


# MammoRisk® v2.7.6

## Instruction manual

Version 4 (Date September 2023)

MammoRisk®   
2018

Manufacturer: Société Predilife, Institut Gustave Roussy,  
39 rue Camille Desmoulins, 94800 Villejuif

## Table of content

<b>1</b>	<b><i>Introduction</i></b> .....	<b>3</b>
1.1.	<b>Aim</b> .....	<b>3</b>
1.2.	<b>Scope of the software</b> .....	<b>3</b>
1.3.	<b>Contraindications and warning</b> .....	<b>4</b>
1.4.	<b>Labellings standard</b> .....	<b>4</b>
1.5.	<b>CE marking</b> .....	<b>4</b>
1.6.	<b>Users training</b> .....	<b>5</b>
1.7.	<b>Logotypes meaning</b> .....	<b>5</b>
<b>2</b>	<b><i>Installing the software</i></b> .....	<b>6</b>
2.1	<b>Compatible browsers</b> .....	<b>6</b>
2.2	<b>Start a new session</b> .....	<b>6</b>
2.3	<b>Interface language</b> .....	<b>7</b>
2.4	<b>Contact us</b> .....	<b>8</b>
<b>3</b>	<b><i>Risk module</i></b> .....	<b>9</b>
3.1	<b>Patient’s data record</b> .....	<b>9</b>
3.2	<b>Preliminary questions (specific cases)</b> .....	<b>11</b>
3.3	<b>Risk estimation for women the general population (MammoRisk® score)</b> .....	<b>14</b>
3.4	<b>Personalized follow-up program</b> .....	<b>21</b>
3.5	<b>Personalized result report</b> .....	<b>22</b>
3.6	<b>Update patient profile</b> .....	<b>23</b>
3.7	<b>Specific cases</b> .....	<b>24</b>
3.8	<b>Other available information</b> .....	<b>24</b>
<b>4</b>	<b><i>Appendices</i></b> .....	<b>29</b>
	<b>Appendix 1: Related publication</b> .....	<b>29</b>
	<b>Appendix 2: Default recommendations</b> .....	<b>30</b>
	<b>Appendix 3: MyPeBS study</b> .....	<b>31</b>
	<b>Appendix 4: Results report</b> .....	<b>32</b>
	<b>Appendix 5: Other risk scores for high-risk populations</b> .....	<b>34</b>
	Eisinger Score (only validated in France) .....	<b>34</b>
	Tyrer-Cuzick score .....	<b>36</b>

# 1 Introduction

## 1.1. Aim

The aim of this document is to provide a detailed description of how to use the MammoRisk® software, in terms of its workflow and configuration.

## 1.2. Scope of the software

The breast cancer risk module provides, for women in the general population, a risk evaluation based on Predilife's nearest neighbor search algorithm. For other women, previously identified as being at high-risk for breast cancer, different risk scores or recommendations linked to the specifics of their case are proposed.

MammoRisk® does not help interpret or diagnose, it provides supplementary information to enable the physician to estimate breast cancer risk and to adapt the screening tests for each patient.

### **Indications for use**

MammoRisk software evaluates the risk for a woman of developing a breast cancer.

MammoRisk software is intended to provide information about the patient's risk of developing breast cancer.

MammoRisk software output is a synthesis report with patient's risk and graph that facilitates the visualization of the patient risk level in relation to the general population

### **Intended users**

The users of MammoRisk software are healthcare professionals with scientific background and medical knowledge in BC risks, screening and prevention.

The intended target group of MammoRisk are asymptomatic women of 40 and over, with no previous breast cancer and who do not belong to the high-risk population of developing a breast cancer

### **Intended clinical use**

MammoRisk shall be used for patients of 40 years-old or over, which do not belong to the high-risk population of developing a breast cancer, and who are asymptomatic of breast cancer when the MammoRisk test is performed.

## 1.3. Contraindications and warning

Mammorisk® is a software that does not expose the user or the patient to any immediate danger: it can be used as often and for as long as necessary, at any time and with any setting set by the user.

The following patients are not eligible for MammoRisk®:

- women with a personal history of breast cancer,
- women with a personal history of ovarian cancer,
- women who have undergone thoracic radiation,
- women with a previous biopsy with high-risk lesions on the breast, or women under 40 years-old

## 1.4. Labellings standard

Warning: This medical device is a healthcare product which has had, regarding the regulations, the CE marking since 2018

## 1.5. CE marking

The MammoRisk® software obtained the CE marking in 2018.

MammoRisk® is a class I device, manufactured by Predilife. It is designed to estimate the risk of breast cancer.

MammoRisk® has been verified and validated according to the company's software testing procedure, and according to the standard EN 62304. A risk analysis in

compliance with the standard EN ISO 14971 has been provided. The software tests included unit tests and integration tests.


## 1.6. Users training


Users of the MammoRisk® software must have undergone training. If this training course has not been given to the person in charge of using the software, please contact us (see the “contact us” section).

## 1.7. Logotypes meaning

 Unique device identification


 Medical device


 Manufacturer's name and address

 Software identification

 Software version number

 Special instructions for use

 CE marking

 Manufacturing date

## 2 Installing the software

### 2.1 Compatible browsers

The software functions in client-server mode. To use the software and open the interface on the user workstation, a compatible Windows (XP, 7, 8 or 10) or MacOS from 10.9 and a web browser is required:

- Mozilla Firefox, version 32 or higher
- Google Chrome, version 33 or higher
- Microsoft Internet Explorer version 11 or higher
- Microsoft Edge
- Apple Safari 11 or higher

### 2.2 Start a new session

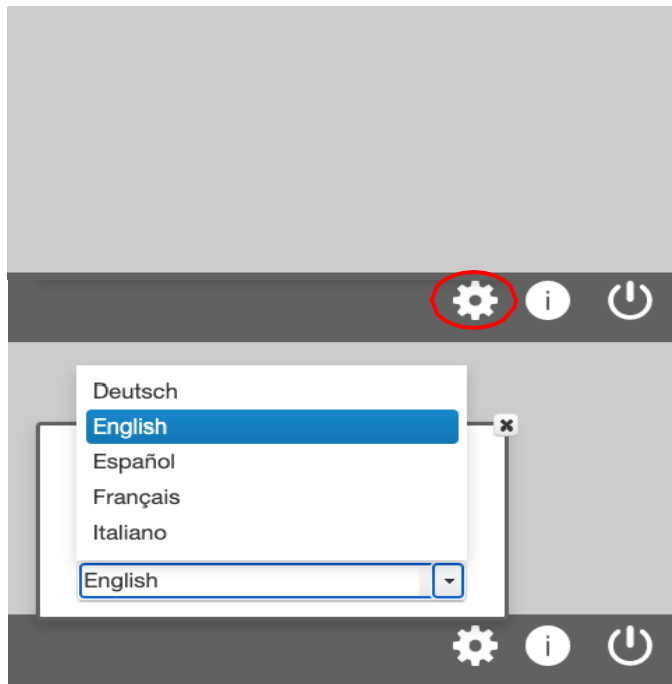
The default browser must be open and if it is compatible, the software interface will be displayed on the screen, after the user name and password have been entered.



## 2.3 Interface language

By default, the interface language chosen is the one set on the browser. It is possible to modify the language used:

1. By accessing the settings via the cogwheel icon situated in the bottom right of the interface:



2. By clicking on the desired language  
The following language are available:

- French
- German
- English
- Spanish
- Italian


Changing the language of the interface does not affect the breast cancer risk estimation. This modification is saved by the browser.


## 2.4 Contact us


To carry out new setting request, please contact us via this address: [support@predilife.com](mailto:support@predilife.com).



To inform us of any errors, after clicking on the “i” button at the bottom of the page, it is possible to click on the sentence “If you wish to make a complaint or report an error” and access the screen to report an error.


### ABOUT THE SOFTWARE


 UDI


 MD


 **MammoRisk V2.7**


 **v2.7.6**  **2022-07-25**


 Statlife SAS  
Institut Gustave Roussy  
39 rue Camille Desmoulins  
94800 Villejuif  
FRANCE

 [Click here to read the user manual](#)

 [Click here to read the general terms and conditions](#)

 [Click here to read the reference publication](#)

 [Click here to read the risk categories and screening recommendations defined by default](#)

 Copyrights and licenses

©

If you have a reclamation concerning the software or an error to report





## ERROR REPORT FOR THE SOFTWARE MAMMORISK

Name of the medical office:

Name

Version of MammoRisk:

1.0

Type of problem met with:

- Non-functional (understanding difficulty, bad use or interpretation of the results)
- Technical (Functioning fault, breakdown or computing bug)
- Other/Doesn't know

Is it an error due to the expiration date of the software ?

- Yes
- No
- Other/Doesn't know

# 3 Risk module

Following the options chosen by the client, MammoRisk® offers different risk scores:

For women between 40 and 74 years old belonging to the general population:

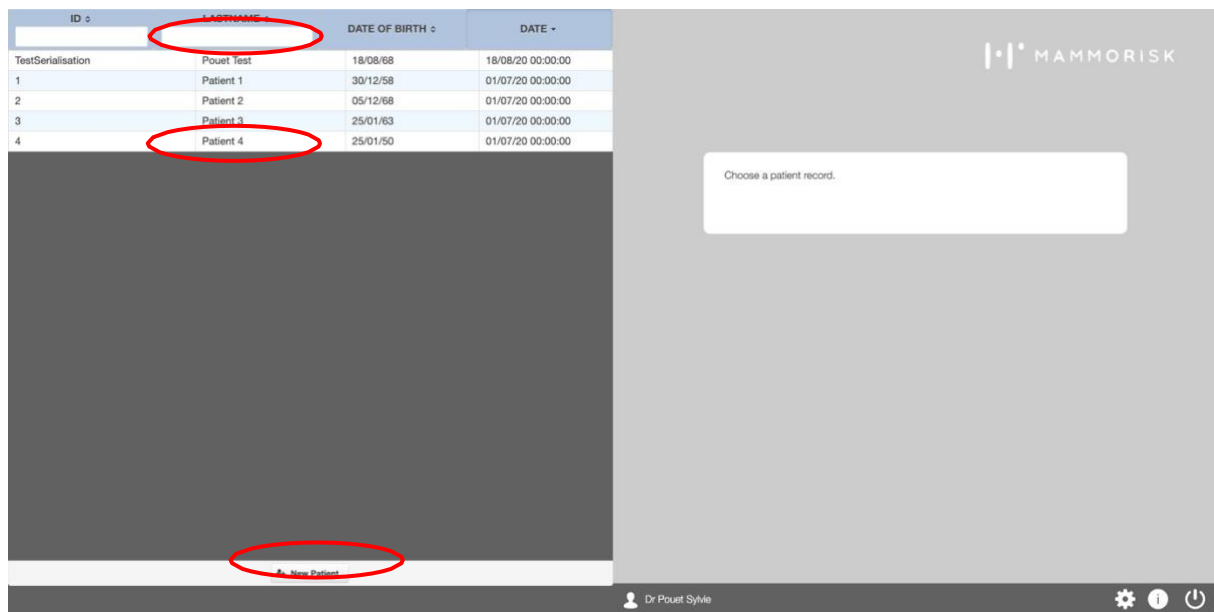
- The MammoRisk® risk score (for the general population of women aged between 40 and 74)

For women with a significant family history of breast or ovarian cancer:

- For France only: the Eisinger score (analysis of the family tree to validate or not the oncogenetic consultation). (**See Appendix 5: Other risk scores for high-risk populations**).
- The Tyrer-Cuzick score (estimation of breast cancer risk advised in a context of high family risk. (**See Appendix 5: Other risk scores for high-risk populations**).

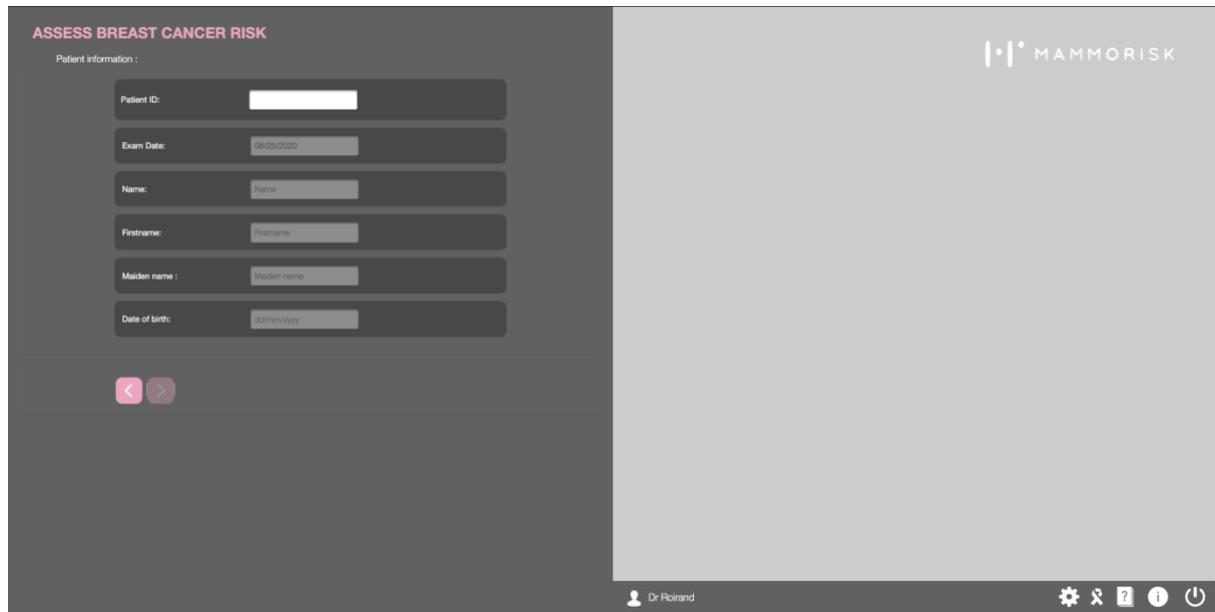
## 3.1 Patient's data record

To assess the risk of breast cancer for a new patient, a patient record must first be created: click on the “New Patient” button.



