My-PeBS

International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70

Protocol no. UC-0109/1805

ID-RCB no. 2018-A00535-50

INFORMATION LEAFLET AND CONSENT FORM

Version 1.0 UK – 09 AUG 2018

INVESTIGATOR COORDINATOR	**Dr Suzette Delaloge MD** Medical Oncology Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France Tel: + 33 (0)1 42 11 42 93 Fax : + 33 (0)1 42 11 52 74 Email: Suzette.Delaloge@gustaveroussy.fr

SPONSOR	**UNICANCER** 101, rue de Tolbiac - 75654 PARIS CEDEX 13 - FRANCE *Tel: +33. (0)1.44.23.04.04* *Fax: +33.(0)1.44.23.55.69*

COUNTRY COORDINATING INVESTIGATOR	**Professor Fiona J Gilbert** University Department of Radiology, Level 5, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0QQ Tel: +44 (0)1223 746439 Fax: +44 (0)1223 330915

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

INFORMATION LEAFLET FOR PATIENTS PARTICIPATING IN THE INTERVENTIONAL RESEARCH PROTOCOL*

Dear Madam,

You are invited to participate in a clinical research study, MyPeBS.

My-PeBS
(Personalising Breast Screening)
International Randomized Study Comparing personalized, Risk-Stratified to Standard Breast Cancer Screening In Women Aged 40-70

This study aims to evaluate the effectiveness of more personalised breast cancer screening compared to current screening practices. This document describes the study and summarises the study procedures, objectives, potential benefits, and possible disadvantages for you.

Before you decide whether to participate in this study, please take your time to understand the aims of this study, what it involves, and the potential benefits and possible risks. We recommend that you read this information leaflet carefully. *A glossary of terms can be found at the end of the document (terms marked with an*).*

Do not hesitate to discuss MyPeBS with your family, friends, and general practitioner. Please contact the study doctor who has asked you to participate, if you would like further clarification.

This study will be conducted in five countries and is financed by the European Union. MyPeBS was designed and is conducted by a group of doctors, researchers, and scientists, all experts in breast cancer prevention and screening, together with patients' advocates. Our objective is to improve screening for breast cancer. This study is supervised and controlled by the executive committee of MyPeBS project, by the study's steering committee and an independent ethics, data monitoring and study conduct committee (EDMC). More information about MyPeBS is available on the website: www.mypebs.eu.

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by *(Name of Ethics committee, date)*. It has also been reviewed by the NHS Breast Screening Programme Research Advisory Committee (*date*). Finally the Health Research Authority gave approval for this study on (*date*).

1) What is the objective of the research?

MyPeBS was designed to assess if breast cancer screening adapted to a woman's projected 5-years risk of breast cancer is more effective than current standard screening, in women aged 40 to 70 years old. We hope that "risk-based screening" will reduce the frequency of stage 2 and higher breast cancers* (i.e., breast tumours larger than 2 cm or with the cancer having spread to the axillary lymph node)* at breast cancer diagnosis.

MyPeBS will also assess whether this personalised risk-adapted screening strategy will reduce negative potential consequences of standard screening: unnecessary biopsies and treatments relating to overdiagnosis,* particularly in women at low risk. In addition, we will compare the sociopsychological and socioeconomic impact of the two screening strategies, assessing women's satisfaction, anxiety etc. Finally, we will assess, in each country, if the resources used justify the results obtained with these screening strategies.

After analysing all the results of the study, the European MyPeBS project will propose general recommendations for more effective breast cancer screening in Europe.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

2) What is already known about the advantages and disadvantages of current breast cancer screening, and the estimation of individual breast cancer risk

Breast cancer is the most common cancer in Western women. It is a serious disease since around one in 5 women with breast cancer unfortunately die from it.

Appropriate cancer screening enables early detection of cancer, the treatment of which is generally less intense and chances of recovery greater, compared with cancers diagnosed at a more advanced stage.

Breast cancer screening has been generalised for about fifteen years in most Western countries.

Currently in the UK women aged between 50 -70 years of age are invited every three years for mammography. Only a few women, with very high specific risk factors have more intensive screening: women with a predisposing genetic modification, or those who had chest radiotherapy before the age of 25, who have already had breast cancer or a pre-cancerous lesion.

Breast cancer screening and known benefits

- Breast cancer screening usually involves mammograms* (radiological examinations of both breasts with two images per breast). This is part of national organised screening programme with monitoring of screening quality and with double reading of the mammograms. Certified radiologists and radiographers are responsible for quality of the diagnostic performance.

- Apart from patients known to be at high-risk of developing breast cancer, age is currently the only criterion for starting screening. Depending on the country, mammograms are offered every 1 to 3 years, starting from the age of 40-50 years up until between 69-74 years.

- These screening recommendations are based on large-scale studies that have shown that screening reduced breast cancer deaths by about 20%, i.e. prevented one in 5 deaths. The benefit of screening between the age of 40 and 50 is controversial and each country currently states on that. Screening, by mammography, also reduces the number of stage 2 and higher cancers at diagnosis in women older than 50.

