Antegenes

White Paper

Breast Cancer Polygenic Risk Score Test
AnteBC

AnteBC is a genetic test that assesses a woman's risk of developing breast cancer using polygenic risk score (PRS) technology.
AnteBC is a clinical tool that estimates the breast cancer risk level of an individual for precise and efficient prevention and screening. It aims to reduce breast cancer morbidity and mortality. AnteBC test is recommended for women between the ages of 30 and 75.

AnteBC is a clinical test registered as a CE-marked medical device (in vitro diagnostics, IVD) in the EUDAMED database (UDI-DI: 04745010362019), in the Estonian Medical Devices Database (EMDDB code: 14726), and the UK MHRA Registry (GMDN code: 59918).
AnteBC has been developed by the health-tech company Antegenes and is performed by Antegenes' medical lab.

The test results provide information about a woman's polygenic risk level for breast cancer. This includes a breast cancer-specific PRS value, the absolute risk for breast cancer in the next 10 years, and the relative risk in comparison to women in the same age group and population on average.

Depending on the application, the test report may include individual clinical recommendations to reduce the risk of developing breast cancer such as:

- What age the individual should start breast cancer screening and how.
- Whether the individual should take additional measures to prevent breast cancer.
- What possible changes and symptoms regarding her breasts should the individual focus on.

The results of the AnteBC test can be used in the CanRisk (BOADICEA) combined breast cancer risk assessment model by entering the z-score in the AnteBC test report and the alpha value of 0.437.

AnteBC test can also be used in healthcare facilities only as CE-marked software as medical device if genotyping or sequencing is performed by an on-site laboratory.

Aim of the AnteBC Test

The main purpose of the AnteBC test is to reduce the risk of premature mortality from breast cancer. It provides more precise recommendations for breast cancer screening and additional preventive measures. Breast cancer risk stratification increases the precision and efficiency of methods in breast cancer prevention. The AnteBC test incorporates PRS technology into screening programs, enabling targeted recommendations for more efficient primary and secondary prevention.

AnteBC Test Methodology, Development and Validation

For the PRS calculation, AnteBC uses the patient's DNA data from genotyping and summarizes the impact of 2803 breast cancer-related single nucleotide polymorphisms (SNPs) (1).
To develop the AnteBC test, different PRSs and their risk differentiation estimations were validated using anonymous data from the Estonian Biobank and UK Biobank. Based on large-scale genetic data, various risk prediction models published in the international scientific literature were compared (1). Models were validated on the Estonian Biobank dataset consisting of 32,548 quality-controlled genotypes with 315 prevalent and 365 incident breast cancer cases and on 249,062 samples in the UK Biobank dataset consisting of 8637 prevalent and 6825 incident cases. The best-performing model was selected based on the AUC in prevalent data, adapted and independently validated in both incident datasets for practical use. The PRS underlying AnteBC test is based on the report by Mavaddat et al. (2) and includes 2803 SNPs (1).
The test is based on genome-wide association studies of patients and study participants of primarily European ancestry. However, the test is adapted by Antegenes to other ethnicities based on the analyses of risk performance in the ethnically diverse UK Biobank data.
Interpretations based on individual risk scores are dependent on the underlying population data. AnteBC estimates the distribution of individual risk levels relative to the rest of the population, using the population distribution and the risk differentiation between patients included in the validation. The patient's 10-year population-based risk is estimated using Choudhury et al. absolute risk model (1). The absolute risk model applies the risk differentiation estimates from the Estonian Biobank. The absolute risk model additionally uses patient sex, age, and country-based epidemiological background including overall breast cancer incidence and morbidity, and overall mortality information.

Analytical Validity

AnteBC only includes common SNPs and uses imputation with genotyped data to estimate un-genotyped positions. This allows the incorporation of information about a large number of genetic positions into the polygenic risk estimate that ultimately leads to increased predictive performance.
The interpretable output from AnteBC tests is the risk percentile (from 1 to 100). Considering all potential sources of variation in repeated sampling with the variation from workflows used in reference Estonian Genome Center data that were used in establishing AnteBC model assumptions, current estimates for a 95% confidence interval (CI) for women on the 90th of risk percentile is 71.1%-94.1%, for women on the 95th percentile it is 82.2%-97.3%, and for 99th percentile the CI would be 94.5%-99.5%.