It is then necessary to provide various information (last name, first name, date of birth and patient ID if available).

When the user creates a new patient record, it is automatically saved in the list of records, accessible on the left screen. To access a previously saved patient record, simply click on it in the drop-down list. It is also possible to search it by patient ID or patient name.



**ASSESS BREAST CANCER RISK**

Patient information :

Patient ID:

Exam Date: 09/25/2020

Name:

Firstname:

Maiden name :

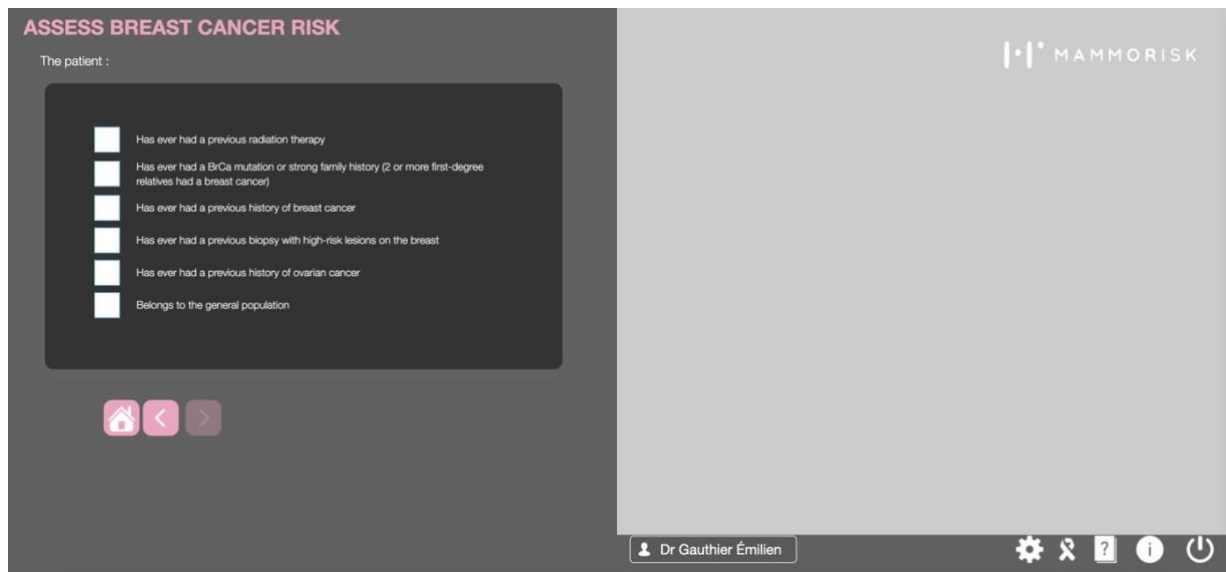
Date of birth:

< >

MAMMORISK

Dr. Roland

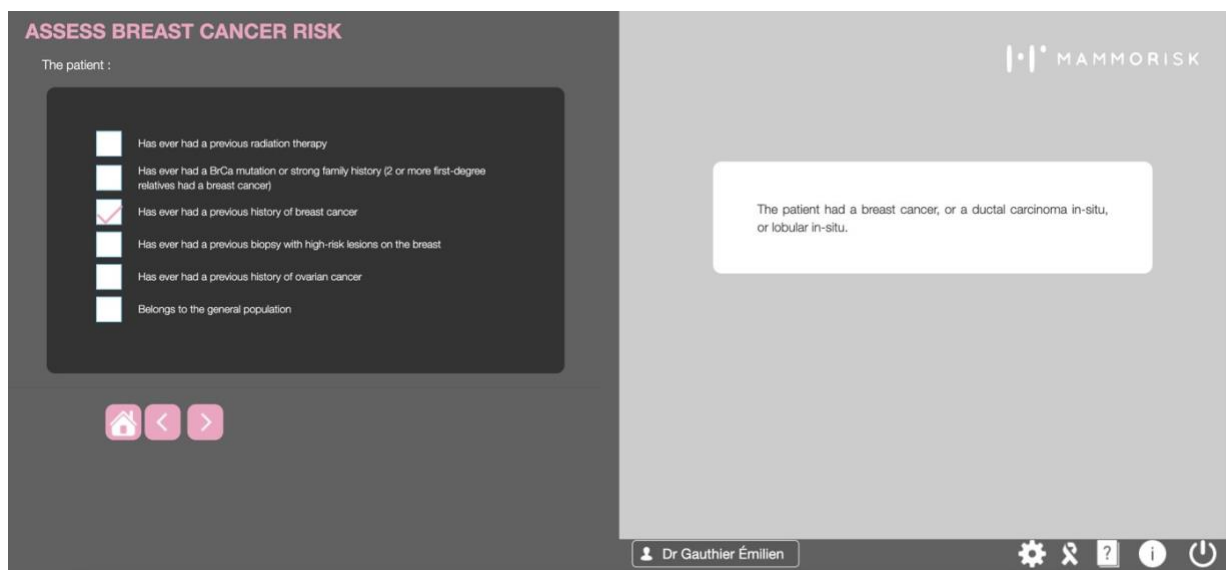
## 3.2 Preliminary questions (specific cases)



The preliminary questions screen allows you to check if the patient belongs to the general population and therefore if she is eligible for the MammoRisk® score.

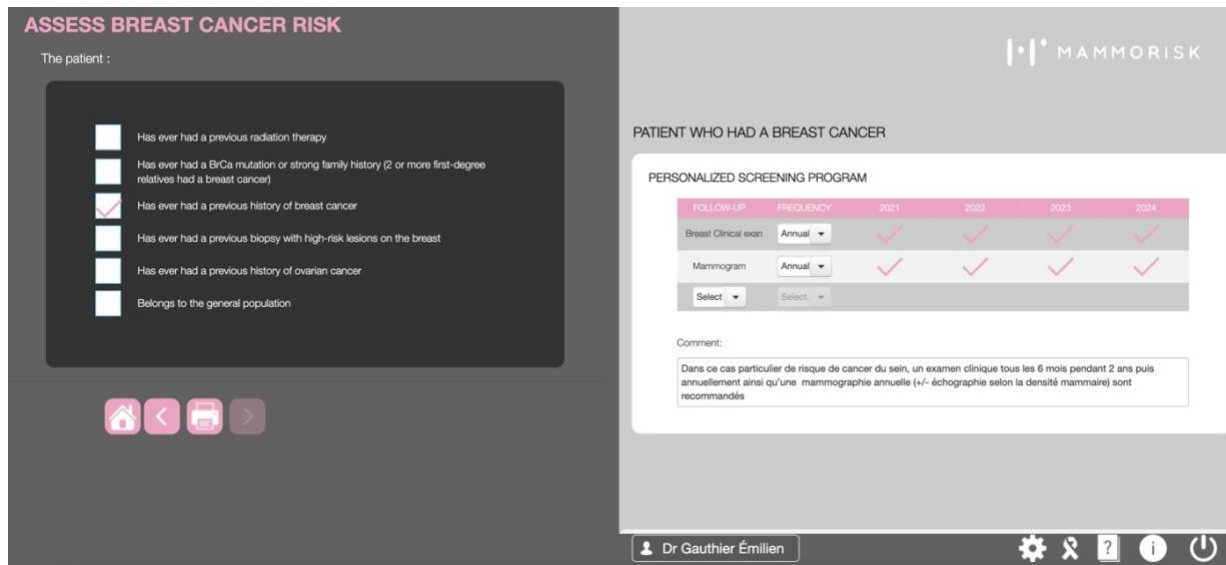
The following patients are not eligible for MammoRisk®:

- women with a personal history of breast cancer,
- women with a personal history of ovarian cancer,
- women who have undergone thoracic radiation,
- women with a previous biopsy with high-risk lesions on the breast,



Patients with a personal history of breast cancer, who have undergone thoracic radiation, or with a history of atypical hyperplasia of the breast are associated with a

specific risk category (high or very high). Follow-up recommendations are suggested based on official recommendations (**see Appendix 2 : Default recommendations**)



**ASSESS BREAST CANCER RISK**

The patient :

- Has ever had a previous radiation therapy
- Has ever had a BRCA mutation or strong family history (2 or more first-degree relatives had a breast cancer)
- Has ever had a previous history of breast cancer
- Has ever had a previous biopsy with high-risk lesions on the breast
- Has ever had a previous history of ovarian cancer
- Belongs to the general population

**MAMMORISK**

PATIENT WHO HAD A BREAST CANCER

PERSONALIZED SCREENING PROGRAM

FOLLOW-UP	FREQUENCY	2021	2022	2023	2024
Breast Clinical exam	Annual	✓	✓	✓	✓
Mammogram	Annual	✓	✓	✓	✓
Select	Select				

Comment:

Dans ce cas particulier de risque de cancer du sein, un examen clinique tous les 6 mois pendant 2 ans puis annuellement ainsi qu'une mammographie annuelle (+/- échographie selon la densité mammaire) sont recommandés

Dr Gauthier Émilien

For patients with a significant family history on the father's or mother's side, namely:

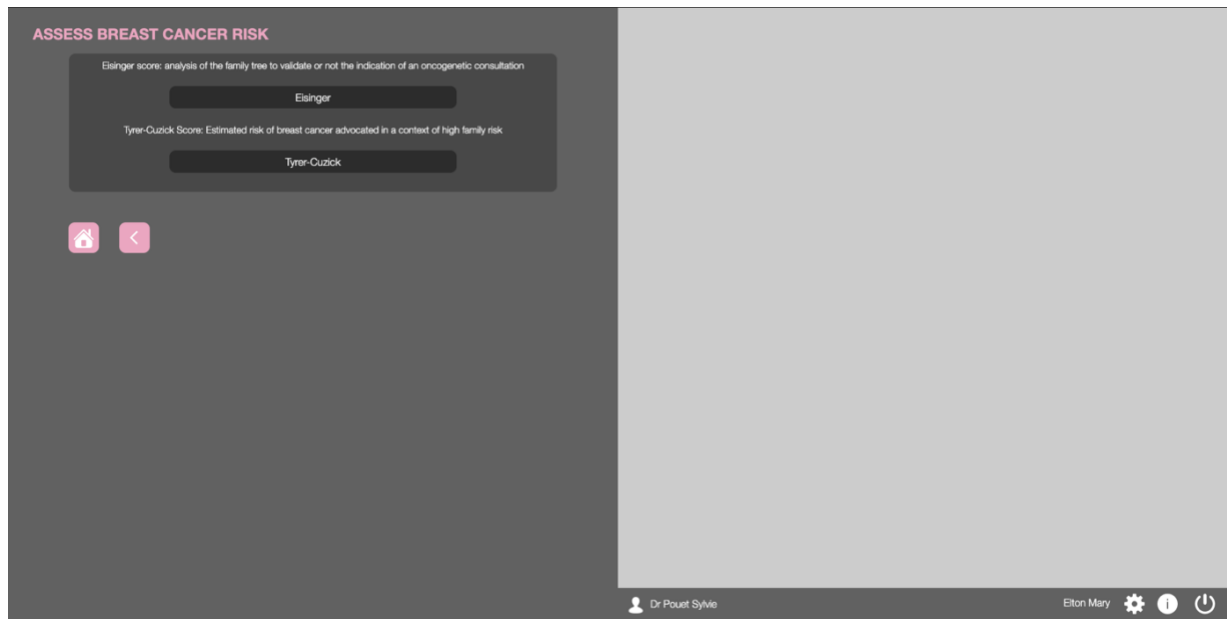
- BRCA1 or BRCA2 mutations,
- Breast cancer in a woman under 40 years old,
- Breast cancer in a man,
- Ovarian cancer,

The Eisinger (in France) or Tyrer-Cuzick score can then be offered.

The Tyrer-Cuzick score gives a % risk of developing breast cancer at 5 years.

For France, the Eisinger score validates or not the indication of an oncogenetic consultation. (**See Appendix 5 : Other risk scores for high-risk populations**).

- If the Eisinger score  $< 3$ , then the patient belongs to the general population. She is eligible for risk calculation with the MammoRisk® score.
- If the Eisinger score  $\geq 3$ , according to the HAS recommendations, the patient is advised to make an appointment with an oncogeneticist.