Breast cancer screening by mammography: disadvantages

Current screening by mammography has disadvantages:

- It is not completely effective: 1-2 (or more for UK) breast cancers every 1,000 examined women appear between screening invitations ("interval cancers*")

- About one quarter of cancers occurring in regularly screened women are diagnosed at stage 2 or more.

- A small percentage of screening mammograms lead to additional recalls for further investigations or biopsies* for what turns to be a benign/non-cancerous lesion "false-positives".

- A number of cancers which are diagnosed (estimated on average about 10% i.e. 1 in 10) by breast screening are growing so slowly that they would never cause problems during the woman's life, leading to unnecessary treatment. These breast cancers are called "overdiagnoses*".

- Finally, mammography delivers a small dose of X-rays which in the long-term can increase the risk of breast cancer (radio-induced cancers*). However, this risk is extremely low (about 1 in 1,000 women screened during 30 years) compared to the benefits of early diagnosis. Radiation doses delivered in screening are very closely monitored.

Estimating individual breast cancer risk to more effectively "target" screening:

Our ability to identify women at higher or lower risk of developing breast cancer should make targeted breast cancer screening possible. This would result in offering more intensive screening for women at higher risk and reduced screening for those at lower risk. The reduced screening may lower the risk of the unintended adverse effects of screening – false positive recalls and biopsies of benign lesions.

To do this, we need to estimate the risk of breast cancer in each woman in the general population.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

For around twenty years, European and American research teams have developed "scores", to estimate a woman's risk of developing breast cancer. These scores are now well-established and widely validated, especially in Europe.

They use simple personal and clinical data like the woman's age, family history of cancer, personal history of benign/non-cancerous disease, and exposure to natural hormones (age of first period/menstrual cycle, pregnancy, age of menopause etc.), and medical hormones (hormone replacement treatments, the contraceptive pill etc.). The mammogram shows the amount of dense breast tissue and this "breast density score" also contributes to predicting individual risk.

In the last ten years, European and American researchers were able to show that "genetic polymorphisms*" (variations in the sequence of certain genes, in a substantial portion of the population) influences the individual risk of developing breast cancer. At present, more than 150 such polymorphisms have been described. Each individual variation only contributes a small amount of risk. However, a score that includes about a hundred polymorphisms becomes much more predictive. Finally, by combining clinical risk scores with the influence of polymorphisms we can identify women with different levels of breast cancer risk with more certainty.

Personalised screening based on evaluating each woman's risk of developing breast cancer with a score using both clinical data (described above) and polymorphisms is now feasible, and should be more effective. It will allow us to offer more intensive screening in women at high risk, possibly with earlier detection of cancer (associated with more cures and less intensive treatments). Furthermore in women at low risk, a reduced frequency of screening is expected to lead to fewer false positives and overdiagnosed lesions.

MyPeBS aims to test this hypothesis. In MyPeBS, half of the women will follow the standard breast screening programme whilst the other half will follow a screening programme adapted to estimated breast cancer risk. This "risk-based screening" may include a mammogram, performed at various intervals, and in a few cases, an Magnetic Resonance Imaging (MRI)* examination. In some women with very dense breast tissue, supplementary ultrasound may be offered.

3) Why Have I been invited?

You live in one of the regions in the five countries participating in MyPeBS study and you are being routinely invited for breast screening. You have been invited to participate in this study and have had this information leaflet given to you because based on the information held by the NHS Breast Screening Service it is thought you meet the eligibility criteria for the study.

To be eligible you must be eligible for breast cancer screening in the NHS Breast Screening Programme, you should not have already been identified as having a high risk of breast cancer (in case of *BRCA1* or *BRCA2* gene mutation or equivalent), nor have a personal history of breast cancer and your most recent mammogram should be normal.

4) Do I have to take part?

Participating in this trial is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the study at any time without giving a reason. If you choose not to participate or to leave the study, you can continue with the standard breast cancer screening programme in your country. Similarly, the study healthcare professional may decide to withdraw you from the study if she/he believes it is in your best interest.