Clinical Validity: AnteBC Performance Indicators

AnteBC uses summarized calculations from 2803 SNPs. The C-index of the Cox regression model associating breast cancer status with PRS was 0.656 (SE = 0.05) with a hazard ratio of 1.66 (95% confidence interval 1.5 - 1.84) on the incident EGC dataset. The PRS can identify individuals with more than a 3-fold risk increase. The observed 10-year risks of individuals in the 99th percentile exceeded the 1st percentile more than 10-fold.

AnteBC versus PRS313

Several alternative PRSs have been formulated for breast cancer, each containing a slightly different set of genetic variants and/or their associated effect estimates. One of the key resources for the development of breast cancer PRS tests remains the dataset of over 200,000 women collected by the Breast Cancer Association Consortium (BCAC) (3). These data have been used to generate two well-established PRS models the BCAC 313 model and the BCAC 3820 model (2). The BCAC 313 PRS is attractive for its good

performance achieved with a relatively small number of SNPs. The AnteBC PRS has been formulated based on the larger and more powerful BCAC 3820 PRS for its improved performance over BCAC 313 in diverse and independent datasets. AnteBC consistently exhibits approximately a 5% increase in predictive performance (as measured by odds ratio per standard deviation of PRS) over BCAC 313 in Estonian, United Kingdom (1) and Norwegian samples (4) (Figure 1). BCAC 313 also contains two pathogenic variants responsible for monogenic forms of breast cancer (in BRCA2 and CHECK2) complicating the interpretation of its results, especially when used in conjunction with MPV testing (2).

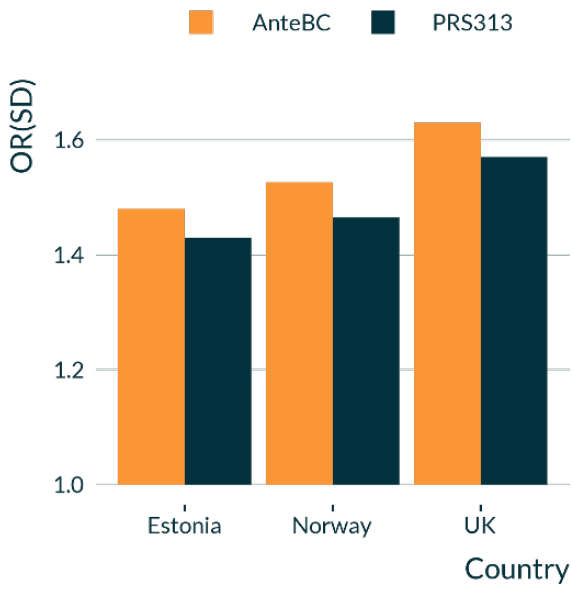

Figure 1. Comparison of the predictive performance of AnteBC and BCAC313 PRSs measured by odds ratio / standard deviation of PRS (1, 4, 5).

Clinical Indications for the Use of the AnteBC Test

AnteBC test is recommended for women between the ages of 30 and 75.
AnteBC test assesses a woman's personalized risk of developing breast cancer using a PRS information.

Based on individual risk level of a woman, medical professionals can give clinical recommendations on when to start screening, how to perform screening, and what additional risk reduction methods to use.

The primary clinical scenarios where the use of the AnteBC test is indicated:
1. Management of healthy women with a family history of cancer in hereditary cancer clinics.
2. Individual personalised breast cancer prevention and screening.
3. Breast cancer screening programs to make screening more precise and effective.

If non-genetic risk data is available, and the process is feasible, then it is possible to use AnteBC test results combined with other risk factors within combined risk prediction models such as CanRisk (6).

Breast cancer is the leading cause of cancer deaths in women. Every year adds 2.3 million new diagnoses and more than 660,000 deaths worldwide (7). Breast cancer morbidity and mortality can be reduced through primary and secondary prevention.

Personalised breast cancer risk-based management of healthy women with a family history of cancer in hereditary cancer clinic.

Extensive evidence form many studies demonstrate that for women with breast cancer familial history, but with negative findings in monogenic pathoigeniuc variant (MPV) testing, individual risk assessments and corresponding clinical recommendations are incomplete without PRS information and are not therefore the most complete clinical practice anymore (8-18).

Also, research evidence demonstrates that addition of PRS impact gives additional information for more informed decisions regarding the management of breast cancer risk from MPVs, especially in the case of MPVs in moderate-risk genes *CHEK2* and *ATM* (12, 15, 19-23).

