriers. Therefore, carrier testing is recommended in your family. Female carriers also have an increased risk of gynecological cancer. A gene variant in the BRCA1 gene does not affect men as much as it affects women, however, carrier testing is recommended for men with daughters.

This genetic analysis fully captures all genetic variations in your genome (i.e. all the DNA in a single cell). In the current analysis we have looked at a subset of your genome, more specifically those genes that are associated with hereditary cancer. Therefore, this analysis does not exclude that you have a pathogenic variant in another place in your genome. However, since your genome has been fully sequenced, it enables updates on genetic findings, as well as new offerings, without a retest.

About the report

Assessment scope

For this report, we have assessed your hereditary risk of developing the cancer types illustrated in the figure below. These cancer types are known to have a hereditary component, which is linked to certain genes (see Table 1). This does not exclude that other cancer types are hereditary. However, to date, there are not any specific genes that have been associated with an increased risk of these other cancer types.



About the report

For this purpose, we have analysed 50 genes in your DNA for the absence or presence of pathogenic variants associated with an increased cancer risk. These genes were selected based on their known association with certain cancer types or cancer syndromes. The table below illustrates ten cancer types and their associated genes (i.e. genes where we know that individuals have an increased risk of developing cancer if they have a pathogenic variant).

Table 1

Cancer type	Genes associated
Breast	BRCA1, BRCA2, PALB2, TP53, PTEN, CDH1, STK11, NF1, ATM, CHEK2, BARD1, RAD51C, RAD51D
Ovarian	BRCA1, BRCA2, PALB2, RAD51C, RAD51D, BRIP1, MLH1, MSH2, EPCAM, MSH6, PMS2
Colon	MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, STK11, SMAD4, BMPR1A, PTCH, PTEN, NTHL1, POLD1, POLE, MSH3, TP53
Prostate	BRCA2, HOXB13, BRCA1, MLH1, MSH2, MSH6, EPCAM, PMS2, ATM, CHEK2, PALB2, TP53
Melanoma	CDKN2A, BAP1, CDK4, POT1, TERT, MITF1, MC1R, ASIP, TYR, TYRP1, TP53
Kidney/Renal	VHL, FLCN, FH, MET, PTEN, SDHB, BAP1, SDHA, SDHC, SDHD
Thyroid	RET, APC, PTEN, DICER1, TP53
Uterine	MLH1, MSH2, MSH6, PMS2, PTEN
Pancreatic	BRCA1, BRCA2, ATM, PALB2, MLH1, MSH2, EPCAM, MSH6, PMS2, STK11, CDKN2A
Hereditary diffuse gastric cancer	CDH1, CTNNA1

Germline (i.e. hereditary)

The genetic analysis only examines germline variation, which are the DNA variants that you were born with, specifically those that have their origin in your parents' reproductive cells (sperm and egg cells). These variants are thus inherited from a parent and can be passed on to the next generation. In some cases, a germline variant can occur in an early embryo (de Novo variant). De Novo variants can also give an increased risk of cancer but are not inherited from a parent (but can be passed on to the next generation).

The report doesn't consider somatic variants, which are spontaneous DNA changes that occur in your cells during life.

About the report

Hereditary risk and risk assessment

What is “risk”?

This report only covers **hereditary cancer risks**.

Risk is the likelihood of developing cancer and is based on population studies. It is important to understand the following:

- Risk is not the same as having a cancer diagnosis.
- Having a high risk does not mean you will definitely develop cancer. But you are more likely to develop cancer when compared to the general population.
- Conversely, even those with low risk may still develop cancer (at least one in three in the general population in Sweden will develop cancer during their life).
- An individual's perceived risk of cancer can differ from the actual risk of cancer. Individuals with a family history of cancer often overestimate their risk.

While it cannot predict the future, this profile aims to:

- Give you a better understanding of your risk of cancer.
- Inform you about risk management measures to prevent or detect cancer early.
- Help you discuss with your doctors about what to do next.

About the report

Hereditary risk and risk assessment

How does the risk assessment work?

A risk assessment is typically based on the result of the genetic test (i.e. absence or presence of a pathogenic variant) and your family history of cancer. In cases of familial risk for breast and ovarian cancers, we also use your personal health profile information in risk computation.

No pathogenic variant doesn't mean no cancer risk. While some genetic risks stem from one gene variant, known as monogenic disorders, others arise from interactions among multiple genes, known as polygenic or complex disorders. Environmental factors also influence cancer risks. Cancers like colorectal, prostate, breast, and pancreatic are particularly influenced by these polygenic elements. A genetic test alone isn't comprehensive; we incorporate family history to improve the risk assessment.