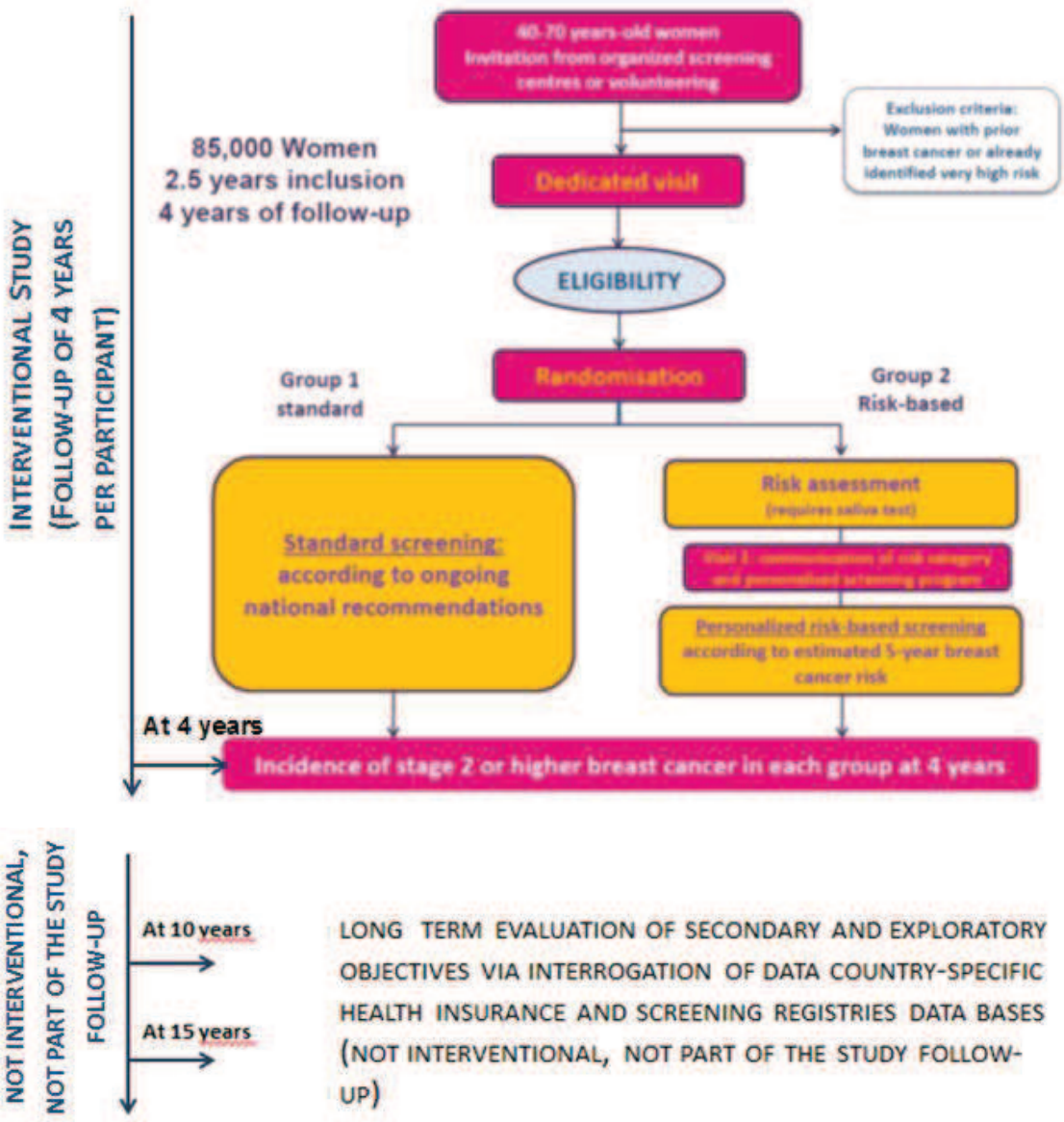
5) What is the methodology and the procedure?

MyPeBS will take place in five countries (France, Italy, United Kingdom, Belgium, and Israel). The study will include 85,000 women aged 40 to 70 years, each of whom will participate in the study for 4 years.

It is a randomised study, which means that the women who wish to participate will be randomly allocated (by a computer) to one of two screening programmes: standard screening (group 1) or risk-based screening (group 2). Thus, women will have a 1 in 2 (50%) chance of being in either programme.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Study design:



The general study schedule is provided in detail in table 1 (below)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Table 1: Schedule of visits and examinations:

VISITS	Inclusion for both group (1 &2)	Only for Personalised screening group (group 2)	Follow-up for both group (1 & 2)			
Visits N°	**Visit (V0)**	**V1**	**V2**	**V3**	**V4**	**V5**
Visit dates	**D0**	**Month 3 V0 ± 8 -12 weeks**	**Month 12 V0 + 12 ± 6 months**	**Month 24 V0 + 24 ± 6 months**	**Month 36 V0 + 36 ± 6 months**	**Month 48 V0 + 48 ± 6 months**
Type of visit	Telephone or physical	physical	On-line on the web platform			
Inclusion/exclusion criteria	X					
Consent form signature	X					
Mammogram (if applicable)	X					
Minimum medical data	X					
Randomisation	X					
Result of the risk score and schedule of examinations		X				
SALIVA TEST **(only for women randomised in personalised screening group)**	X					
RADIOLOGICAL EXAMINATION						
Mammogram	Need and frequency determined according to your schedule					
Other radiological examinations (according to requirements, ultrasound or MRI-scan)	Need and frequency determined according to your schedule					
QUESTIONNAIRES						
Compilation of various questionnaires (in your personal portal)	X	X	X	X		X
UPDATE OF YOUR DATA IN THE WEB PLATFORM (in your personal portal)			X	X	X	X