Individual personalised breast cancer prevention and screening.

Many healthcare providers and wellness programs offer more comprehensive and personalized health controls and monitoring than the usual population-based public screening programs or are such programs implemented by employer organizations (corporate wellness). As breast cancer is the most common malignancy among women, screening and prevention of breast cancer should be mandatory part of these services. Consideration of genetic risks must be an important part of such services because without these relevant clinical recommendations are not accurate. Therefore, they should include both MPV and PRS testing. PRS is not directly inherited and is a risk factor independent of family history. Whilst MPVs on a population basis only substantially impact risk in 1.7% of women who carry them, around 50% get a meaningful change in risk from a PRS (24).

Enhancement of systematic public breast cancer screening programmes.

Breast cancer is the leading cause of cancer deaths in women in the world. Screening with mammography reduces breast cancer mortality risk by 20-40% (25-27). Current breast cancer screening guidelines are mostly based on age only and do not support regular screening of women below the age of 50. The relationship between the benefits and potential harms of mammography screening in the age group under 50 years has been controversial. Hence, a risk-stratified approach is highly desirable.

It is possible to classify patients based on the PRS according to their relative risk of developing breast cancer compared to the average risk in their age group. In the European Union, mammography screening in the age group 50-69 years at two-year intervals is currently a recognized standard practice to reduce breast cancer mortality. Consequently, the risk level at the beginning of the screening is the average risk level of 50-year-old women. Using AnteBC, it is possible to detect younger women with similar or higher risk levels already from age 30-35. This allows the implementation of targeted mortality reduction measures while avoiding increased screening for women at lower risk. A patient's individual and the corresponding population's average 10-year breast cancer risks are reported in the AnteBC test report.

For all women, the AnteBC test can also serve as a tool for individual informed "shared decisions" for mammography screening participation. Shared decision-making is the process by which patients and physicians share information, express diagnostic, and treatment preferences, and jointly agree on a diagnostic and treatment plan. The decision to implement screening should be a shared decision. Women should be able to make an informed decision to participate in a screening program, taking into account its

benefits and risks, i.e. women should be provided with adequate information (28). Both the U.S. Preventive Services Task Force, the American Cancer Society, and the American College of Obstetricians and Gynecologists recommend a shared decision in their guidelines and highlight the need for physicians to individualize patients' decisions to participate in breast cancer screening and involve patients in a joint participatory decision.
High-risk AnteBC test results may warrant the use of hormonal chemoprevention (29). Tamoxifen, raloxifene, anastrozole, and exemestane have been shown in several phase III randomized studies to reduce the risk of breast cancer (16-49%) in women at increased risk (30-35). The US Preventive Services Task Force recommends the use of tamoxifen, raloxifene, and aromatase inhibitors in women at increased risk for breast cancer and low risk of side effects. Hormonal chemoprevention, however, is not recommended for women with non-increased risk (29).

Clinical recommendations based on the AnteBC test

The clinical recommendations accompanying the AnteBC test are based only on the patient's age and polygenic risk results and do not consider other possible risk factors. Therefore, taking into account other risk factors, it is possible to modify the current recommendations if feasible and necessary.

The clinical recommendations are developed for CE-marked IVD level breast cancer PRS test AnteBC by medical professionals at the University of Tartu, Estonia, and in health-tech company Antegenes (5). AnteBC test results provide information about a woman's polygenic risk level for breast cancer. This includes a breast cancer specific PRS value (z-score), the absolute risk for breast cancer in the next 10 years, and the relative risk in comparison to women in the same age group and population on average. Currently, the reporting of the absolute risk for breast cancer in the next 10 years is chosen, as this is more relevant than the 5-year risk, but more clearly understandable than the lifetime risk. The interpretable output from AnteBC tests is the risk percentile (from 1 to 100).
Based on the PRS, it is possible to divide a 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.

Clinical recommendations based on AnteBC test results may depend on the clinical setting of the use, and also from relevant national guidelines for risk-stratified breast cancer prevention and screening.
Accordingly, the AnteBC test report may include individual clinical recommendations to reduce the risk of developing breast cancer such as:

- What age the individual should start breast cancer screening and how
- Whether the individual should take additional measures to prevent breast cancer
- What possible changes and symptoms regarding her breasts should the individual focus on.