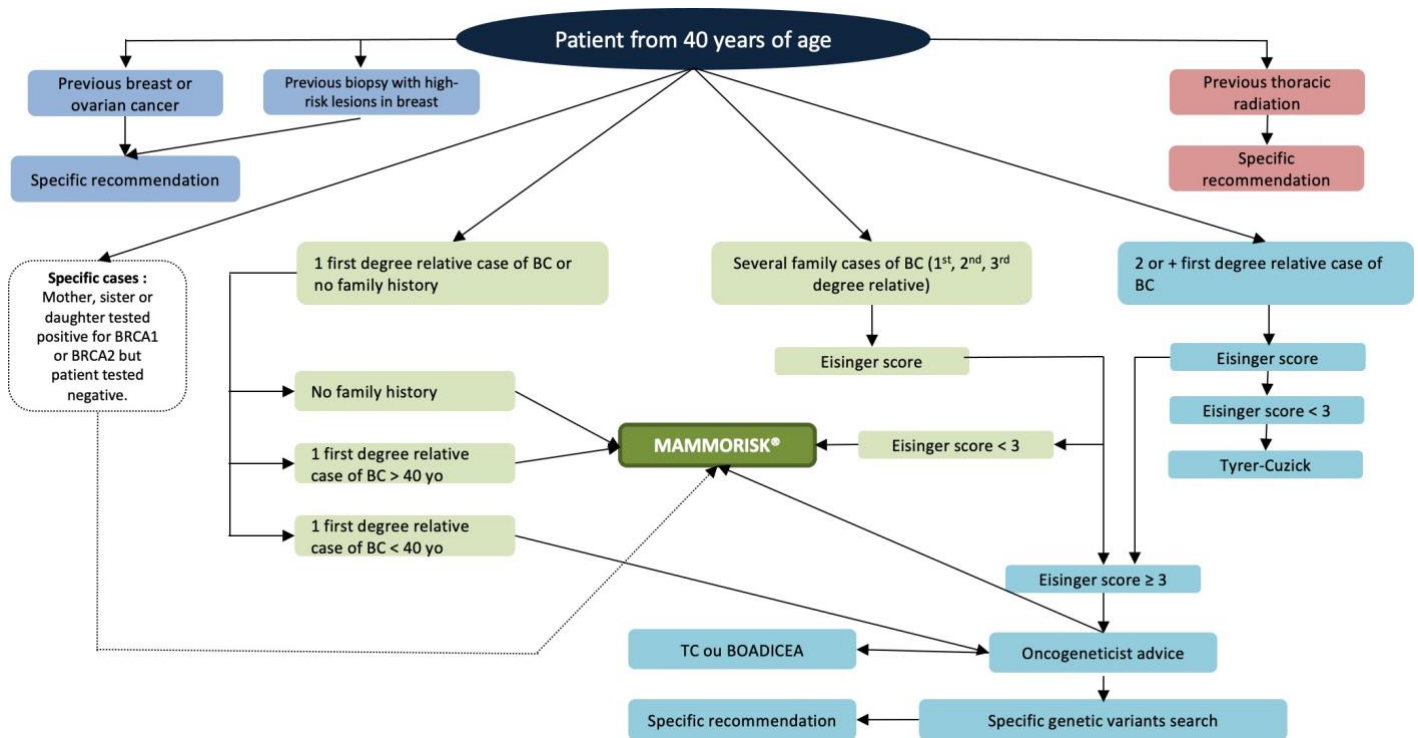


The use of the Eisinger score is recommended by the HAS. It has only been validated on a French population and is not adapted for other countries.

If the patient does not belong to the categories mentioned, then the user can select "belongs to the general population" and click on the pink arrow to go to the next screen and reach the MammoRisk® risk calculation screen.

The risk for patients under 40 yo or over 74 yo (in the absence of other specific conditions) is not calculated because the MammoRisk score has not been validated for these age groups.

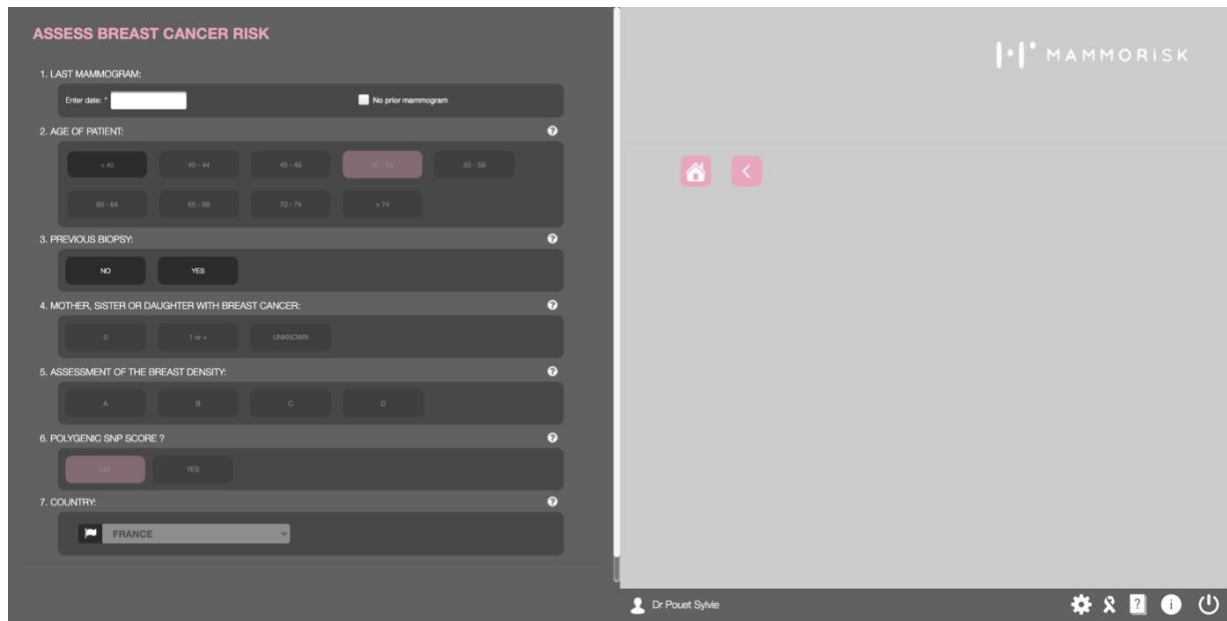
**MammoRisk® indications diagram:**



**3.3 Risk estimation for women the general population (MammoRisk® score)**

MammoRisk® estimates the 5-year risk of breast cancer for the general population based on 5 criteria:

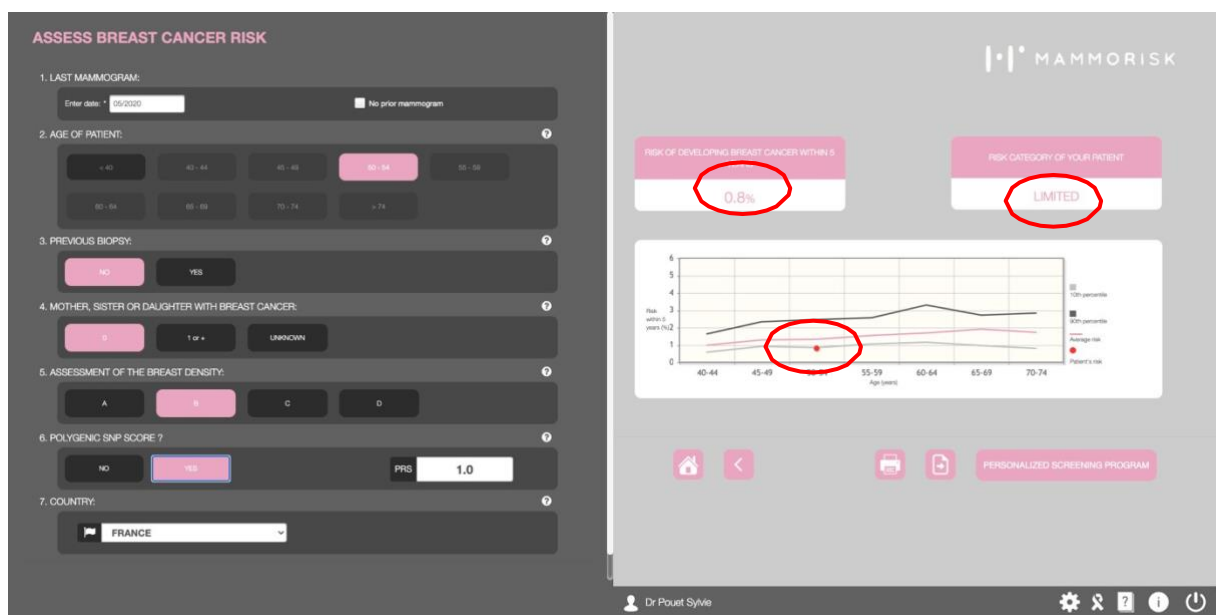
- Patient’s age
- Family history (first degree)
- Biopsy history
- Breast density
- Polygenic risk score



After completing this information, the patient's 5-year breast cancer risk is automatically assessed.

According to the risk thresholds proposed by the experts of the MyPEBS study, a risk category (limited, intermediate, high, very high) is assigned according to the estimated risk. A figure representing the patient's assessed risk relative to the average risk of women in her age category is also provided. The red dot represents the patient's estimated risk. Follow-up recommendations from the MyPeBS study are proposed (**see Appendix 2: Default recommendations**).

The information entered is automatically saved in the patient's file.



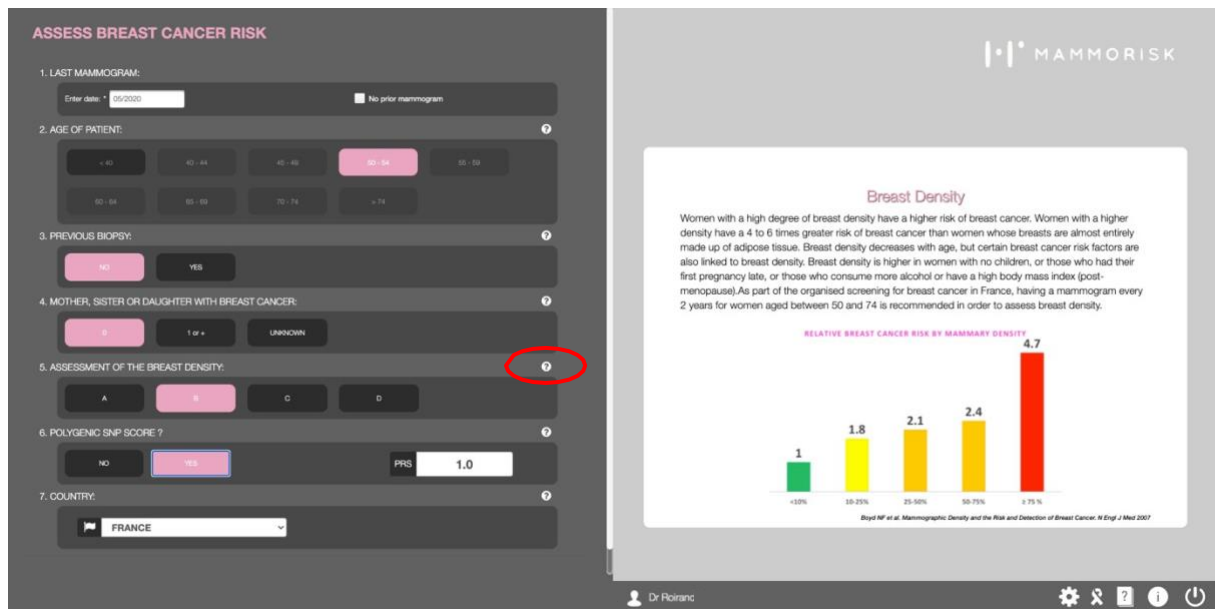


Entering information concerning the date of prior mammogram displays the month and year of exams scheduled in the personalized follow-up protocol.



Training in the use of MammoRisk® software is required to avoid errors in filling out the questionnaire.

More information about risk factors used in the MammoRisk® risk calculation is available when the user holds the mouse cursor over the “question mark” button to the right of every criterion used (marked in red in the image below).



**ASSESS BREAST CANCER RISK**

1. LAST MAMMOGRAM:  
Enter date: 09/2020  No prior mammogram

2. AGE OF PATIENT:  
1-10 11-20 21-30 31-40 41-50 51-60 61-70 >70

3. PREVIOUS BIOPSY:  
 NO  YES

4. MOTHER, SISTER OR DAUGHTER WITH BREAST CANCER:  
 0  1 or +  UNKNOWN

5. ASSESSMENT OF THE BREAST DENSITY: ?  
 A  B  C  D

6. POLYGENIC SNP SCORE ?  
 NO  YES PRS: 1.0

7. COUNTRY:  
FRANCE

**Breast Density**

Women with a high degree of breast density have a higher risk of breast cancer. Women with a higher density have a 4 to 6 times greater risk of breast cancer than women whose breasts are almost entirely made up of adipose tissue. Breast density decreases with age, but certain breast cancer risk factors are also linked to breast density. Breast density is higher in women with no children, or those who had their first pregnancy late, or those who consume more alcohol or have a high body mass index (post-menopause). As part of the organised screening for breast cancer in France, having a mammogram every 2 years for women aged between 50 and 74 is recommended in order to assess breast density.