5.1 Enrolment visit: By telephone for all participants

Once you have had the opportunity to read this information sheet and are satisfied that you have had all of your questions answered by the study staff, if you decide to participate in the study an online profile will be created for you in the MyPeBS web-platform. You will be asked to sign the online informed consent form. The study healthcare professional will then confirm your eligibility to participate in the trial and also sign the consent form. You will then be asked to complete the online questionnaires on your profile. All of these activities will occur over the telephone and internet in order to minimise additional visits to a breast screening centre. (It is important that you have access either to a mobile telephone or computer to enter this study – this is because you will receive text updates and will be asked to enter details over the course of the study)

Questionnaires to be completed at the first visit

Regardless of the screening programme to which you are allocated, at the first visit, you will be asked to:

- complete a questionnaire about your personal and family medical history, and your lifestyle.

- complete a questionnaire describing your knowledge of breast cancer screening and breast cancer risk factors, your level of anxiety, and your understanding of the information received

All study data will be de-identified* (so that it will be impossible to identify you outside of your personal secured space in the participants' portal of the study. Your name, surname and contact details will only be known by those responsible for your clinical care but they will not be revealed to researchers or others)

Once you have completed the questionnaires the study health professional will log into the web platform and trigger 'randomisation*' the computer will randomly allocate/assign you to one of the two screening programs below. .

1. **If you are 'randomised' to the 'standard screening' group (group 1)**, you will receive your breast screening follow-up schedule immediately (schedule of your mammograms, if required, for

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

the next 4 years, the duration of your study participation). These examinations will be done following the usual/standard procedures (see 3.4). There will not be a second visit.

2. **If you are 'randomised' to the 'personalised risk-based screening' group (group 2)**, you will be asked to provide a saliva sample when you attend for your baseline mammogram at the screening centre or mobile van which will be used to analyse your DNA*. This analysis will check for a set of gene polymorphisms* that are known to be associated with breast cancer risk. This type of analysis is called genotyping*. Your saliva sample will be sent and tested at a central laboratory in France.

   Your risk score, including the polymorphisms results will be available after a few weeks. This risk score will be given to you, at your second visit (3.2), together with your personalized follow-up schedule.

5.2 Analysis of genetic polymorphisms indicating susceptibility to breast cancer in your saliva DNA

In this research, if you are randomised to the 'personalised risk-based screening' group (group 2), **you will be asked to have a saliva test when you attend for your baseline mammogram. This test requires you to spit a little saliva into a special tube.**

Your sample will be identified by a bar code on the tube without your name and surname not any other identification mean, and will be sent for testing.

The sample will be analysed by the study's centralised platform, this analysis could take 10-12 weeks.

The testing method uses a standardised 'DNA chip' with a large number of genetic polymorphisms (between 600,000 and 900,000). Among the polymorphisms analysed, about 142 are known and validated for predicting individual breast cancer risk. 313 polymorphisms will be used to estimate your individual risk. The result of the tests on the 313 polymorphisms will be added to your clinical data to estimate your risk of developing breast cancer within 5 years.

The complete polymorphism tests results (between 600 000 and 900 000) will be stored confidentially and may be used during the study to re-estimate your risk. For instance, if new polymorphisms, of major interest, are identified during the study your risk score will be re-estimated using the saliva test results from the first visit. If this occurs or if there is a change in your risk score, you will be informed. However, the chance of a significant change in your risk score is extremely low. These test results may also be used for additional research in the future but they will not be communicated to you as part of MyPeBS.

No other routine genetic analysis will be carried out for this study. In particular, we will not be testing for very rare breast cancer susceptibility* genes (type *BRCA1* or *BRCA2)*. However, if we think you may have an hereditary predisposition given your family history, you will be advised to attend an oncogenetic consultation where you will be provided with more information, if required. If this occurs during the study after a new event, you will receive a message on your personal web platform space or you will be contacted directly by your study healthcare professional.

.

5.3. The second visit for women allocated to the "personalised risk-based screening" group

If you are assigned to receive "personalised risk-based screening", you will be asked to attend an appointment at your screening centre, when you will be informed of your estimated breast cancer risk and given your screening schedule for the next four years. You can opt to have this discussion over the telephone if you prefer or if you live far away from the screening centre.

Your estimated risk of developing an invasive* breast cancer will be expressed verbally as a risk category (low, medium, high, or very high) but if you prefer, the risk level can be given as a percentage, or a position on a graph, so that you can compare your personal risk to that of women of a similar age. Your personal result integrating clinical data and the polymorphisms evaluation will be available in your private web platform space after it has been explained to you by a healthcare professional..

Breast cancer risks levels and corresponding screening schedules are shown in the table below. Note that

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

- A woman with a low risk has a less than 1% chance (one in 100 women) of developing invasive breast cancer within the next 5 years (this is lower than the average risk for a 45-year-old woman in Europe)
- A woman with a medium risk has between 1 and 1.67% risk of developing invasive breast cancer within 5 years (around 1 in 60 women).
- A woman with a high risk has between 1.67 and 6% risk of developing invasive breast cancer within 5 years (around 1 in 30 women).
- A woman with a very high risk has more than 6% risk of developing invasive breast cancer within 5 years. (around 1 in 16 women)

The Table below summarises the examinations required according to the risk categories:

Risk at 5 years	Low risk	Medium risk	High risk	Very high risk
Definition as a percentage (at 5 years)	Risk < 1%	1 ≤ Risk < 1.67%	1.67% ≤ Risk < 6%	Risk≥ 6%
Mammogram*	After 4 years	Every 2 years	Every year	Every year
Additional examination	-	Ultrasound if high breast density	Ultrasound if high breast density	MRI every year until age 60

*Or digital tomosynthesis (3D mammogram + synthetic 2D mammogram) for centres that will use this technique instead of mammogram

Closer to the date of your scheduled visit(s)/examination(s) you will receive a reminder by mail, e-mail or SMS.

5.4. Study examinations and schedule

To participate in this study, the enrolment visit must be done by a study healthcare professional at an investigator site participating in the study. If you are allocated to the 'personalised risk-based screening' group', your health professional will see/call you for the second visit, around 10 weeks after the initial visit. At that time, your estimated personalised breast cancer risk results will be given to you, as well as your personalised screening programme.

No other specific visit with the study personnel is scheduled.

The radiologists and radiographers involved in the standard breast screening programme (NHS Breast Screening Programme) will perform the examinations for risk-based screening using procedures identical to those used for the standard screening (examination quality, second reading, etc.). Only the schedule may vary.

Mammograms: in both groups radiologists may use, depending on national guidelines, either standard mammography, or a new technique, called digital breast tomosynthesis* (DBT). This new technology produces 3D and reconstructed (synthetic) mammogram images of the breast and it has been approved by European Guidelines as an alternative to standard mammography.

You will receive your examination results and a detailed written report of your mammogram or DBT exactly as you would have for standard breast screening.

We would be grateful if you could follow your screening examination schedule, as closely as possible, regardless of the screening programme allocated.

An end of study mammogram will be required for those women who had no mammograms during the 4 years participating in the study (i.e. the low risk group). For all other women the last mammogram in their personalised schedule will count as their end of study mammogram. The date and result must be entered on the web platform. The end-of-study mammogram will be indicated on your screening schedule.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Cost of examinations

You will not have to pay for the mammogram, MRI examination, nor for the saliva test or any other procedure scheduled within the study.

Nor will you have to pay for any other additional examinations which are necessary based on mammogram or MRI' results (ultrasound, biopsy, additional mammogram, or even treatment in case a lesion requiring therapy is identified).

5.5 What happens if the results of examinations carried out during the study are not normal?

If an abnormal finding is confirmed and further investigation is required (a repeat mammogram or ultrasound, additional MRI examination, biopsy or treatment), all the arrangements will be organised according to standard practice by your radiologist and/or your referring doctor.

If investigations of this type are necessary, we would appreciate it if you could complete the relevant section in your personal space on the web platform. Reporting this information is very important and your cooperation is essential.

If you have a confirmed breast cancer, you will receive care and treatment according to the applicable national regulations and according to good practice guidelines. Your referring doctor will be in charge of organising your health care.

If this occurs, we would be grateful if you could report it using your private web platform space. In addition, we would be grateful if you would indicate the treatment(s) proposed.

What if I notice an abnormality in my breast(s)? Regardless of your allocated screening schedule, if you notice an abnormality in your breasts (deformation, nipple discharge, lumps etc.) you should consult your referring doctor* as soon as possible. Your referring doctor will organise complementary tests/examinations, if necessary. Even in women with an estimated low risk of breast cancer, breast cancer may occur. A negative screening test does not mean that there is no risk at all.

5.6. Update of your information in the study

Once you have joined the study, the study healthcare professional will create your private access to your personal secured space in the participants' portal of the study's web platform.

During the study, all participants, regardless of screening programme will have a personal, private, and secure access to the MyPeBS study web platform. On the web platform, you can access your personal space, your screening schedule, the questionnaires, study information, letters to print out for your various doctors, if necessary, etc. The personal space on the web platform is private and confidential; all information is fully pseudonymised* outside this space.

We would like to thank you in advance for updating your personal data during your study participation (for 4 years). Please indicate any changes to your personal or family history or any new personal information you consider relevant.

We would also like to thank you in advance for completing the follow-up questionnaires (see detailed questionnaires in table 1: schedule of visits and examinations):

- psychological follow-up and satisfaction questionnaires: after 3 months, 1 year and 4 years from the first visit
- your radiological examination dates and results
- reporting of events that may occur during the four years of follow-up, such as the need for a breast biopsy or noteworthy medical events such as a cancer diagnosis.