Carrying a pathogenic variant doesn't guarantee a uniform cancer risk for everyone. The estimated risk from a specific gene is based on studies of groups with that variant. Thus, an individual's risk could be higher or lower than the general estimation for that gene. By considering family history, we can provide a more accurate individual risk assessment.

From a clinical perspective, we determine if someone has a significantly increased cancer risk using **Swedish national guidelines**. These guidelines detail who qualifies for preventive actions or specialised screenings. An individual with only a moderate risk increase might just be recommended standard screenings, like mammography for women starting at age 40.

Keep in mind, that cancer risk is influenced by various factors. Our assessment focuses solely on genetic factors, so the risk outlined in this report is an estimate, not an exact measure of your true risk.

Information provided by you

The analysis performed in this report has taken the key information that is available in your account on YYYY.MM.DD.

Information about you:

- You have no personal history of cancer.
- You have Swedish ethnicity

Family tree:

List of relatives with cancer diagnosis:

- Mother: breast cancer at 51 years of age.
- Sister: ovarian cancer at 35 years of age.
- Maternal aunt: breast cancer at 40 years of age

Your results

What did your genetic test show?

A **pathogenic** variant was identified in the **BRCA1** gene.

Gen	Variant	Klassificering
BRCA1	Identification: NM_007294.4(BRCA1): c.3048_3052dup (p.Asn1018fs) Position: 17q21.31 17: 43092478-43092479 (GRCh38) Zygosity: Heterozygous HGVS: NM_007294.4:c.3048_3052dup	Pathogenic

What does this mean?

- The genetic analysis did identify a pathogenic variant in the BRCA1 gene in your DNA.
- That your lifetime risk of breast and ovarian cancer is significantly increased compared to the general population.

What is the function of the BRCA1 gene?

- The BRCA1 gene contains the instructions needed to make a functional **BRCA1 protein.**

Why is this protein important?

- The BRCA1 protein is a protein that acts as a so-called tumor suppressor, which means that the BRCA1 protein repairs damaged DNA. If the BRCA1 gene can´t make functional BRCA1 protein, as a result of a gene variant in the gene, damaged DNA cannot be repaired properly. This leads to an increased risk of breast and ovarian cancer.

Your results

What did your genetic test show?

What does having a pathogenic genetic variant in this gene mean?

- **Affects protein function:** when a gene contains a pathogenic genetic variant the protein product, for which the gene encodes, will be non-functional or have impaired function.
- **Not all with a pathogenic variant will develop cancer:** Given that we all have two copies of the BRCA1 gene, you have a functioning backup copy. However, if the backup copy also is altered in a cell (which can happen during cell division) then that cell will lack a functional BRCA1 protein. Other genetic, environmental and lifestyle factors do therefore affect the risk of developing prostate.
- **Increased Risk:** Women with a pathogenic variant in the BRCA1 gene thus have a higher probability of losing BRCA1 protein function and therefore have an increased risk of breast and ovarian cancer.

Preventive measures available: Allows for special precautions like frequent screenings.

Your results

What are your overall risks?

Based on the genetic test and your family history, your **lifetime risk of breast and ovarian cancer** is significantly **increased** compared to the general population.

What does this mean?

- That the assessment of your genetic test result, in combination with your family history of cancer, did identify an increased hereditary risk of one or several cancer types.
- This means that your risk of cancer is higher than that of the general population for one or several cancer types.

What is this risk assessment based on?

- This risk assessment is based on the genetic test as well as your family history of cancer, which includes your mother's breast cancer diagnosis at age 51, your sister's ovarian cancer diagnosis at age 35, and your aunt's breast cancer diagnosis at age 40.

Your results

The risk management options

1) Screening and monitoring

According to Swedish national guidelines the following measures are recommended:

i) Breast cancer: Screening program for breast cancer through annual mammography from age 25 to 74, together with annual MRI examination from age 25 to 55.

ii) Ovarian cancer: Contact with a gynecologist from the age of 30 to check the ovaries, and possible risk-reducing surgery of the ovaries and fallopian tubes after discussion with your gynecologist. .