**RELATIVE BREAST CANCER RISK BY MAMMOGRAPHY DENSITY**

Mammography Density	Relative Breast Cancer Risk
<15%	1
15-25%	1.8
25-50%	2.1
50-75%	2.4
>75%	4.7

Bloyd NP et al. Mammographic Density and the Risk and Detection of Breast Cancer. N Engl J Med 2007

Dr Polranc

### **Estimation method of breast cancer risk:**

MammoRisk® risk estimation is based on the nearest neighbor *Machine-Learning* algorithm. Based on the patient's profile, MammoRisk® searches the database for its "neighbors", i.e., those who have similar characteristics prior to their cancer: age, breast density, family history, etc.

Among the patient's neighbors, after 5 years, a few women have been diagnosed with breast cancer. If, for example, the algorithm finds that 11 out of 1000 'neighbors' with similar characteristics have developed breast cancer after 5 years, the patient's breast cancer risk is estimated to be 1.1%.

The model has been developed and validated on a population of women from the American screening population (1 million women from the Breast Surveillance Cancer Consortium). MammoRisk® has also been exported and validated on a French cohort of women (350,000 women of the E3N cohort). The model can be exported from one country to another by adjusting for local breast cancer incidence.

The source used to obtain the local incidence of breast cancer is indicated in the MammoRisk® report.



**MAMMORISK**

Patient:	Last mammogram : 10/2019
Françoise DUPONT	Age: 55-59 years-old
Exam Date: 21/01/2021	Mother, sister or daughter with a breast cancer: 0
	Previous biopsy: no
	Breast density assessment: Scattered areas of fibroglandular density (B)
	PRS: not available

**PERSONALIZED RESULTS MAMMORISK**

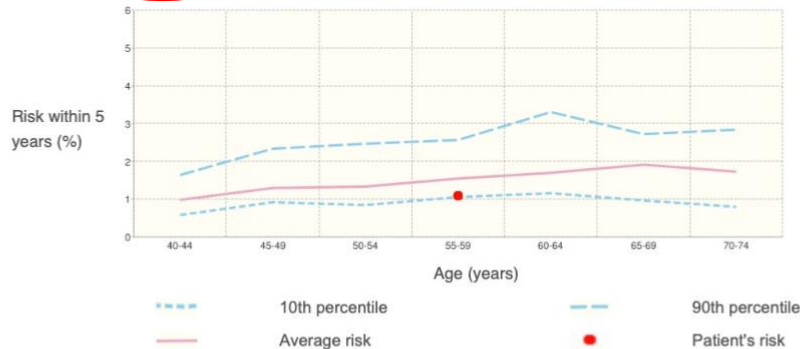
Your doctor has offered you an estimate of your individual risk of breast cancer in the years to come. This evaluation may potentially allow each woman to undergo more personalised screening for breast cancer.

This document is drawn up based on your personal and family medical history. As such, any new events can modify these recommendations. In any case, these recommendations should be reviewed at least every 5 years.

**Breast cancer risk assessment**

According to the data collected, your risk of developing breast cancer in the next 5 years is 1.1 %. This means that, of the 100 women with the same characteristics as you, between 1 or 2 women out of these 100 may develop breast cancer in the next 5 years.

For your information, the average risk of developing breast cancer within 5 years for a woman of the same age as you in the general population is 1.5 %.



**Personalized screening program**

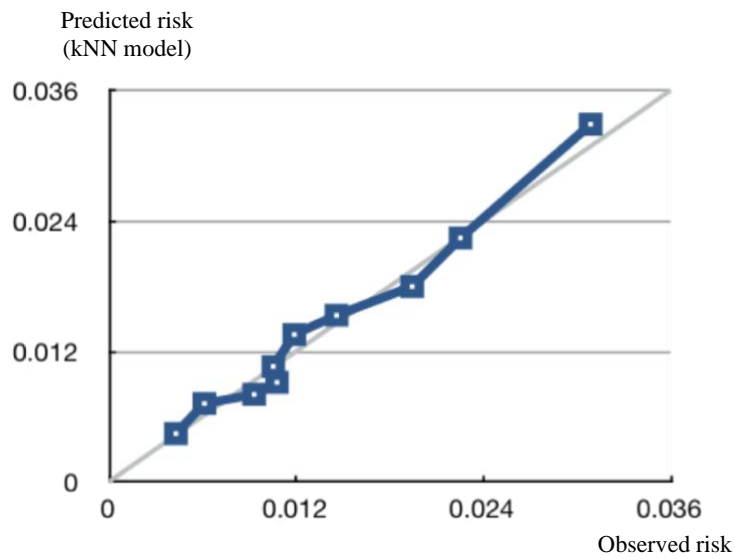
Your personalised screening programme allows you to have an easy overview of how often you will need to be examined, and this depends on an assessment of your risk.

FOLLOW-UP	FREQUENCY	10/2021	10/2022	10/2023	10/2024
Breast Clinical exam	Annual	✓	✓	✓	✓
Mammogram	Every two years	✓		✓	

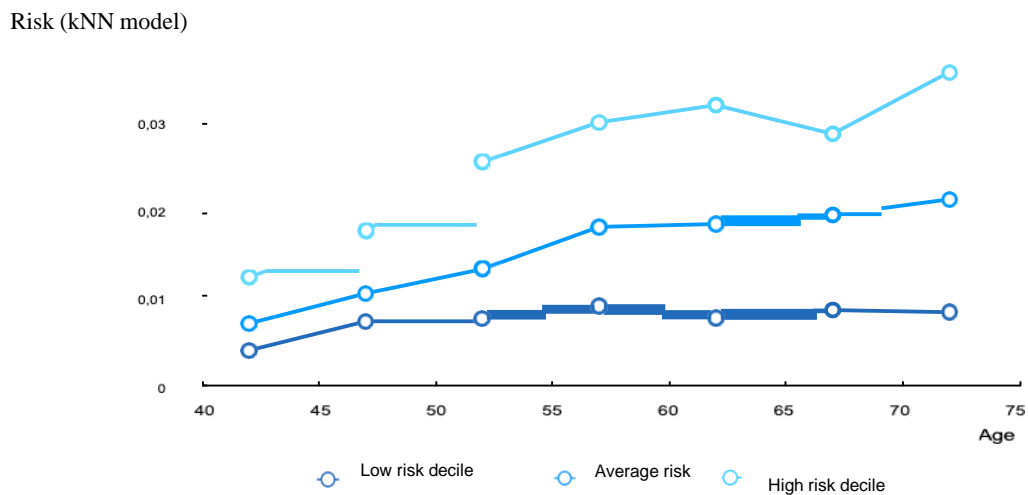
Selon les informations fournies, un examen clinique annuel et une mammographie tous les 2 ans (+/- échographie selon la densité mammaire) sont recommandés à partir de 40 ans

Institut National du Cancer, France 2018

**Summary of clinical results (see Appendix 1: Related publication for references)**



***Figure 1:*** Reliability diagram of the MammoRisk® risk score (correspondence between the observed risk and the predicted risk per decile on the reference population)



***Figure 2:*** Level of risk in absolute terms

**Results show :**

- An excellent calibration (E/O ratio = 1.001)
- A good discrimination (c-statistic = 0.65)

**Integration of the PRS into the MammoRisk® test (see Appendix 1: Related publication for references) :**

The complementarity of SNPs (Single Nucleotide Polymorphism) in predicting cancer risk, alongside other breast cancer risk factors such as breast density or reproductive history is now demonstrated with increased discrimination (c- statistic  $\approx 0.65$ ).

Polymorphisms are frequent variations in genomic DNA. Some have been associated with an increased risk of breast cancer. Each of these variations have a limited impact on breast cancer risk, but when they are combined into a Polygenic Risk Score (or PRS), some combinations have a significant impact on breast cancer risk, comparable to well-known risk factors such as breast density or first-degree family history (mother, sister, daughter who had breast cancer).

MammoRisk® combines classic clinical variables, breast density and PRS, when available, to more accurately estimate the risk of developing breast cancer, and to refine membership in a high or moderate risk group.

**Validation of MammoRisk and PRS (see Appendix 1: Related publications)**

MammoRisk was shown to be as efficient as the BCSC risk score in a validation study on screening cohorts leading to the conclusion that MammoRisk score is substantially equivalent to BCSC risk tool.

Based on this substantial equivalence, we consider that the results obtained with BCSC risk score combined with a PRS could be transposed to MammoRisk score combined with the same PRS. The MammoRisk PRS signature is based on the work published in 2015 by Vachon et al. including 76 SNPs. Vachon et al. showed that a PRS including 76 SNPs was an independent risk factor and enhanced the breast cancer risk prediction using the BCSC model. Given the complementarity of SNPs in predicting breast cancer risk along with other known risk factors, a PRS was included in MammoRisk. PRS is integrated in MammoRisk score as described by Pharoah et al.

According to substantial equivalence with BCSC score demonstrated on screening cohorts, expected results with MammoRisk-PRS on BCSC cohort are described in the table below:

	AUC	Calibration
MammoRisk (Ragusa et al.)	0.65	1
MammoRisk-PRS (Vachon et al.)	0.69	Close to 1

### **Conclusion**

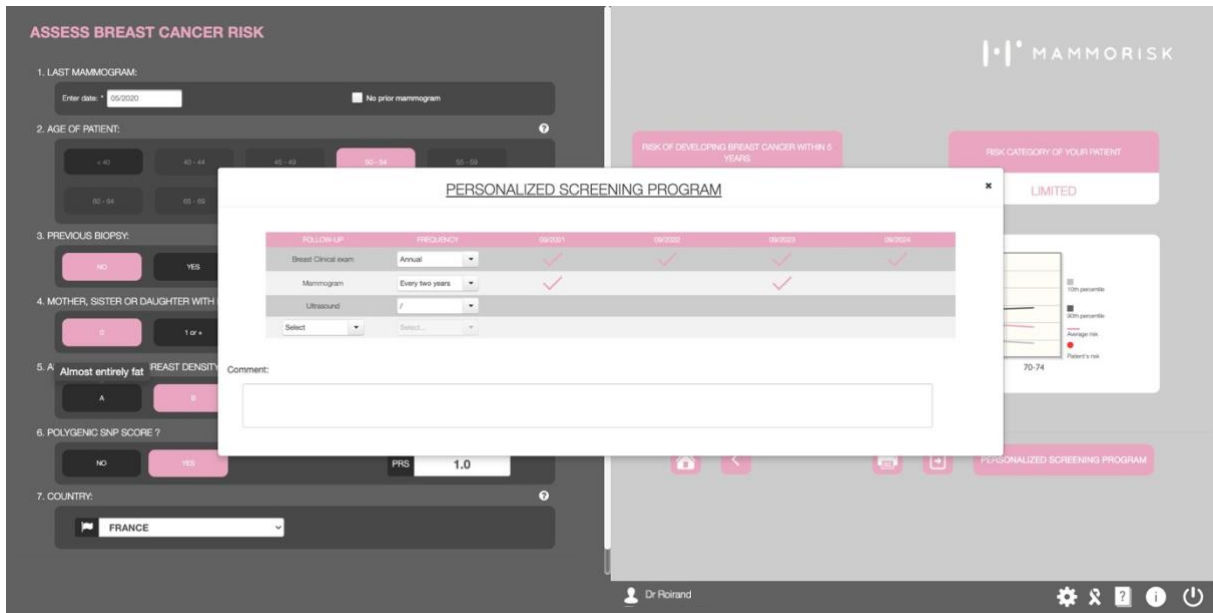
The PRS improved discrimination of the MammoRisk risk model and could help identify subsets of women at different levels of risk, for whom management would differ.

The PRS currently used with MammoRisk score is a 76-SNP signature. It may evolve according to the latest literature data.

### 3.4 Personalized follow-up program

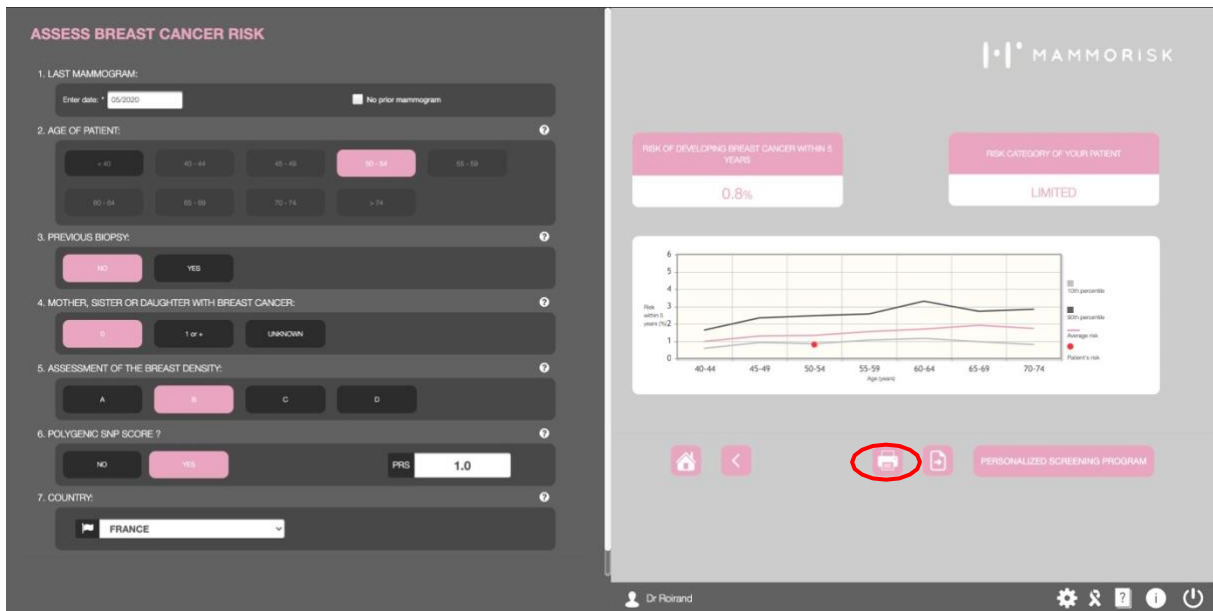
According to the estimated breast cancer risk, a personalized follow-up program is proposed by default based on the recommendations of the MyPeBS study. (**see Appendix 2: Default Recommendations & Appendix 3 : MyPebs study**). The detail of the follow-up exams may be visualized and modified by the user (deleting or adding exams, modifying exam frequencies) by clicking on the “personalized follow-up program” button. The user is responsible for the follow-up recommendations indicated in the MammoRisk® report. The report must be signed by the user before it is given to the patient.