If you have been randomized to the 'risk-based screening' group: your estimated individual breast cancer risk may change over time, depending on the change in your personal characteristics and family history; this is why it is very important that you continually update the information in the secure study web platform. Your personal risk will be reassessed and updated if necessary.

If your risk category/level changes after a significant event (such as a new case of breast cancer in the family, or breast biopsy etc), a new screening schedule will be sent to you. Please then follow this new

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

screening schedule. If you have any questions, please do not hesitate to discuss these with your study – healthcare professional. Your personal portal will contain all information on your current updated screening schedule.

5.8 What happens at the end of the study

At the end of the study you will re-enter the national breast screening programme according to your level of risk and the UK guidelines..

When the results of the whole study are available, they will be communicated to you and all study participants and clinical investigators, as soon as possible.

The information concerning your continuing care, for up to 15 years after your entry into the study, is very important for us. However, the study follow-up only lasts for 4 years. We request that you give us permission to collect this longer term information. More information can be found about thie aspect of the study in the "Additional research – Optional" section.

6) What are the expected benefits relating to participation in this study?

If you were allocated to standard breast screening, no specific benefit is expected. However, you will receive information about breast cancer screening, which we will update during the study. Data obtained from study participants, including your data, may change future breast cancer screening in Europe. Once we publish the results of MyPeBS and if personalised risk-based screening becomes the standard, you may be offered a risk-based screening schedule in the future.

If you are allocated to the 'personalised risk-based screening' programme and your risk level indicates more frequent examinations than standard screening, and if unfortunately you develop breast cancer it may be detected at an earlier stage than in standard conditions.

We estimate that of the women assigned to risk-based screening, about 50 women will be diagnosed with breast cancer at an earlier stage, preventing about 50 stage 2 and higher cancers*. A diagnosis at an earlier stage is associated with a better prognosis and less intense treatments. Also, we hope to see fewer cancers develop between two negative screens (interval cancer).

In women who are allocated risk-based screening: if your breast cancer risk level is low, then you will have fewer examinations than standard screening. This may reduce the risk of false positive recalls*, of overdiagnoses*, of cancers* due to x-ray exposure, and of the stress/anxiety induced by these examinations.

7) What are the potential risks and side effects relating to participation in this study?

If you are assigned to the standard breast screening programme, there are no expected additional risks or side effects if you are 50 or older. The advantages and disadvantages of standard screening have previously been described (Section 2).

If you are younger than 50, there might be no additional benefit to risk based screening. Additionally, you will have an end-of-study mammogram. In countries where this mammogram is not standard, this additional mammogram may lead to false positives, overdiagnosis and/or overtreatment as described above (Section 2)

Mammography and tomosynthesis use ionising radiation to form images of the breast. Ionising radiation is associated with a risk of cancer induction. The amount of radiation dose you will receive by participating in this study will vary depending on which study group you are in however the risk associated

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

with these exposures is considered to be low. Each examination is equivalent to around 4 months of the dose received from naturally occurring background sources of radiation.

If you are allocated to personalised risk-based screening, the potential risks and side effects include:

- the risk of a cancer being detected later than with standard breast screening

- an increased risk of false positive recalls and overdiagnoses* (see Section 2) which may cause unnecessary anxiety and emotional trauma.

7.1 Risks related to the radiological examinations

The medical risks of radiological examinations (mammograms, ultrasound and MRIs) undertaken during the study are identical to the risk of these examinations done routinely.

8) Additional Research – Optional

Alongside the main study the researchers would like to seek your consent for the following research. You can decline to participate in this part of the study without affecting your participation in the rest of the study, your participation in the NHS breast screening programme or your relationship with your health professionals.

8.1 DNA storage during the study

If you consent to donate the residual DNA that will remain after the saliva test, it will be stored in a fully secure, de-identified DNA bank, specifically opened for the MyPeBS study. This residual DNA may be used for future research, such as more complete sequencing of all genes. It will only be used for research purposes and neither you nor your study healthcare professional will receive these results.

8.2 Image storage during the study

The pseudonymised mammographic images performed during the study will be, wherever possible, stored for further research. If you consent for your images to be stored, they may be transmitted to a central database dedicated to MyPeBS project or stored locally.

These images would be made available for research projects either within MyPeBS or other studies, related to screening, assessing breast density and risk prediction. They may be used to develop or test diagnostic tools in the future.

8.3 Long Term Follow-up

The information concerning your continuing care, for up to 15 years after your entry into the study, is very important for us. However, the study follow-up only lasts for 4 years. We request that you give us permission to collect this longer term information. If you agree, the study health professionals at your coordinating screening centre will use your NHS number and / or NHS breast screening programme number and information held by the national cancer registry to obtain up to date information about you. The confidential follow-up data at 15 years after your entry into MyPeBS, will be de-identified and transferred to us by your screening coordination centre. An item on the last page of this informed consent form requests you permission for collecting this information. You have the right to change your mind at any time.

