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Be RIGHT with breast cancer risk management (BRIGHT) breast cancer precision prevention study

Submission date	Recruitment status	[ ] Prospectively registered
07/09/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
13/01/2023	Ongoing	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
13/01/2023	Cancer	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Breast cancer (BC) is the leading cause of cancer deaths in women. Current BC screening guidelines are primarily based on age and do not support regular screening of women below the age of 50. This largely excludes young women at high risk for developing BC. On the other side, mammography screening also has potential harms and costs, therefore it is not reasonable to implement screening for all women under the age of 50. It is no longer appropriate to apply a single recommendation to women across all age groups and risk profiles and a far more precise and personalized risk estimation is needed.

To improve the effectiveness of mammographic screening for breast cancer there needs to be a risk-based way to identify subgroups of women for targeted screening programmes. Targeted screening based on genetic risk could allow precision prevention of breast cancer. This could decrease the societal and economic burden of the condition while adding healthy life years for participating women. This trial aims to evaluate the impact of implementing a population-based genetics testing strategy for BC precision prevention. The testing methods used will include the calculation of a polygenic risk score which tells you how a person's breast cancer risk compares to others with a different genetic constitution and testing for cancer-causing variations in single genes (monogenic pathogenic variant testing) method. The study will also evaluate the feasibility, potential clinical utility and cost-effectiveness of the population-based genetic testing strategy for BC precision prevention.

Who can participate?

Healthy adult women in Estonia, Portugal and Sweden. The participants will be split into three groups:

1. (In Estonia and Portugal) women aged between 35 to 49 years old and not currently invited to regular BC screening
2. (In Sweden) women aged between 30 and 39 years old who are not currently not invited to regular BC screening
3. (In Sweden) women aged between 40 and 50 years old who are currently in a BC screening group before age 50 years

What does the study involve?
The study evaluates the implementation of a comprehensive program of genetic-risk-based personalized BC screening and prevention for women aged 35-49 years, an age group younger than in the current population screening in most countries. For genetic risk prediction, the study uses polygenic risk score and questionnaire-based referral for monogenic pathogenic variants testing to assess their feasibility with follow-up diagnostic screening and prevention activities. The study will investigate the effectiveness, cost-efficiency, feasibility, acceptability and healthcare system readiness of this approach.

What are the possible benefits and risks of participating?
Participants may benefit by being given their personalized risk estimates, counselling and most appropriate management. There are possible risks associated with participation from possible under- and/or over-management due to model imprecision.

Where is the study run from?
The University of Tartu (Estonia)

When is the study starting and how long is it expected to run for?
April 2022 to December 2025

Who is funding the study?
European Commission via EIT Health

Who is the main contact?
Prof. Neeme Tõnisson (Principal investigator) (Estonia)
neeme.tonisson@ut.ee

Contact information

Type(s)
Principal investigator

Contact name
Prof Neeme Tõnisson

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
220720

Study information

Scientific Title
Be RIGHT with breast cancer risk management (BRIGHT) breast cancer precision prevention feasibility study

Acronym
BRIGHT

Study objectives
1. A genetics-based breast cancer (BC) prevention program has a clinical utility and is cost-effective for women under age 40 or 50 years
2. A genetics-based BC prevention program is feasible and acceptable and healthcare systems are ready to implement it

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Estonia: approved 12/04/2022, Estonian Council of Bioethics and Human Research (Eesti Bioeetika ja Inimuuringute Nõukogu) (Estonian Ministry of Social Affairs; Suur-Ameerika 1, 10122 Tallinn, Estonia; Tel: not available; info@sm.ee), ref: 1.1-12/1930, latest amendment 1.1-1/2894, amendment date 01/09/2022
2. Portugal: approval pending, Comissão de ética (Av. Professor Egas Moniz, 1649-035 Lisboa, Portugal; +351 (0)217 805 000)
3. Sweden: approved 24/10/2022,, Etikprövningsmyndigheten (Box 2110, 750 02 Uppsala, Sweden; +46 (0)104750800; registrator@etikprovning.se), ref: 2022-03074-01

Study design
Multicenter single-arm observational cross-sectional trial

Primary study design
Observational

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Breast cancer

Interventions

Personalized referral to mammography screening by polygenic risk score and monogenic pathogenic variant (MPV)-based risk level estimates.