Based on the PRS, it is possible to divide the patients' relative risks of developing breast cancer into different categories compared to the average risk in the given age group.
At the same time, an accurate assessment of the risk for a particular PRS percentile is provided.
Different Levels of Disease Risk:

- Lower or at the same level.
- Slightly elevated (up to two times).
- Moderately elevated (two to three times).

- Elevated more than three times.

Applying the logic of the model:

In the European Union, mammography screening in the age group 50-69 years at two-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 translates into a 10-year morbidity risk of **N %** using the patient's population data (N – depends on a population), calculated by Choudhury et al. using an absolute risk assessment model (36).

A patient's individual and a patient's population average 10-year breast cancer 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:

Category 1. The risk is below average or at a medium level:

- Participate in a standard mammography screening from the age of 50.
- Follow general guidelines for reducing the risk of breast cancer.

Category 2. The risk is slightly increased - up to two times (moderate increase in risk depending on age):

- Implement mammography screening at **two-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.
- Follow general guidelines for reducing the risk of breast cancer.

Category 3. The risk is increased two to three times (moderate increase in risk compared to the same age on average):

- Implement mammography screening at **two-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

- Implement mammography screening at one-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).
- Follow general guidelines for reducing the risk of breast cancer.
- Discuss the use of breast cancer risk-decreasing hormonal chemoprevention (tamoxifen, aromatase inhibitors) with your doctor.

Category 4. The risk Is increased more than three times the average (high-risk increase):

- Implement mammography screening at **two-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

- Implement mammography screening at one-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).
- Follow general guidelines for reducing the risk of breast cancer.
- 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 one- or two-year intervals at the age at which the three-fold risk level of the average 50-year-old woman is reached.

AnteBC Test Limitations

- AnteBC cannot be used to diagnose breast cancer.
- High risk does not necessarily mean that the patient will develop breast cancer during her lifetime.
- Moderate or lower risk does not necessarily mean that the patient will never develop breast cancer during her lifetime.
- AnteBC test results are individual and patient-specific. The AnteBC test does not assess the risk for the patient's family members or relatives. The inheritance pattern of PRS is complex and each person has to be tested separately.
- AnteBC does not analyse rare monogenic pathogenic variants in genes that significantly increase the risk of breast cancer, such as *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, RAD51C, RAD51D, TP53*, and others. If a woman's biological relative has a monogenic pathogenic variant in these genes, or if a woman has several breast or ovarian cancer cases in her family, Antegenes recommends additional counselling and testing for such monogenic variants.
- AnteBC test is based on the most recent scientific data, which may be supplemented and/or changed in the future if additional information becomes available. The field of genetics is constantly evolving, which may lead to changes in risk assessments over time, changes in test selection, and clinical recommendations.
- Different polygenic risk scores predicting risks of the same trait may give different estimates of the individual's risks due to differences in the genetic variants included in these models and their weights.
- The results of this test should be applied in combination with other relevant clinical data. In addition to genetic predisposition, other risk factors influence the risk of developing breast cancer.

Getting started with AnteBC Test

To perform the test, a DNA sample must be taken using a buccal swab or saliva kit. This is an easy and safe procedure. The buccal swab or saliva collection kit is convenient to use independently at home or at a medical facility. Detailed instructions are included in each kit.
The sample is sent to the Antegenes laboratory via organized delivery.
Based on patient data, individual test reports are generated. Reports are available only for an individual or for her doctor if a test is ordered by a healthcare professional.

Regulatory Status of the AnteBC Test

AnteBC as a registered CE-marked IVD is currently in full compliance with EU and UK regulations. Additionally, Antegenes is ISO13485 certified (Quality Management System for Medical Devices).

The EU Regulation 2017/746 on vitro diagnostic medical devices states (37):
"It should be made clear that all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are *in vitro* diagnostic medical devices.
and
'*in vitro* diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used *in vitro* for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
(c) concerning the predisposition to a medical condition or a disease."
Accordingly, PRS estimations for clinical use are genetic tests and must be in vitro medical devices.

AnteBC as a registered CE-marked IVD is currently in full compliance with EU regulations.

AnteBC test is registered in the United Kingdom MHRA Registry (GMDN code: 59918), and as a registered CE-marked IVD currently in full compliance with UK regulations.

Additional Information

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