8.4 Further research and commercial development based data from this study

The data collected during this study may be used for further research, such as research dedicated to better understanding of cancer risk or early detection or prevention of breast cancer. We will ask for your permission to use your pseudonymised* data for the purpose of further research.

This research may lead to commercial exploitation. For example a new predictor of cancer risk may be commercialised to enable it to be used widely. We therefore also will ask you whether or not you consent to use of your pseudonymised* data for this purpose.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

9 What are your rights as a trial participant?

a. Safety, ethics and treatment

UNICANCER is the sponsor of this study and is responsible for study management.

The sponsor will take all the necessary measures required by the law to protect all the women who participate in this interventional study. The study will be conducted in compliance with the current Declaration of Helsinki, the current ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP) and for Good Manufacturing Practice (ICH-GMP), the European Directive 2001/20/CE on the conduct of clinical studies and subsequent texts (Eudralex Vol 10), Regulation (EU) 2016/679 (General Data Protection Regulation) and the national legal requirements.

.

Your participation is voluntary and will not incur any additional costs for you. The screening tests (mammogram and MRI examination) scheduled in this clinical study will be free of charge.

If you agree to participate, you must be registered with a general practitioner. At the end of the study, the clinical study databases, the breast screening programme database and that the national cancer registry data will be paired. Your NHS Breast screening programme number and personal identifiers (name, date of birth, postcode) and NHS number will be used to link these datasets. Once the UK dataset is completed all your information will be de-identified before sending for central analysis.

UNICANCER shall assume liability for any injuries sustained by any person participating in the interventional research, and has taken out interventional research insurance in accordance with current legislation, policy no. <To be completed>, with HDI-GLOBAL SE (Tour OPUS 12 - La Défense 9, 77 Esplanade de la Défense – 92914 PARIS LA DEFENSE Cedex) via the insurance brokerage firm Biomedic Insure (Parc d'Innovation Bretagne Sud, 56038 Vannes, tel. 02.97.69.19.19). This insurance certificate can be consulted at your centre on request.

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this study you should speak to your study healthcare professional who will do their best to answer your questions.
In the event that something does go wrong and you are harmed by taking part in the research and this doesn't fall within the Sponsor's liability you may have grounds for a legal action for compensation against <Name of recruiting site>. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).
If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact <Name of local PALS or alternative independent body>

.

The terms and conditions of this protocol have been submitted for authorisation by two bodies responsible for checking the scientific relevance of the study and the conditions governing your protection and compliance with your rights:

1) The Competent Authority (Health Research Authority) authorised this trial on <DD month YYYY> under no. <to be completed>.

2) The Ethics Committee (EC) xxx approved the trial on <DD month YYYY>.

In accordance with the recommendations of the 2014-2019 French Cancer Plan (Action 5.4. Associate patients and their representatives with clinical trials and pathways providing access to such research), this document was submitted for proofreading, opinion and recommendations to the French Cancer League's patient committee.

Your general practitioner will be informed of your participation in MyPeBS study, unless you object.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

MyPeBS' results may be published in scientific/medical publications. However, this will not occur in the near future since time is required to collect, analyse, and interpret the data. The results of each individual woman will not be published.

According to the provisions of law No. 2002-303 dated 4 March 2002, relative to patients' rights, you will be informed of the overall study results by contacting any of the doctors who were involved in your screening schedule during the study.

b. *Personal data protection*

[Name of site] will keep your name, NHS number and contact details confidential and will not pass this information to UNICANCER. [Name of site] will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from UNICANCER and regulatory organisations may look at your medical and research records to check the accuracy of the research study. UNICANCER will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

[Name of site] will keep identifiable information about you from this study for a maximum of 25 years after the study has finished.

If you agree, the data collected during the trial may be used by UNICANCER or its partners in a confidential and secure manner in order to continue breast cancer screening research, as mentioned previously (see section 8, Additional Research – Optional).
To this end, your personal medical data will be sent to the research Sponsor, or persons or companies working on their behalf, to their partners and to the competent authorities, in France and abroad. In case of further research conducted by a UNCANCER partner, further information will be available on the web platform dedicated to the study.

Your data will be kept for up to two years after the last scientific publication related to research projects. They will then be archived, with very limited access, for a maximum of twenty-five years.

You have the following rights on the data concerning you:

- access rights to the data concerning you,
- right to correct erroneous data,
- right of erasure of data in case of unlawful processing,
- the right to limit treatment, particularly if the treatment is called into question.

You also have a right to oppose treatment. This prevents further processing data by the controller. If the treatment is necessary in the public interest, UNICANCER cannot respond favourably to the exercise of this right of opposition.

These rights are exercised by the Data Protection Officer UNICANCER: Delegate for Protection data, 101 rue de Tolbiac 75654 Paris Cedex 13 - dpo@unicancer.fr.