2) Prevention and lifestyle factors associated with increased or decreased risk of cancer

- Participate in recommended control programs for breast to facilitate early detection of cancer.
- Examine your breasts monthly. This facilitates early detection of any potential changes in your breasts, for example, using Cancerfonden's self-exam guide "Lär känna dina bröst"
- Avoid smoking. Tobacco contains carcinogenic chemicals, making it a risk factor for cancer development.
- Reduce or avoid alcohol consumtion. When alcohol is broken down in the body, a chemical called acetaldehyde is produced, which is carcinogenic.
- Try to eat no more than 500g of cooked red and smoked meat per week. This because these icontains nitrite, which in the body degrades into nitrosamines, which are carcinogenic.
- Maintain a healthy weight. The association between weight and cancer is not fully known, however, observational studies has shown a correlation between obesitas and cancer development.
- Stay physically active. An inactive lifestyle has been associated to development of various cancer types, among these is breast cancer.
- Breastfeeding, if you have this option can in some individuals help reduce the breast cancer risk

Your results

Actions to be taken

Personal

- Contact your primary health care service in order to be referred to controls for above mentioned cancer types (you can bring this report to your doctor). Note that it may be so that the cancers in your family need to be verified first, which is done as part of an hereditary assessment at an oncogenic clinic or clinical genetics. Please read more in the section Available measures to manage your increased risk of cancer at the end of the report.

Your family

- Inform family members that they may also have an increased risk of above mentioned cancer types. Please read more in the note below regarding which family members this concerns.
- Inform family members that there is hereditary cancer in your family and that family members are recommended to get a genetic test.

Additional information regarding how this result may affect your family member can be found in the section Implication for family members at the end of the report.

Note

Pathogenic variants in BRCA1 increaseS the risk of breast and ovarian cancer. Therefore, these types of cancer affects individuals with breasts and ovaries. Breast cancer, on the other hand, can affect men, although this is unusual, and hence no breast control programs are available for men with this gene mutation. All males, however, are encouraged to check their breasts themselves.

Because pathogenic variants in BRCA1 are inherited in an autosomal dominant manner, your parents, siblings and children have a 50 percent probability of being carriers of the same variant. Therefore, carrier testing is recommended in your family.

Information about the general population

For your reference, we provide you below the cancer risks, monitoring/screening and prevention information about the general population.

The average cancer risks for women:

To help you understand the below table, here is an example: **Breast, 9.4%** and **<80**, it signifies that among 1000 women, 94 are likely to develop breast cancer before they reach 80 years of age.

Cancer type	< 40 years	< 50 years	< 60 years	< 70 years	< 80 years
Breast	0.43%	1.9%	4.2%	7.5%	9.4%
Colorectal	0.05%	0.16%	0.44%	1.2%	1.9%
Ovarian	0.07%	0.17%	0.42%	0.81%	0.95%
Uterine	0.01%	0.02%	0.06%	0.12%	0.16%
Melanoma of skin	0.29%	0.63%	1%	1.6%	2.2%
Pancreatic	0.01%	0.63%	0.14%	0.44%	0.68%

Sources: Nordcan

The risk management option:

The following options are recommended by national guidelines in Sweden.

1) Screening and monitoring

While screening does not prevent cancer, early detection significantly increases the chances of recovery and survival. In Sweden, the following screening options are automatically offered to women:

- **Breast cancer:** mammography is offered to all women aged 40 - 74 years, at least every two years.
- **Cervical cancer:** cell sampling every five years for women aged 23 - 49 years and every seven years for women aged 50 - 70 years.
- **Colon and rectal cancer:** within a few years, everyone aged 60 - 74 years will be offered screening for this type of cancer every two years.

Source: Cancerfonden (https://www.cancerfonden.se)

Information about the general population

2) Prevention and lifestyle

According to Cancerfonden, **23.1 % of all cancers** are caused by **preventable factors**.

While there are no guaranteed ways to avoid cancer completely, you have the power to make a positive impact. It may sound cliche, but participating in screening programs and being mindful of your physical activity, diet and lifestyle can play an important role.

Every lifestyle change you make to reduce the risk helps!

Source: Cancerfonden (https://www.cancerfonden.se)

Changes that help to reduce the risk

Avoid smoking

Maintain healthy weight.

Reduce or avoid
alcohol consumption

Stay physically active

Try to eat no more than 500g
of cooked red meat per week
and avoid smoked meats

Breastfeeding
(if you have this option)
can help reduce breast cancer
risk

Source: RCC (https://cancercentrum.se)

Disclaimers

Eiira is not responsible for errors in the genetic data provided by you.

This report is based on a statistical analysis of the data provided and should be viewed as a preliminary guide to potential hereditary predispositions.

The data from ancestry genetic tests only represents a fraction of the entire genome. As such, the accuracy and comprehensiveness of this report are inherently limited.

This document is not a substitute for medical advice, diagnosis, or treatment. Always consult with a healthcare professional for personalised guidance. We strongly recommend more in-depth genomic testing, such as Eiira Classic (WES) or Eiira Premium (WGS), for a thorough and reliable assessment of hereditary cancer risks.

Available measures to manage your increased risk of cancer

According to our assessment, you have an increased risk of cancer that qualifies you for measures that are beyond what is offered as part of national screening programs. Depending on where in Sweden that you live, there are different ways to get access to these measures (read more below).

Please note that the assessment regarding your familial risk is made by information provided by you, i.e. the information has not been verified in hospital records. Thus, your healthcare provider may require that you undergo a hereditary assessment in order to get access to these measures.

Stockholm-Gotland region

- All measures are coordinated through 'Mottagning för Ärftlig Cancer' at Karolinska University Hospital in Solna. They can be contacted by phone on the number 08-123 783 80, or through the app 'Alltid Öppet', which can be downloaded from Google Play and App Store. More information can be found on 1177.

Northern region

- In most cases, your primary health care service is the one responsible for referring you to the appropriate measures. It may be so that they initially require that a hereditary assessment is made, which is done by the 'Cancergenetisk mottagningen' at Umeå University Hospital. This will require a referral from your primary health care service. More information can be found on 1177.

Middle Sweden region

- In most cases, your primary health care service is the one responsible for referring you to the appropriate measures. It may be so that they initially require that a hereditary assessment is made, which is either done by 'Klinisk genetik mottagningen' at Örebro University Hospital or 'Onkogenetiska mottagningen' at Akademiska Hospital in Uppsala. This will require a referral from your primary health care service. More information can be found on 1177: Klinisk genetik mottagning in Örebro or Onkogenetiska mottagningen in Uppsala.

Southeast region

- In most cases, your primary health care service is the one responsible for referring you to the appropriate measures. It may be so that they initially require that an hereditary assessment is made, which is done by 'Klinisk Genetik" at Linköping University Hospital. This will require a referral from your primary health care service. More information can be found on 1177.

Available measures to manage your increased risk of cancer

Western region

- In most cases, your primary health care service is the one responsible for referring you to the appropriate measures. It may be so that they initially require that a hereditary assessment is made, which is done by the 'Cancergenetisk mottagning' at Sahlgrenska University Hospital. This will require a referral from your primary health care service or a self-referral. More information can be found on 1177.

Southern region

- In most cases, your primary health care service is the one responsible for referring you to the appropriate measures. It may be so that they initially require that a hereditary assessment is made, which is either done by 'Klinisk genetik mottagningen' at Örebro University Hospital or 'Onkogenetiska mottagningen' at Akademiska Hospital in Uppsala. This will require a referral from your primary health care service. More information can be found on 1177: Klinisk genetik mottagning in Örebro or Onkogenetiska mottagningen in Uppsala.

Implication for family members

It is important that you inform your relatives that they as well may have an increased risk for cancer that qualifies them for the same measures as you do, given that some of your relatives may be carriers of the same pathogenic variant that was identified in your DNA.

Please note that Swedish law prohibits Eiira, as well as healthcare, from contacting your relatives. We therefore recommend that you inform your relatives, so that they may have the opportunity to be proactive in their cancer risk assessment. The choice to do so is your own.

Test method

Eiira uses Next Generation Sequencing (NGS) to analyse your DNA. First, genomic DNA was extracted from buccal epithelial cells and white blood cells in the saliva provided by the customer. Second, the specific regions of interest (i.e. all coding parts of your genome) were amplified and then sequenced on an Illumina NovaSeq 6000 instrument. Third, The sequencing reads were then mapped to the reference genome, after which different and precise bioinformatic tools are used to identify genetic variants. This was done by using the Illumina DRAGEN platform. Lastly, genetic variants from a selected number of genes (see table below) were interpreted by using an ISO 13485 accredited interpretation software. Results are reported as positive if a pathogenic variant is detected.

Gene table

APC, ASIP, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, DICER1, EPCAM, FH, FLCN, HOXB13, MC1R, MET, MITF1, MLH1, MSH2, MSH6, MUTYH, NF1, PALB2, PMS2, POT1, PTCH, PTEN, RAD51C, RAD51D, RET, SDHB, SMAD4, STK11, TERT, TP53, TYR, TYRP1, VHL, NTHL1, POLD1, POLE, MSH3, SDHA, SDHC, SDHD