Interventions are made according to the estimated breast cancer risk levels.
According to genetic information and risk levels following interventions may follow (example of Estonian clinical protocol; protocols in Sweden and Portugal have slight differences, based on the local screening practice):
1. Screening mammography
2. MD consulting
3. Magnetic resonance tomography of breasts
4. Hormonal chemoprevention in case of high-risk with tamoxifen or aromatase inhibitors

In the case of monogenic pathogenic variants (MPV) additionally: gynecological ultrasonography, CA125 tumor marker testing, and potentially risk-reducing surgeries based on personalized decisions.
A Polygenic Risk Score (PRS) test uses a buccal swab sample and can be done as a home-based test (using parcel machines) or can be done at the site in clinics. Sample collection instructions are given in the attached PD-058 document.
Recommendations based on the PRS test:
Based on the PRS, it is possible to divide the patient's relative risk of developing breast cancer into different levels compared to the average in the given age, while accurately assessing the risk of a particular percentile.
Different levels of disease risk:
1. Lower or at the same level
2. Slightly elevated (up to two times)
3. Moderately elevated (two to three times)
4. Elevated more than three times

Applying the precision prevention model:
In Estonia, mammography screening in the age group 50-69 years at 2-year intervals is currently a recognized standard practice. Consequently, the “zero point” of the risk level at the beginning of the screening is the average risk level of 50-year-old women, which is a 10-year morbidity risk of N % using patient’s population data, calculated by Choudhury et al. using an absolute risk assessment model.
Patient’s individual and patient population average 10-year BC risks are reported in the AnteBC test report.
When assessing individual risk levels, the above risk groups can be advised based on current scientific knowledge:
Variant 1. If the risk is below average or at a medium level:
1. Participate in a standard mammography screening from the age of 50 years
2. Follow general guidelines for reducing the risk of breast cancer (see accompanying recommendations)

Variant 2. If the risk is slightly increased - up to two times (moderate increase in risk depending on age):
1. Implement mammography screening at 2-year intervals from the age at which the risk of the average 50-year-old woman is reached (depending on the age at which the 10-year risk reaches N %), i.e. screening is recommended for those under 50 years of age due to an increased risk.
2. Follow general guidelines for reducing the risk of breast cancer (see accompanying recommendations).

Variant 3. If the risk is increased two to three times (moderate increase in risk compared to the same age average):
1. Implement mammography screening at 2-year intervals from the age at which the risk of the average 50-year-old woman is reached (depending on the age at which the 10-year risk reaches N %.
and/or
2. Implement mammography screening at 1-year intervals from the age at which the average 50-year-old woman reaches twice the risk level (depending on the age at which the 10-year risk exceeds twice the corresponding age level or for women under 50 from the risk level of 2 x N %, which is twice the risk level for women aged 50 years)
3. Follow general guidelines for reducing the risk of breast cancer (see accompanying recommendations)
4. Discuss the use of breast cancer risk decreasing hormonal chemoprevention (tamoxifen, aromatase inhibitors) with your doctor