### 3.5 Personalized result report

The personalized results report which presents the patient’s information, the estimated risk and the personalized follow-up program proposal is accessible via the “printer” button.

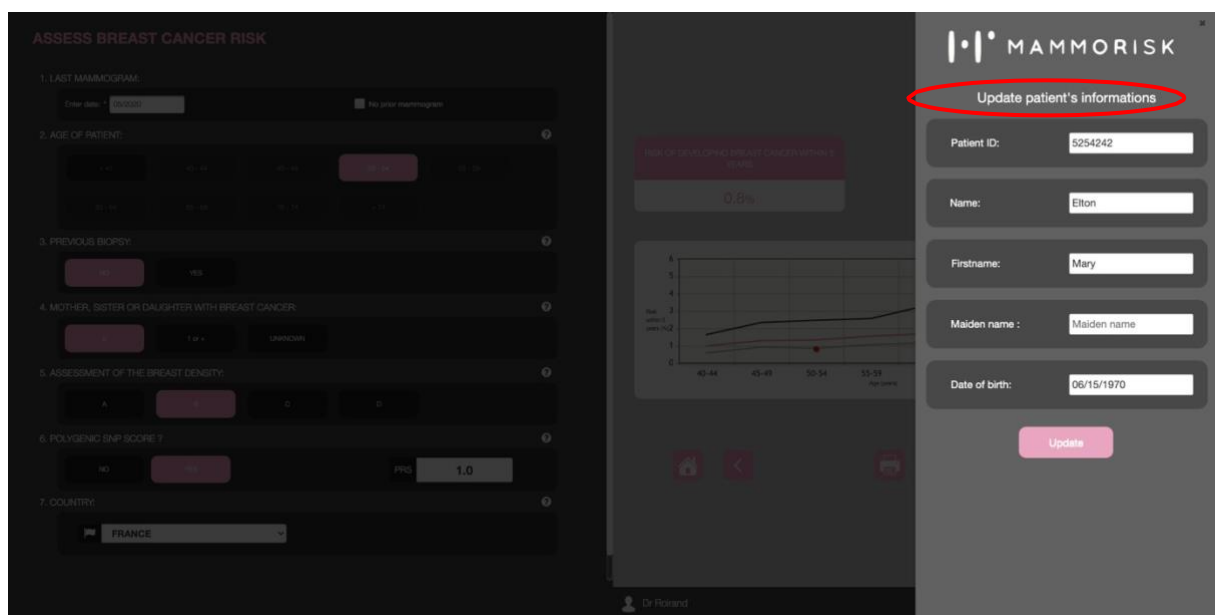


After clicking the print button, a new tab on the web browser will open, presenting the personalized results report. It is possible to print or save this report locally (**see Appendix 4: Results report**).

The personalized report can be downloaded in PDF format. It is automatically synchronized with the patient's information previously filled in.

### 3.6 Update patient profile

If an error was made while entering information during the creation of the patient record, the user can modify the patient information from the risk calculation interface by clicking on the button located at the bottom right of the screen.

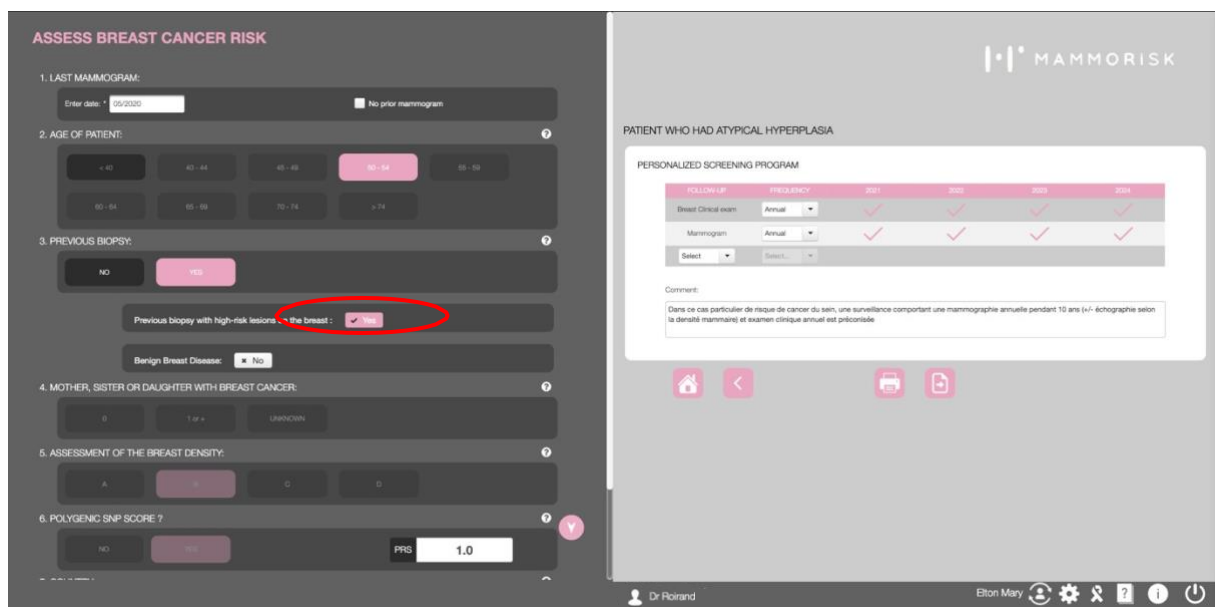




### 3.7 Specific cases

In order to avoid estimating a risk for a woman who does not belong to the general population, new confirmations are appearing in some places:

- If the patient has had a biopsy: checking that it is a benign breast disease. In the specific case of a history of atypical hyperplasia of the breast, the user is redirected to the corresponding risk category and recommendations.
- If 1 case of 1<sup>st</sup> degree relative breast cancer or more: in the case of 2 1<sup>st</sup> degree relative breast cancer cases or more, the user is directed to the 2 specialized scores for patients with important family history (Eisinger (for France) or Tyrer-Cuzick score).



The screenshot displays the MAMMORISK interface. On the left, the 'ASSESS BREAST CANCER RISK' form is shown with the following sections:

- 1. LAST MAMMOGRAM:** Enter date: 25/2020, No prior mammogram.
- 2. AGE OF PATIENT:** Radio buttons for age groups: < 40, 41-44, 45-49, 50-54 (selected), 55-59, 60-64, 65-69, 70-74, > 74.
- 3. PREVIOUS BIOPSY:** Radio buttons for NO and YES (selected). Below, a dropdown menu for 'Previous biopsy with high-risk lesions -> the breast:' is set to 'Yes' (circled in red). Below that, 'Benign Breast Disease:' is set to 'No'.
- 4. MOTHER, SISTER OR DAUGHTER WITH BREAST CANCER:** Radio buttons for 0, 1 or +, and UNKNOWN.
- 5. ASSESSMENT OF THE BREAST DENSITY:** Radio buttons for A, B (selected), C, and D.
- 6. POLYGENIC SNP SCORE ?** Radio buttons for NO and YES (selected). Below, 'PRS' is set to 1.0.

On the right, the 'PERSONALIZED SCREENING PROGRAM' is displayed for a 'PATIENT WHO HAD ATYPICAL HYPERPLASIA'. It includes a table with columns for 'FOLLOW-UP', 'FREQUENCY', and years 2021, 2022, 2023, and 2024. The table shows 'Breast Clinical exam' and 'Mammogram' both set to 'Annual' with checkmarks in all years. A comment at the bottom reads: 'Dans ce cas particulier de risque de cancer du sein, une surveillance comportant une mammographie annuelle pendant 10 ans (+/- échographie selon la densité mammaire) et examen clinique annuel est prioritaire'.

### 3.8 Other available information

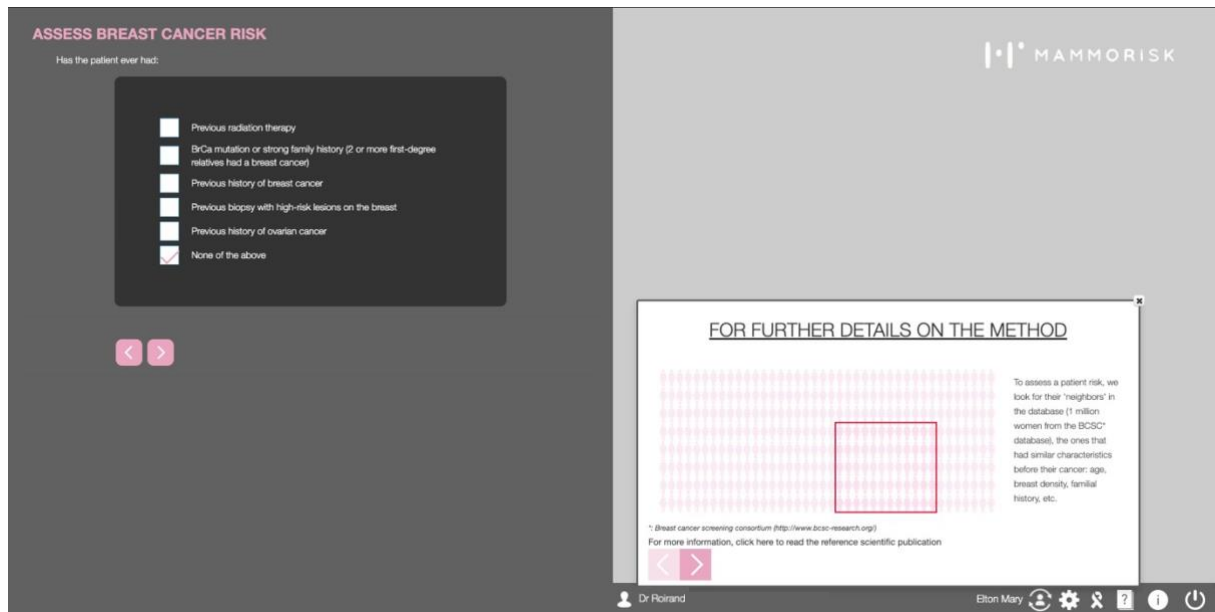
From the “i” button in the radiologist’s interface, it is possible to access:

- To recommendations associated with the risk categories. Risk thresholds and automatically associated recommendations can be customized. To modify them, please contact us, see the “Contact us” section. Available recommendations include those used for the pan-European MyPeBS study. (**see Appendix 3: MyPeBS study**)
- To this user manual.

- To the reference publication

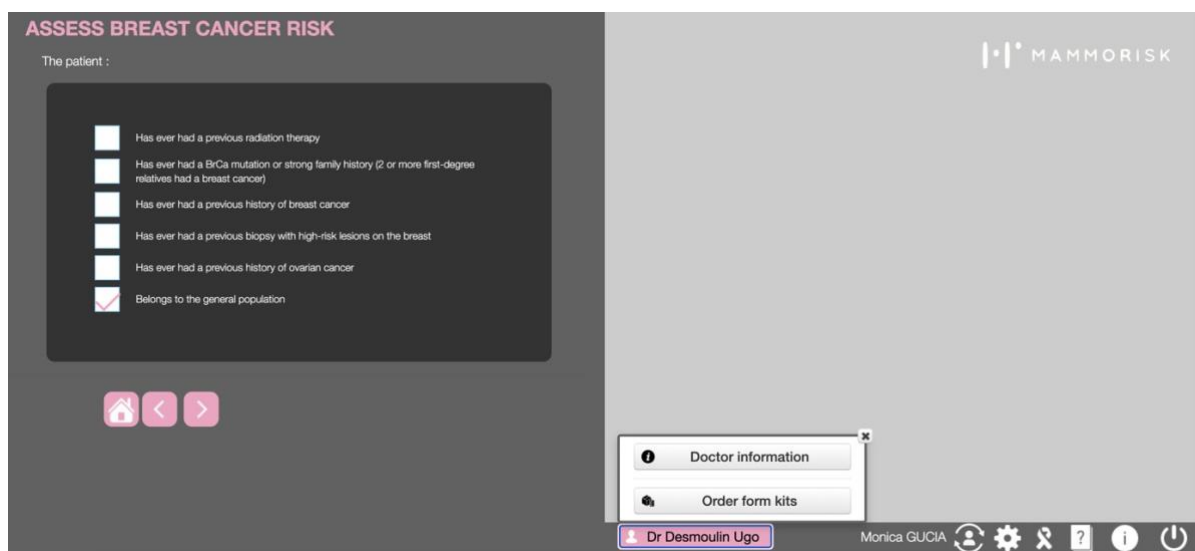


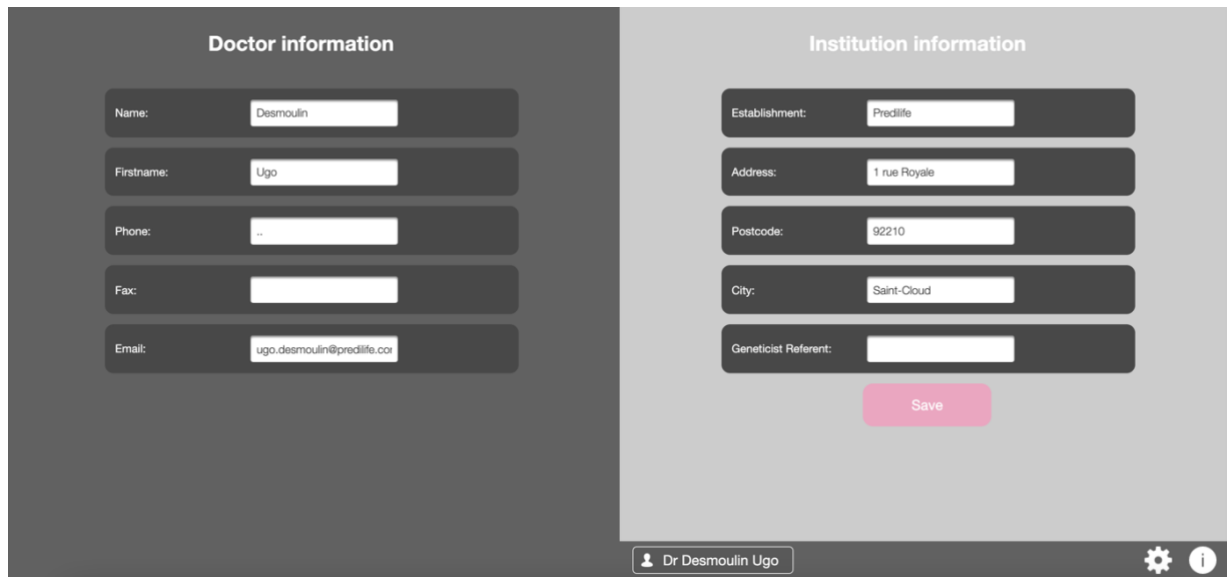
By clicking the “?” button at the bottom of the page, further information on the MammoRisk® risk calculation will be displayed.



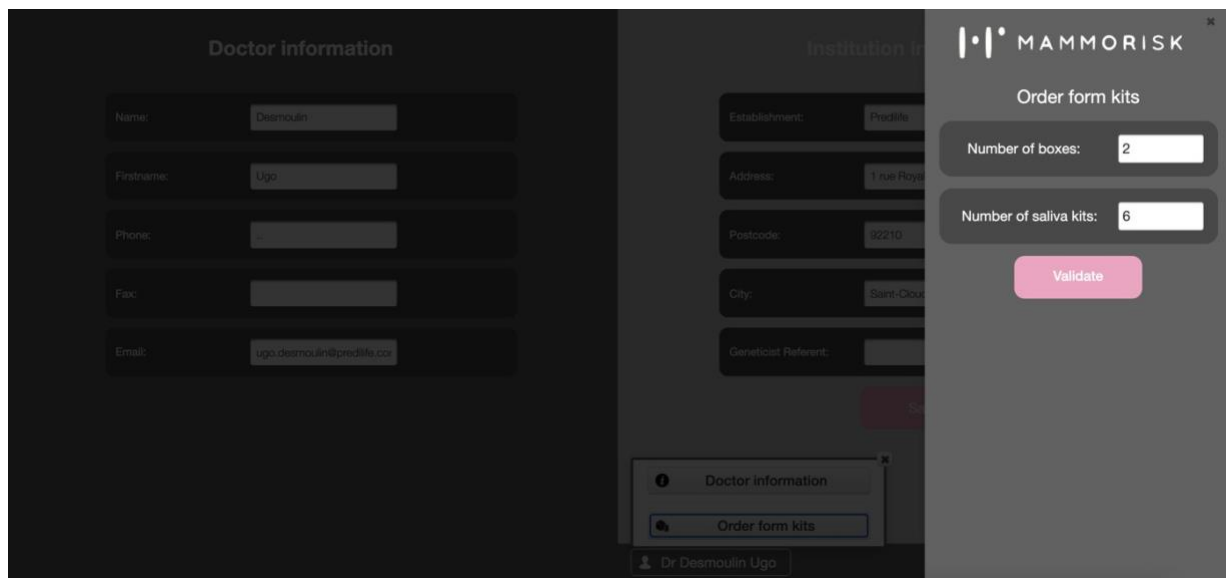
By clicking the user name "Dr XXX", it is possible to access:

- The configuration of user data from: " Doctor information ". Here, it is possible to configure the "Doctor information" and the "Institution information".
- The "kits order form" for replenishment of the shipping box and/or MammoRisk® saliva collection kits. This form is automatically synchronized with the "Doctor information" and the "Institution information".





The screenshot shows two side-by-side form panels. The left panel, titled 'Doctor information', contains fields for Name (Desmoulin), Firstname (Ugo), Phone, Fax, and Email (ugo.desmoulin@predlife.co). The right panel, titled 'Institution information', contains fields for Establishment (Predlife), Address (1 rue Royale), Postcode (92210), City (Saint-Cloud), and Geneticist Referent. A pink 'Save' button is located below the institution information fields. At the bottom of the interface, there is a user profile indicator 'Dr Desmoulin Ugo' and a settings/info icon.



This screenshot shows the same interface as above, but with an 'Order form kits' modal window open on the right side. The modal has the MAMMORISK logo at the top and contains two input fields: 'Number of boxes' with the value '2' and 'Number of saliva kits' with the value '6'. A pink 'Validate' button is positioned below these fields. At the bottom of the modal, there is a navigation bar with 'Doctor information' and 'Order form kits' options. The background forms are dimmed.

By clicking on the "Ribbon", additional information on all the risk factors for breast cancer is available: family history, biopsy, breast density, but also oral contraception, breastfeeding, alcohol, age at 1st child, menopause, physical activity, ...



### ASSESS BREAST CANCER RISK

1. LAST MAMMOGRAM:  
Enter date: 05/2020  No prior mammogram

2. AGE OF PATIENT:  
< 40 40 - 44 45 - 49 50 - 54 55 - 59  
60 - 64 65 - 69 70 - 74 > 74

3. PREVIOUS BIOPSY:  
NO YES  
Previous biopsy with high-risk lesions on the breast:  Yes  
Benign Breast Disease:  No

4. MOTHER, SISTER OR DAUGHTER WITH BREAST CANCER:  
0 1 of + UNKNOWN

5. ASSESSMENT OF THE BREAST DENSITY:  
A B C D

6. POLYGENIC SNP SCORE ?  
NO YES PRS 1.0

### MAMMORISK

PATIENT WHO HAD ATYPICAL HYPERPLASIA

#### PERSONALIZED SCREENING PROGRAM

FOLLOW UP	FREQUENCY	2021	2022	2023	2024
Breast Clinical exam	Annual	✓	✓	✓	✓
Mammogram	Annual	✓	✓	✓	✓
Select	Select				

Comment:  
Dans ce cas particulier de risque de cancer du sein, une surveillance comportant une mammographie annuelle pendant 10 ans (+/- échographie selon la densité mammaire) et examen clinique annuel est préconisée

Dr Pouet Sylvie Eton Mary

# 4 Appendices

## Appendix 1: Related publications

### **Scientific papers:**

- Laureen Dartois et al, A comparison between different prediction models for invasive breast cancer occurrence in the French E3N cohort, Breast Cancer Research and treatment, 2015
- Stephane Ragusa et al, A new non-parametric breast cancer risk- assessment model developed on a US cohort and validated on European screening populations: Performance and potential use for stratification (in press, European Journal of Cancer, 2017).
- Weigert J, Cavanaugh N, Ju T. Evaluating Mammographer Acceptance of MammoRisk Software. Radiol Technol. 2018 Mar.
- Vachon Vachon et al. The Contributions of Breast Density and Common Genetic Variation to Breast Cancer Risk. JNCI J Natl Cancer Inst (2015) 107(5):dju397
- Stephane Ragusa et al, A machine learning-based breast cancer risk model developed on the US Breast Cancer Screening Consortium cohort and validated on two French screening cohorts: Performance and potential use for stratification (in press, European Journal of Cancer).
- Pharoah PD, Antoniou AC, Easton DF, Ponder BA. Polygenes, risk prediction, and targeted prevention of breast cancer. N Engl J Med. 2008

### **Posters and oral communications :**

- Gauthier E, et al. Breast cancer risk score: a data mining approach to improve readability. Proceedings of The 2011 International Conference on Data Mining, July 18-21, 2011, Las Vegas, Nevada, USA. CSREA Press: Athens, GA, 2011;15-21.
- Tlemsani C et al, Receipt of breast cancer risk assessment and personalized prevention information among women diagnosed with a benign breast lesion (BBL) in a One Stop Breast Unit: a prospective assessment. SABCS 2015 (poster), Cancer Res 2015
- Stephane Ragusa et al, Development and validation of a new non- parametric breast cancer risk assessment model on US and European screening population. SABCS 2016 (poster), Cancer Res 2016.

- C. Balleyguier et al, New automated image recognition-based software to evaluate 2D breast mammographic density (BMD) according to BI-RADS® Atlas Fifth Edition recommendations, ECR 2017, oral communication
- Automated qualitative assessment of 2D breast density for breast cancer risk calculation (Corinne Balleyguier et al), 8th International Breast Density and Breast Cancer Risk Assessment Workshop, SF, June 2017
- Veron L. et al, Feasibility of breast cancer risk assessment and personalized breast screening recommendations delivery in community practice: a national prospective study (poster), EBCC 2018
- Balleyguier C. et al, Feasibility of risk assessment and personalized breast screening recommendations delivery in community radiology practice: a national prospective study (NCT02997384), oral communication, ECR 2018

## Appendix 2: Default recommendations

**General population case:** recommendations from European experts in the MyPEBS study



Risk category Limited, Moderate, Intermediate, High and Very High	« By default » MammoRisk's recommendations (To be adapted according to the benefit / risk assessment of each patient)
Limited R BCSC 5-year risk <1 % Or R Tyrer-Cuzick 10-year risk < 2%	From the age of 40: Clinical exam each year Mammography exam each year + Ultrasound if breast density C or D
Intermediate: 1% ≤ R BCSC 5-year risk <1.67% Or 1% ≤ R Tyrer-Cuzick 10-year risk <3.34%	From the age of 40: Clinical exam each year Mammography exam each year + Ultrasound if breast density C or D
High: 1.67% ≤ R BCSC 5-year risk < 6% or 3.34% ≤ R Tyrer-Cuzick 10-year risk < 12%	From the age of 40: Clinical exam each year Mammography exam each year + Ultrasound if breast density C or D
High: - Prior biopsies with high-risk lesions : Ductal or lobular atypical hyperplasia, ductal carcinoma in situ - Personal history of breast cancer	Clinical exam each year Mammography exam each year + Ultrasound if breast density C or D
Very High: R BCSC 5-year risk ≥ 6 % or R Tyrer-Cuzick 10-year risk ≥ 12 (20% lifetime (Tyrer-Cuzick))	From the age of 40: Clinical exam each year Mammography exam each year MRI each year + Ultrasound if breast density C or D
Chest radiation (Hodgkin's disease) Oncogenetics risk	Clinical exam each year Mammography exam each year MRI each year + Ultrasound if breast density C or D

### Specific cases:

- History of thoracic radiation: very high risk
- Personal history of breast cancer or atypical hyperplasia: high risk
- Significant family history:
  - Eisinger score
  - Tyrer-Cuzick risk score

## Appendix 3: MyPeBS study

MyPEBS (My-Personal Breast Screening) is a clinical study financed by the European Union with 24 partners including Predilife. The study aims to compare the standard model of breast cancer screening in 5 different countries (France, Belgium, Italy, United Kingdom and Israel) to a stratified screening depending on the patient's risk. The aim is to clinically validate the superiority of stratified screening (a decrease in 30% of stage II (and above) tumors is expected). The ethical, psychosocial and medico-economic impacts are also evaluated.

85,000 women between the ages of 40 and 70 with no history of breast cancer or any other major risk factors (very high-risk women) were included in the study: these 85,000 women were separated into 2 arms, the first corresponding to the screening strategy in the patient's inclusion country, the second corresponding to a personalized screening strategy based on the risk. The participants are monitored for 4 years.

Predilife is in charge of evaluating the risk for all women; the MammoRisk® score is used to determine the risk for women with 0 or 1 case of 1st degree history. For women with 2 cases of history or more, the Tyrer-Cuzick score is used to calculate the risk of breast cancer





## Appendix 4: Results report



**MAMMORISK**

Patient:	Last mammogram : 10/2019
Françoise DUPONT	Age: 55-59 years-old
Exam Date: 21/01/2021	Mother, sister or daughter with a breast cancer: 0
	Previous biopsy: no
	Breast density assessment: Scattered areas of fibroglandular density (B)
	PRS: not available

### PERSONALIZED RESULTS MAMMORISK

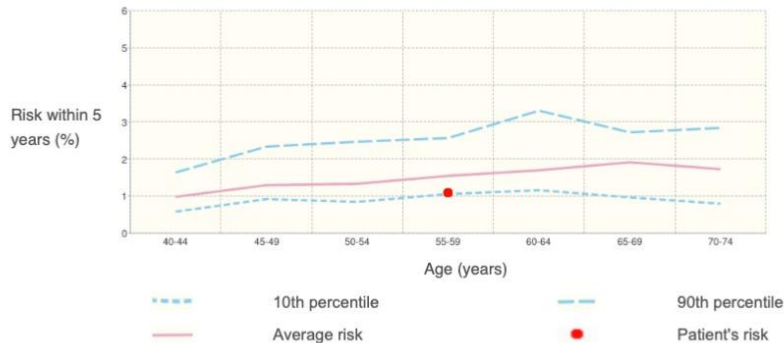
Your doctor has offered you an estimate of your individual risk of breast cancer in the years to come. This evaluation may potentially allow each woman to undergo more personalised screening for breast cancer.

This document is drawn up based on your personal and family medical history. As such, any new events can modify these recommendations. In any case, these recommendations should be reviewed at least every 5 years.

#### Breast cancer risk assessment

According to the data collected, your risk of developing breast cancer in the next 5 years is 1.1 %. This means that, of the 100 women with the same characteristics as you, between 1 or 2 women out of these 100 may develop breast cancer in the next 5 years.

For your information, the average risk of developing breast cancer within 5 years for a woman of the same age as you in the general population is 1.5 %.



#### Personalized screening program

Your personalised screening programme allows you to have an easy overview of how often you will need to be examined, and this depends on an assessment of your risk.

FOLLOW-UP	FREQUENCY	10/2021	10/2022	10/2023	10/2024
Breast Clinical exam	Annual	✓	✓	✓	✓
Mammogram	Every two years	✓		✓	

Selon les informations fournies, un examen clinique annuel et une mammographie tous les 2 ans (+/- échographie selon la densité mammaire) sont recommandés à partir de 40 ans



**Other recommendations**

Having a healthy lifestyle can reduce the individual risk of cancer. You can reduce your risk of breast cancer through a balanced diet, regular physical activity, optimal weight maintenance and limited alcohol consumption.

For more information about the risk of developing breast cancer, screening and prevention, please see your doctor.

Onco-genetic consultation	No indication.
---------------------------	----------------

**Other risk factors taken into account**

Other factors that have been taken into account by your doctor. You had:

Has ever had a previous radiation therapy	NO
Has ever had a previous history of breast cancer	NO
Has ever had a previous biopsy with high-risk lesions on the breast	NO

Delivered by Dr Gauthier Émilien :

Dr Roirand

**About estimating breast cancer risk:**

For women between 40 and 74 years, with no specific risk (strong family history, personal history of breast cancer, chest irradiation, atypical hyperplasia), MammoRisk uses the nearest neighbors method, developed and validated, in collaboration with Gustave Roussy, in a cohort of 1.3 million women (US Breast Cancer Surveillance Consortium and French screening) (S. Ragusa et al, European Journal of Cancer, in press, 2019).

The risk estimate provided by MammoRisk is an estimate of the absolute risk of breast cancer, that is, the probability of developing invasive breast cancer within a defined time interval. Although the risk estimate is accurate, it is a statistical estimate that does not accurately determine which woman is likely to develop breast cancer.

If the risk is limited, it does not mean that the woman has no risk of developing breast cancer. It is important to follow the screening recommendations and do not hesitate to consult a doctor as soon as you identify something abnormal in one of your breasts (change of color, mass, change of shape, flow, etc.). ...). It is also important to reassess one's risk, if one of the risk factors changes, and at least every 5 years.

## Appendix 5: Other risk scores for high-risk populations

### **Eisinger Score (only validated in France)**

The Eisinger score is a family tree analysis score to validate the indication for an oncogenetic consultation and consider screening for mutations.

If the Eisinger score is less than 3, you will be prompted to return to the MammoRisk® Risk Assessment screen.

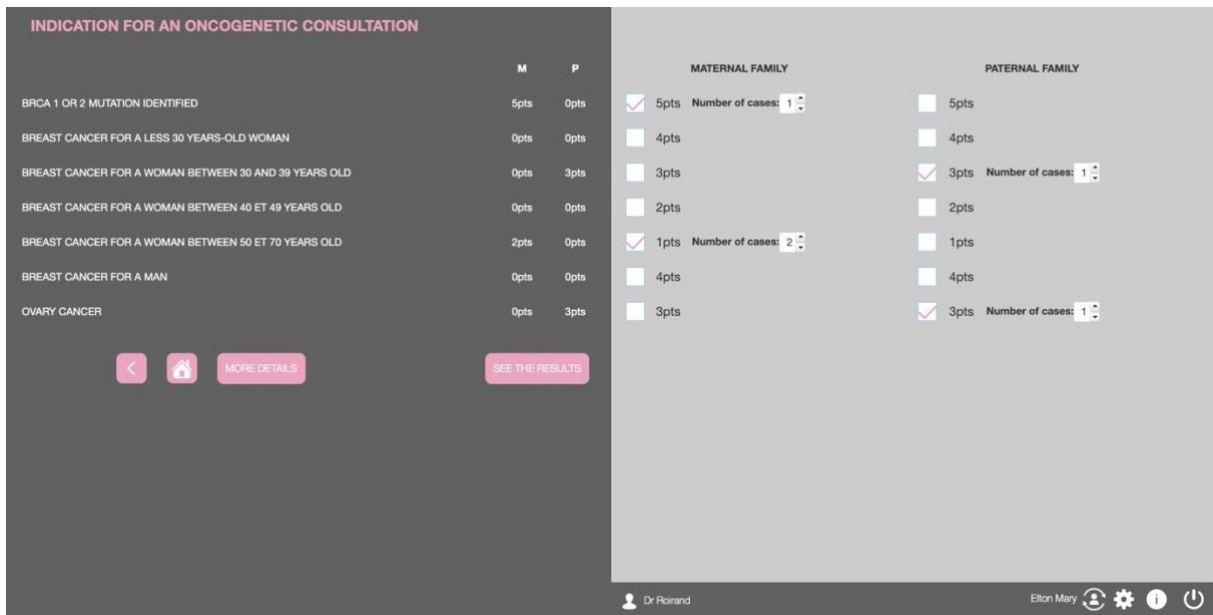
If the Eisinger score is greater than or equal to 3, the indication for an oncogenetic consultation for this patient is validated, and the use of the MammoRisk® risk estimate is not proposed.

In detail, a score of 3 or 4 is considered a possible indication for oncogenetic screening and a score of 5 or more is considered an excellent indication.

Pending the results of the oncogenetic consultation, personalized follow-up is offered:

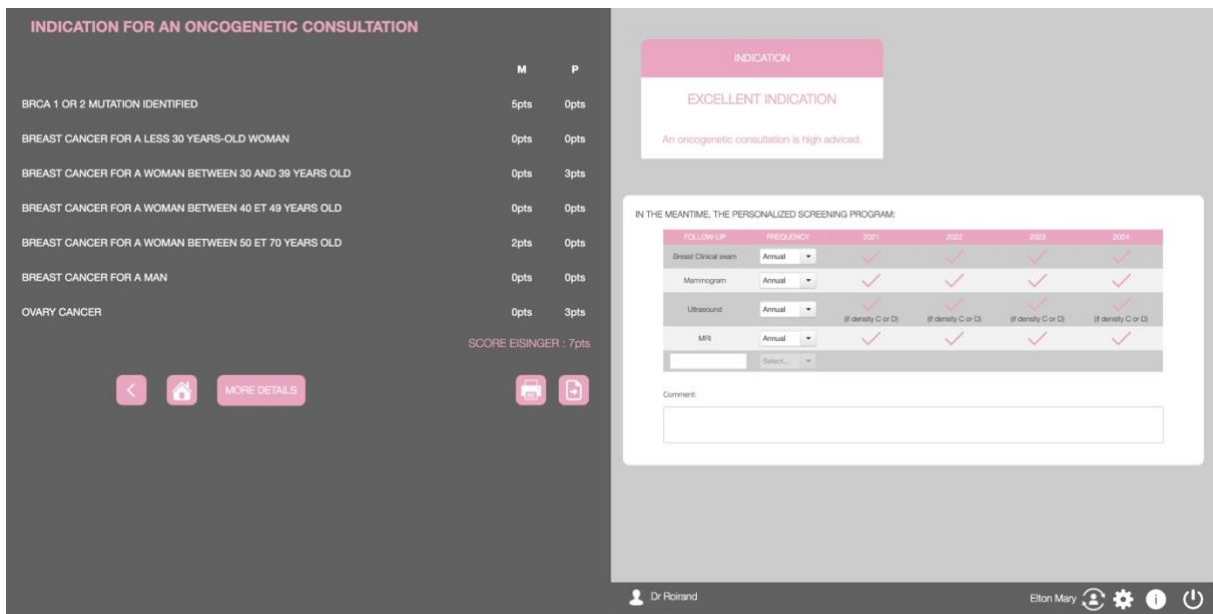
Eisinger Score	Recommendations
Between 0 et 2	No indication of oncogenetics Reference to risk calculation in the general population
between 3 et 4	Possible oncogenetic indication Annual clinical examination Annual mammogram and ultrasound if necessary
Above or equal to 5	Strongly recommended oncogenetic indication Annual clinical examination Annual mammogram, annual MRI (and ultrasound if necessary)

To use the Eisinger score, the user must specify the patient's family history by clicking on the corresponding check boxes for maternal and paternal families.



	M	P
BRCA 1 OR 2 MUTATION IDENTIFIED	5pts	0pts
BREAST CANCER FOR A LESS 30 YEARS-OLD WOMAN	0pts	0pts
BREAST CANCER FOR A WOMAN BETWEEN 30 AND 39 YEARS OLD	0pts	3pts
BREAST CANCER FOR A WOMAN BETWEEN 40 ET 49 YEARS OLD	0pts	0pts
BREAST CANCER FOR A WOMAN BETWEEN 50 ET 70 YEARS OLD	2pts	0pts
BREAST CANCER FOR A MAN	0pts	0pts
Ovary Cancer	0pts	3pts

Once the family history has been entered, when you click on "see the result", the score result and the indication are displayed (weak indication, possible indication or excellent indication).



**INDICATION**

**EXCELLENT INDICATION**

An oncogenetic consultation is high advised.

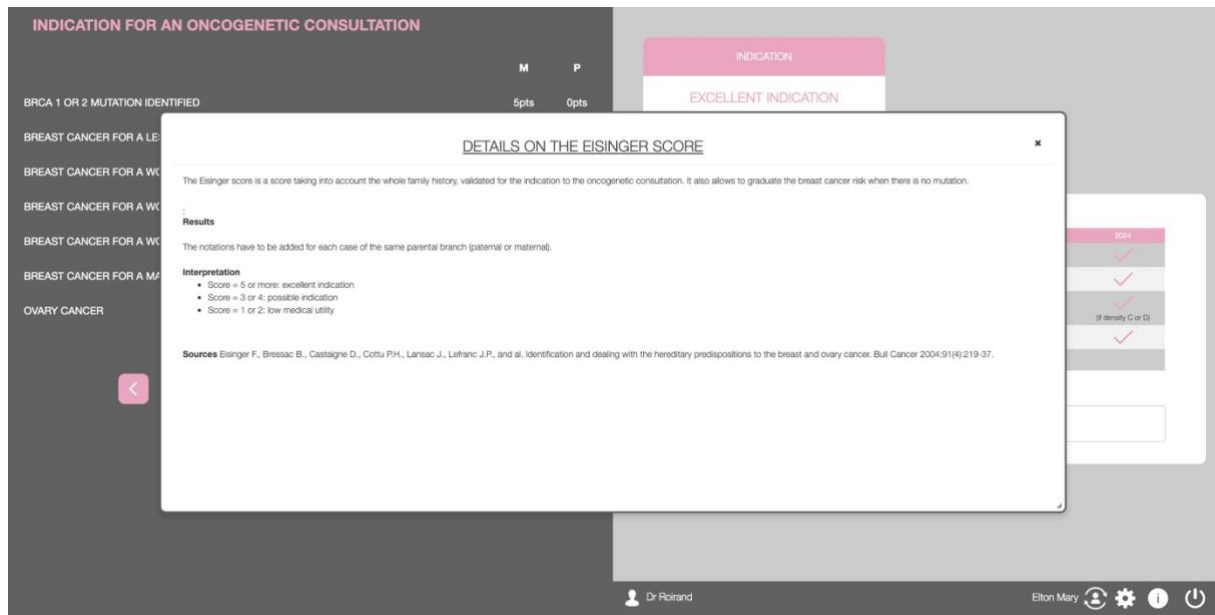
IN THE MEANTIME, THE PERSONALIZED SCREENING PROGRAM:

FOLLOW-UP	FREQUENCY	2021	2022	2023	2024
Breast Clinical exam	Annual	✓	✓	✓	✓
Mammogram	Annual	✓	✓	✓	✓
Ultrasound	Annual	(if density C or D)	(if density C or D)	(if density C or D)	(if density C or D)
MRI	Annual	✓	✓	✓	✓

Comment:

SCORE EISINGER : 7pts

As in the risk calculation screen, it is possible to access the details of the personalized treatment protocol and possibly modify it. It is also possible to print a custom results report. Note that more details on the Eisinger score can be accessed via the "find out more" button.



## Tyrer-Cuzick score

The Tyrer-Cuzick risk score was developed by an academic team from Cambridge, on an English population of women with a familial risk. It takes multiple factors into consideration including family history, hormonal factors, genetic BRCA1/BRCA2 factors, etc. (Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med.* 2004 Apr 15;23(7):1111-30). Tyrer-Cuzick demonstrates a good performance for women with a familial risk, but for others (those from a so-called “general” population), it is poorly calibrated with an overestimation of the number of the breast cancer cases (Brentnall AR, et al “Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort.” *Breast Cancer Res.* 2015).

After the Tyrer Cuzick score has been selected, 15 questions concerning the patient are asked; in the event where no answer is given to a question, a median value will be automatically used for the risk calculation.



**ASSESS BREAST CANCER RISK**

File # Metric :  Metric  Imperial

1. AGE OF PATIENT :  years-old

2. HEIGHT OF PATIENT :  cm

3. WEIGHT OF PATIENT :  kg

4. AGE OF FIRST MENSTRUATION :  years-old

MAMMORISK

Dr Roland Elton Mary

**ASSESS BREAST CANCER RISK**

File #

5. DOES THE PATIENT HAVE CHILDREN ?

\* AGE DURING 1ST CHILDBIRTH

years-old

6. MENOPUSAL STATUS

7. HORMONE REPLACEMENT THERAPY ?

MAMMORISK

Dr Roland Elton Mary

**ASSESS BREAST CANCER RISK**

File #

DID YOUR PATIENT HAVE :

8. GENETIC TESTING BRCA1 - BRCA2 ?

9. OVARY CANCER ?

10. BIOPSY ?

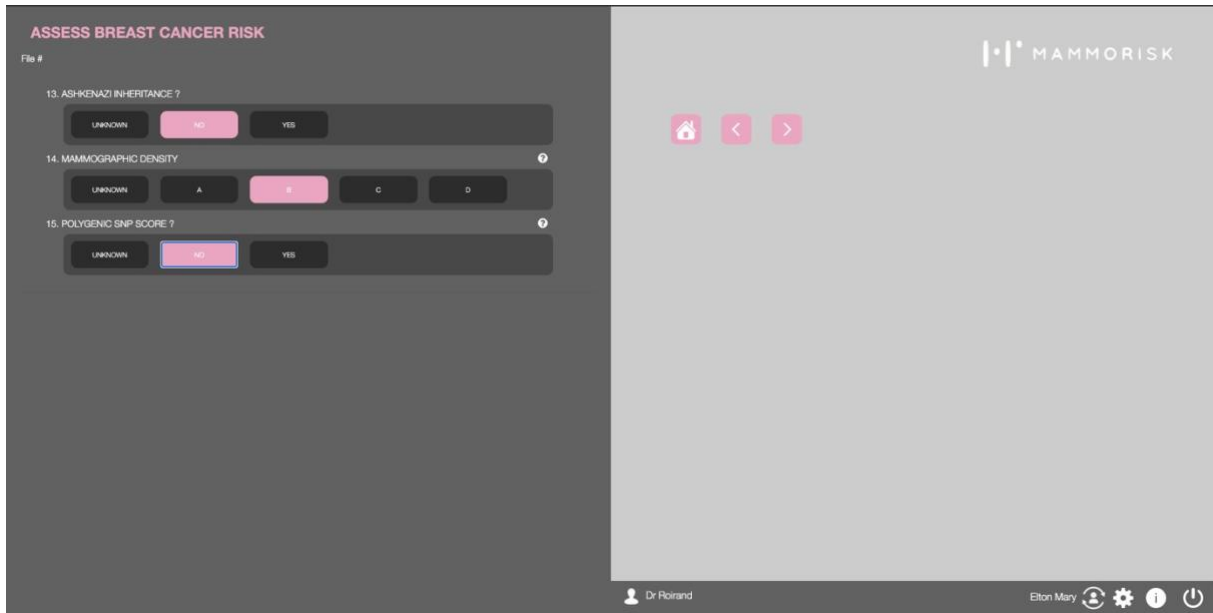
\* KNOWN RESULT ?

11. ATYPICAL HYPERPLASIA ?

12. LOBULAR CARCINOMA IN SITU ?

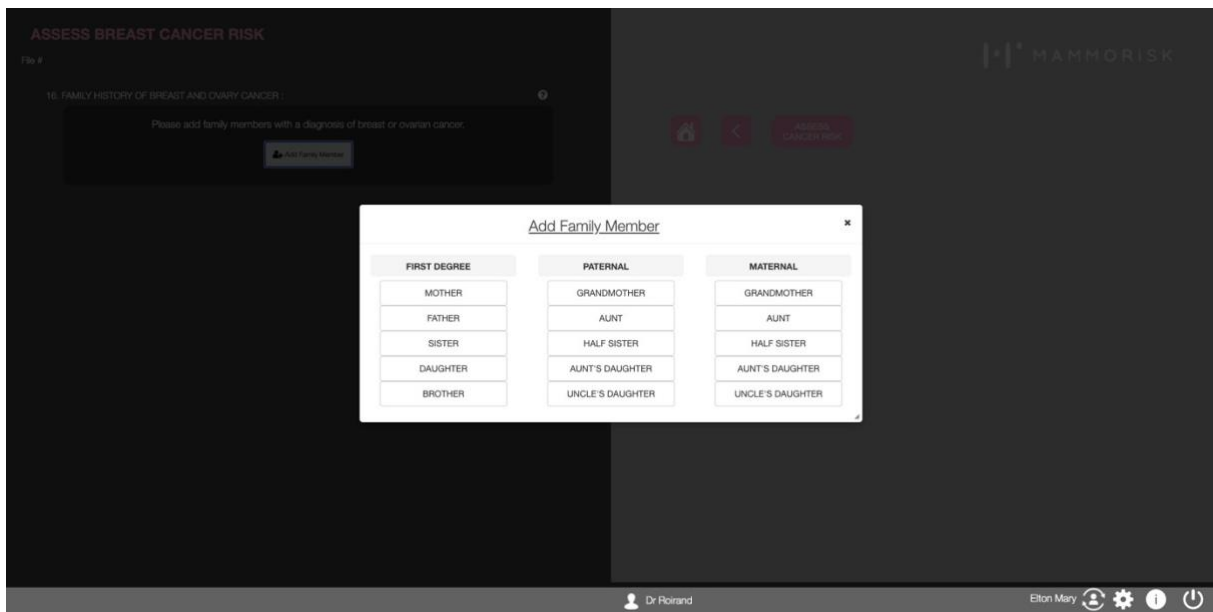
MAMMORISK

Dr Pouet S Elton Mary

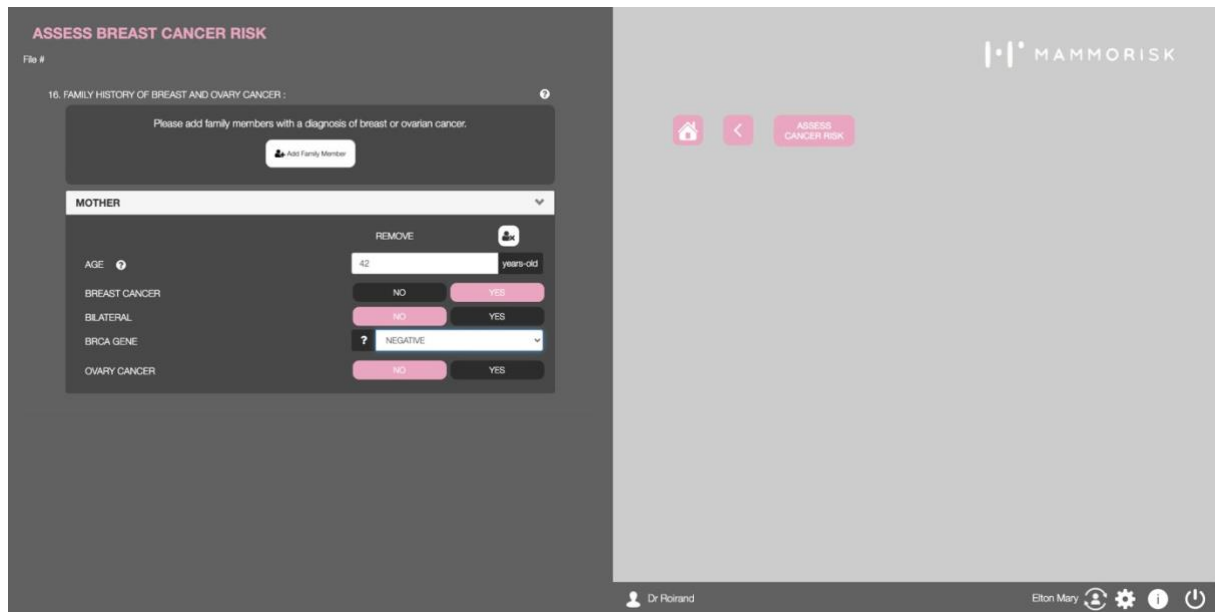


Next, the user will be asked to enter the patient’s family members who have or have had breast or ovarian cancer. The paternal and maternal family members to be considered for this test are as follows:

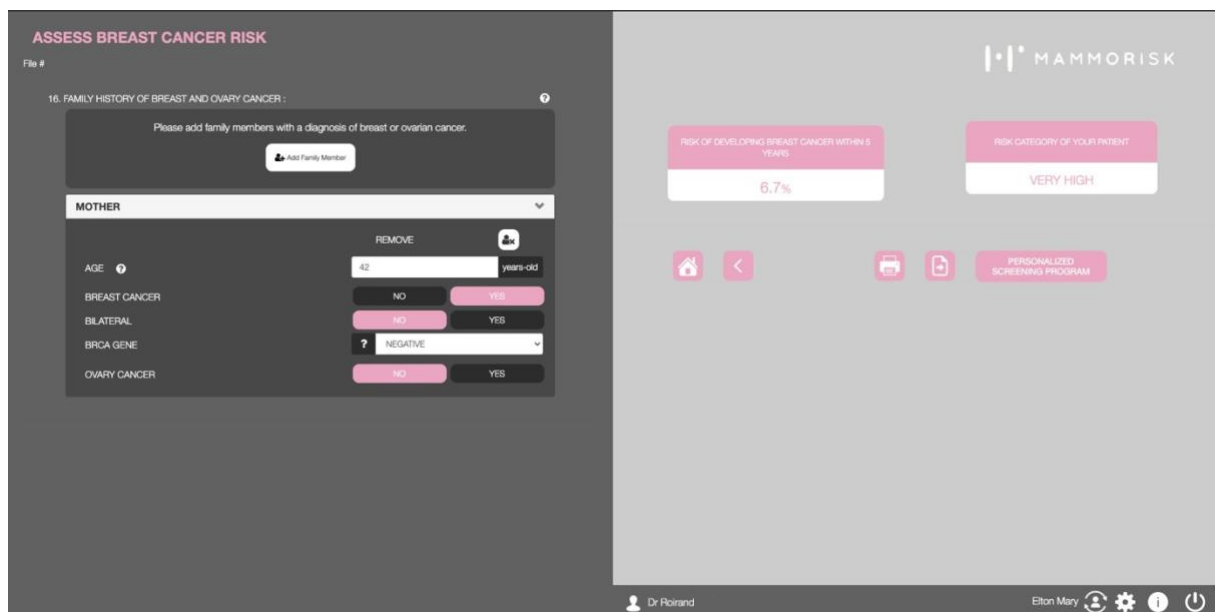
- First degree (mother, father, sister, daughter or brother).
- paternal (grandmother, aunt, half-sister, cousin (aunt’s daughter), cousin (uncle’s daughter)).
- maternal (grandmother, aunt, half-sister, cousin (aunt’s daughter), cousin (uncle’s daughter)).



In the event of one or more cases of family history, the diagnostic age (if not available, use the current age or age at death), the type of cancer (ovarian or breast) and the possibility of a genetic test must be specified.



Once all the family members who have had breast and/or ovarian cancer have been specified, the risk calculation is accessible via the “estimate the risk” button.



Like with the risk calculation screen, it is possible to access the personalized treatment protocol in detail and modify it if necessary. It is also possible to print a personalized results report.