If, despite UNICANCER's undertaking to protect your rights and your personal data, you were not satisfied with the protection of your data, you have the right to file a complaint with the control authority: the French data protection committee (Commission nationale de l'informatique et des libertés - cnil.fr).

You can also access directly or through a doctor of your choice to the entire medical data concerning you in accordance with the provisions of Article L.1111-7 of the Code de laPublic health.

c. *Rights relating to biological samples*

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Your saliva sample will be collected at the screening centre or mobile screening van and transported to France for analysis. In accordance with modified bioethics law No. 2004-800 of 6 August 2004, the use of your saliva for genetic testing as part of the present study (evaluation of breast cancer risk specific polymorphisms) is subject to your prior, written consent.
Additionally, if you give your approval for further research on your biological samples (see section 8, Additional research - Optional), they will be stored by a centre ensuring their protection and their confidentiality. This will be done in accordance with applicable legislation, for later research in oncology, as long as the samples remain of scientific interest. You can however object to this later on if you so wish, by telling your doctor - investigator or by putting it in writing. Also, at any time during the research, you can ask your doctor - investigator to destroy the samples, on the condition they are not useful for your management at diagnosis.

Part of the biological material may be transferred as part of the research partnership to other institutions or private companies.

10 Who to contact in the event of questions or problems during the study?

Please contact the following people in the event of problems or adverse reactions during the study or if you have any questions:

Your study contacts: ***(Title, last name, first name, address and telephone number):***
…… ……
Contact details of the participant's study doctor - investigator
…… ……

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

Glossary:

- **Breast density:** the relative proportion of dense to fatty tissue in the breast on a mammogram. The higher the density, the harder it may be to find abnormalities in a mammogram, and the higher the individual risk of developing breast cancer.
- **Breast MRI examination**: Magnetic resonance imaging (MRI) is an examination used to record two or three-dimensional views of the breast. The MRI-scan provides information on lesions that cannot be seen by standard X-rays, or ultrasound
- **Breast ultrasound**: procedure performed by a radiologist using ultrasound, in order to study the internal breast tissue. It is a painless procedure
- **Digital breast tomosynthesis** (DBT). This new technology produces 3 dimensions (3D) and reconstructed (synthetic) 2D images of the breast. It has been recommended by the European Guidelines as an option instead of standard mammography.
- **DNA**: deoxyribonucleic acid, is a biological macromolecule found in all cells of the human body. DNA contains genetic information in the form of tens of thousands of genes coding for proteins that enable the development, function, and reproduction of human beings.
- **False positive:** mammograms that lead to further assessments (CBE, ultrasound, biopsy) when the lesion is assent or benign/non-cancerous.
- **Genotyping:** analysis of a person's constitutional DNA evaluating normal gene variants (polymorphisms). Genotyping is different from research into gene constitutional mutation that identifies a family predisposition to certain diseases (very high risk of the disease).
- **Interval cancers**: Breast cancers appearing between two negative screening invitations.
- **Interventional research:** Research on humans including an intervention on the person (i.e., a diagnostic procedure, treatment, or monitoring). The care strategies, and diagnostic and monitoring procedures are determined in advance by a research protocol.
- **Invasive**: term describing cancer able to invade surrounding tissue and to potentially metastasise.
- **Mammogram**: Radiological examination of the breasts with two images per breast
- **Overdiagnosis**: Approximately 1 in 10 of the breast cancers detected by screening are growing so slowly that they would never cause problems during the woman's life. That means that treatment was unnecessary in these cases. These cases are called "overdiagnoses".
- **Polymorphisms**: normal but rare variants in gene sequences potentially related to a different function of the protein coded by the gene. Polymorphisms enable genetic variety but can also be associated with different level of sensitivity to certain substances or drugs, or a different risk of certain diseases.
- **Pre-cancerous lesion:** is a term used to describe certain conditions or lesions involving abnormal cells which are associated with an increased risk of developing into cancer
- **Predisposition:** Set of factors, in an individual, which increase the risk of developing a specific disease
- **Pseudonymisation (or de-identification):** The replacement of all data (in a database etc) that identifies a person with an artificial identifier
- **Radio-induced breast cancer**: cancer caused by long-term exposure to small doses of X-rays
- **Randomisation**: random allocation/assignment, by a computer, to randomly divide people participating in the study between two groups
- **Referring doctor**: Doctor looking after you day by day (in general, it is your general practitioner)
- Sociopsychological: Relating to, or characterised by interrelated social and psychological factors
- Socioeconomic: Relating, or concerned with the interaction of social and economic factors
- **Stage 2 and higher breast cancer**: breast tumour 2 or more than 2 cm or with the cancer having spread to the axillary lymph node

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394

- **Study health professional:** a doctor directing and monitoring a clinical trial and ensuring management of the patients participating in that trial.
- **Ultrasound:** breast examination with sound waves to create medical images of the breast tissue.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement N° 755394