Variant 4. If the risk has increased more than three times the average (high-risk increase):
1. Implement mammography screening at 2-year intervals from the age at which the risk of the average 50-year-old woman is reached (depending on the age at which the 10-year risk reaches N %)
and/or
2. Implement mammography screening at 1-year intervals from the age at which the average 50-year-old woman reaches twice the risk level (depending on the age at which the 10-year risk exceeds twice the corresponding age level or for women under 50 years from the risk level of 2 x N %, which is twice the risk level for women aged 50 years)
3. Follow general guidelines for reducing the risk of breast cancer (see accompanying recommendations)
4. Discuss the use of breast cancer risk decreasing hormonal chemoprevention (tamoxifen, aromatase inhibitors) with your doctor
Additional recommendation: magnetic resonance imaging (MRI) is recommended with 1- or 2-year intervals at the age at which the three-fold risk level of the average 50-year-old woman is reached. If the patient's age exceeds the recommended age, the patient's own age is displayed (10-year disease risk is 3 x N %).
In addition to the results of polygenic risk score recommendations, the AnteBC test report gives general guidelines for reducing the risk of breast cancer.

Intervention Type
Genetic

Primary outcome(s)
The impact of implementing a population-based genetics testing strategy for breast cancer precision prevention measured using polygenic risk score and monogenic pathogenic variant (MPV) testing. The estimated risk levels (standard deviation units compared to the population average; 10-year risk levels of breast cancer) are calculated by AnteBC® CE IVDD breast cancer polygenic risk score test (Estonian Medical Devices Registry #14726 Antegenes OÜ, Tartu, Estonia) within 6 to 8 weeks after recruitment and submitted to healthcare providers' information systems (Estonia/Sweden/Portugal), as well as to participants (Estonia). The indication for monogenic pathogenic variant testing is estimated by the corresponding questionnaire completed by participants at recruitment and participants referred to clinical geneticist's counselling. If MPV is found, the interventions will follow the MPV routine. Otherwise, interventions will be based on polygenic risk score reports.

Key secondary outcome(s))
1. Feasibility of a population-based genetic testing strategy for BC precision prevention measured by participant, medical professional and stakeholder feedback at the end of the clinical study, either risk and intervention reports provided to the participants, or after first interventions including mammography and other imaging/oncology interventions if applicable
2. Clinical utility of a population-based genetic testing strategy for BC precision prevention, measured by clinical outcomes and long-term modelling at the study end. The researchers plan an additional long-term follow-up of the study cohort. The results will be compared to the Estonian Biobank cohort data on regular breast cancer screening cases with extended follow-up data available.
3. Cost-effectiveness of a population-based genetic testing strategy for BC precision prevention measured by cost-efficiency calculations, based on actual interventions and modelled follow-up data at study end

Completion date
31/12/2025

Eligibility

Key inclusion criteria
In Estonia and Portugal:
1. Healthy women aged between 35 and 49 years old (women currently not invited into regular BC screening)

In Sweden:
1. Healthy women aged between 30 and 39 years old (women currently not invited into regular BC screening
2. Healthy women aged between 40 and 50 years old (current BC screening group before 50)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
30 years

Upper age limit
50 years

Sex
Female

Key exclusion criteria

1. Women already diagnosed with malignancies or hereditary cancer syndromes
2. Women already tested for MPVs and PRS
3. Ashkenazy Jewish ethnicity

Date of first enrolment
01/06/2022

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
Estonia

Portugal

Sweden

Study participating centre
Tartu University Hospital (Tartu Ülikooli Kliinikum)
L. Puusepa 8
Tartu
Estonia
51014

Study participating centre
Uppsala University Hospital (Akademiska sjukhuset)
Sjukhusvägen
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Sweden
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Study participating centre
North Lisbon University Hospital Center (CHULN)
Centro Hospitalar Universitário Lisboa Norte E.P.E.
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Sponsor information

Organisation
EIT Health e.V.

Funder(s)

Funder type
Government

Funder Name
EIT Health

Alternative Name(s)

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to the privacy protection of the patients and the conditions of the informed consent. The participants have agreed that the data will be used for clinical research, but not for sharing the individual level data with third parties. Full individual-level data will be shared between participating institutions. Additional investigators may be engaged if permitted by Ethics Review Board. Please contact the PI of the BRIGHT study, neeme.tonisson@ut.ee.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes