Scientific and practical background

Personalised Breast Cancer Prevention for Women in the United Kingdom.

Breast cancer is the most common cancer among women in the United Kindgom (UK), with approximately 56,000 women diagnosed annually (1). It is also the second leading cause of cancer death in UK women, resulting in around 11,500 female deaths each year (1). The incidence and mortality of breast cancer can be significantly reduced through primary and secondary prevention (2).

Primary Prevention

Primary prevention focuses on lifestyle modifications, including maintaining a healthy diet, controlling weight, engaging in regular physical activity, limiting alcohol intake, and promoting prolonged breastfeeding. Medical interventions, such as hormonal preventive medications and risk-reducing surgery for individuals at very high risk, are tailored to individual risk factors in consultation with healthcare providers.

Secondary Prevention

Secondary prevention through mammography screening has been shown to reduce breast cancer mortality by approximately 20-30% (3-5). In the UK, the NHS Breast Screening Programme invites women aged 50 to 71 for mammography every three years (6). However, this age-based approach does not account for individual variations in breast cancer risk, overlooking younger women at higher risk and older women who may benefit from more intensive screening. In the UK, approximately 20% of breast cancer cases are diagnosed in women under the age of 50 (1). The traditional one-size-fits-all approach to breast cancer screening does not account for individual variations in risk factors such as genetic predisposition, family history, breast density, and lifestyle factors. Personalised risk-stratified prevention aims to tailor screening strategies to individual risk profiles, enhancing the benefits while minimizing the harms. An alternative to age-based screening is risk-based screening, where individual risk assessments guide screening recommendations (7-9).

Genetic predisposition as a significant breast cancer risk factor

It has been shown that hereditary factors account for approximately one-third of overall breast cancer risk (10). Therefore, genetic predisposition followed by a genetic risk assessments are an extremely important component in risk-based, or personalised, breast cancer prevention.

Monogenic Breast Cancer Risk

Genetic factors encompass rare **monogenic pathogenic variants (MPVs)** in high- and moderate-risk cancer predisposition genes. Recent analyses have specified MPVs in the genes ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, PALB2, RAD51C, RAD51D, TP53, PTEN, and STK11, all associated with higher breast cancer risk levels [18-21]. However, these rare MPVs are connected with only a small proportion (5–10%) of breast cancer cases (11). Only around 1.7% of people and 5.7% of those with breast cancer currently are known to carry MPVs in the 12-13 actionable breast cancer genes conferring at least a reported 2-fold risk (12). For women in the UK, the UK NHS service for MPV testing may be available based on specific criteria. GPs can refer women for gene testing if women have any of the following:

- a first degree relative (parent, sibling or child) with breast cancer diagnosed before age 40
- a first degree relative with cancer in both breasts and one diagnosed before age 50
- two or more first degree, or one first degree and one second degree, relatives with breast cancer
- a relative with a known gene mutation
- you are over 18 and have at least one Jewish grandparent.

See https://www.nhs.uk/conditions/predictive-genetic-tests-cancer/ for more information.
Carriers of MPVs associated with an increased risk of breast cancer are recommended to undergo more intensive surveillance and may also be offered additional preventative options.

Polygenic Breast Cancer Risk

A significant proportion of breast cancer risk variation is attributed to common single-nucleotide polymorphisms (SNPs) located outside high- and moderate-risk genes [16]. These SNPs have been identified through genome-wide association studies (GWAS) (13, 14). **A polygenic risk score (PRS)** represents the cumulative impact of multiple breast cancer susceptibility SNPs. While individual SNPs may confer only a modest risk, their combined effect can be considerable. A breast cancer PRS reflects the cumulative impact of these susceptibility variants, which have been shown to effectively stratify individual breast cancer risk [17,29-33].
PRS is the strongest independent risk factor for breast cancer development on a population basis [34,35] outweighing MPVs. Breast cancer PRSs highlight variations in genetic risk and serve as a foundation for developing personalised screening programmes that consider individual genetic susceptibility [36]. In particular, in contrast to MPV testing, they identify a low-risk population. Modelling studies indicate that incorporating risk profiles into preventive strategies may lead to both cost savings and improved health outcomes [37-39]. A high-risk assessment may also justify the use of hormonal preventive medication [40].
The development of a clinical grade level breast cancer PRS test AnteBC and the clinical implementation outside of research settings have been described by Padrik et al. [44]. The process aimed to develop a clinical-grade PRS test suitable for risk-stratified breast cancer screening, accompanied by clinical implementation guidelines. In the initial phase, previously published PRS models for breast cancer risk prediction were reviewed and validated using data from the Estonian Biobank and UK Biobank. The most effective model was selected based on prevalence data and

independently validated in both incident datasets. This optimal PRS, incorporating 2,803 SNPs (PRS2803), achieved a con-cordance index (C-index) of 0.656 (SE = 0.05) in a Cox regression model assessing breast cancer status. Following absolute risk simulations, risk-based recommen-dations were developed, calibrations to African, East-Asian, South-Asian and mixed populations were performed based on UK Biobank data and the test was registered as a CE-marked in vitro device (the AnteBC test) and implemented into clinical practice [44]. The test performance data is also additionally analysed using Norwegian population genetic data, confirming the risk-separation performance [45].

Utilising Breast Cancer Polygenic Risk Scores in Clinical Practice

Based on published research evidence, breast cancer PRSs have become an increasingly relevant tool in the landscape of breast cancer risk-stratified prevention and screening. The evidence-based clinical use of the breast cancer polygenic risk score is reflected in published clinical guidelines, which outline different clinical use scenarios (9):

1) Management of healthy women with a family history of cancer in hereditary cancer clinics (27-38).
2) Individual personalised breast cancer prevention and screening in healthcare services (20, 39).
3) Breast cancer screening programs to make screening more precise and effective (24, 25, 40-43).

Scientific background of medical recommendations based on the AnteBC polygenic risk score test

There are three key foundations for implementing clinical recommendations based on PRSs, as outlined below. In the article on the development and clinical application of a breast cancer PRS test, authors have described the PRS test output, including the z-score (expressed as standard deviations), risk percentile, relative risk compared to individuals of the same age and population, and the corresponding 10-year absolute risk (15). Authors also outlined a version of clinical recommendations for PRS risk-based breast cancer prevention and screening. These recommendations may be adapted to align with existing country-specific guidelines for risk-based approaches.

Comparison with the average risk of the same population at the same age, combined with a comparison to the average risk upon initiation of mammographic screening

Principally, societies have agreed that the average risk level at age 50 in most European countries is suitable to start public mammography screening (16). It may be logical to start screening at a younger age for women if their PRS driven risk level achieves the same level or is higher than the average risk at age 50. This is according to principles of equitability and equivalence of risks. Figure 1 describes the age difference for women at high PRS risk in reaching same risk level compared to women at average risk at baseline for the start of current screening (age 50).

The WISDOM study applies this approach to women aged 40 to 49 years, recommending screening when their five-year risk meets or exceeds that of the average 50-year-old woman (17). This study employs five-year risk thresholds, as screening and preventive measures are most

effective for individuals at imminent risk of developing cancer. Additionally, five-year risk estimates are commonly used to guide chemoprevention strategies. In the WISDOM study, the five-year risk threshold for women aged 50 was set at 1.3%.

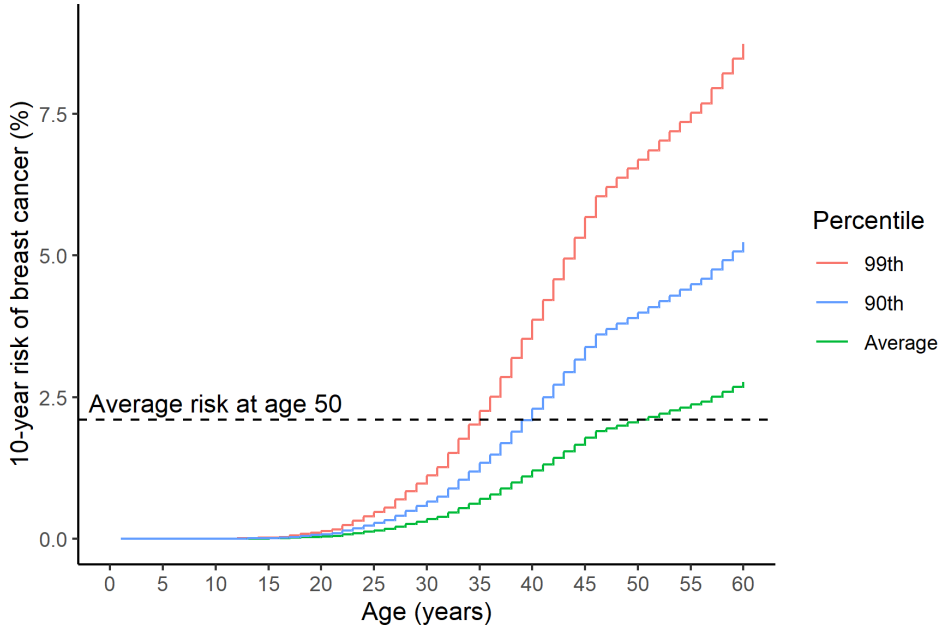

Figure 1. 10-year risk of developing breast cancer according to woman's age and PRS2803 percentile (15). 99th percentile – red, 90th percentile – blue, population average – green. Population background is from breast cancer incidence data for Norway 2018-2020 (from Nordcan 2.0).

Comparison with similar risk MPVs

Like elevated polygenic risk, moderately elevated risk level (lifetime risks 25-30%) applies to MPVs in genes *ATM* and *CHEK2* (18), Figure 2. Accordingly, on the same PRS risk level, similar clinical recommendations can be given as in the case of moderate-risk MPVs. A comparative modelling analysis has shown that for women with *ATM*, *CHEK2*, and *PALB2* pathogenic variants annual MRI screening starting at 30 to 35 years followed by annual MRI and mammography at 40 years may reduce breast cancer mortality by more than 50% (19). A similar approach is feasible for women at the same risk level using PRS testing.

Breast cancer risk management in the case of moderate-risk MPVs is included for example in the NCCN guidelines. NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 3.2024 (20): "In the case of MPVs in *ATM* and *CHEK2* is recommended annual mammography at age 40 years and consider MRI with contrast starting at age 30-53".

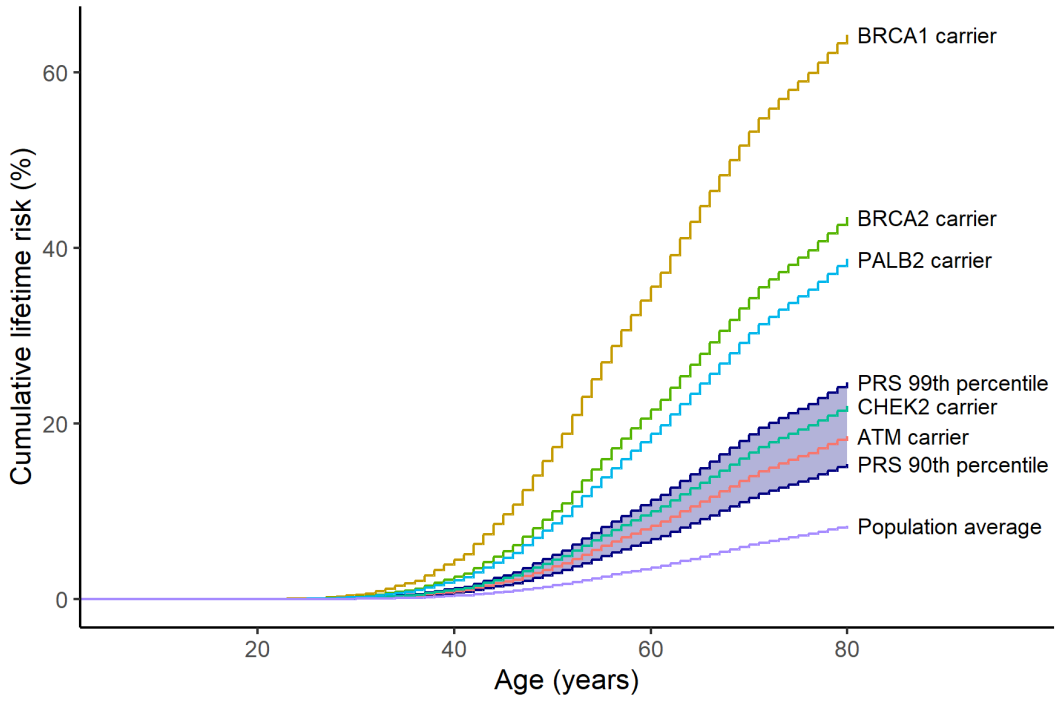

Figure 2. Cumulative lifetime breast cancer risks of carriers of protein truncating pathogenic variants in breast cancer risk genes compared to women in PRS2803 upper decile (blue). Breast cancer risks of pathogenic variant carriers are from the analysis by the Breast Cancer Association Consortium (21). Population background is from breast cancer incidence data for Norway 2018-2020 (from Nordcan 2.0).

Comparison with already existing national guidelines based on other risk factors (not including PRSs) for risk-stratified breast cancer screening according to different risk levels

In this context, it is possible to use PRS isolated risk information as well as total risk estimation using combined models. The current guidelines for breast risk-stratified screening and surveillance of selected countries are reflected below, primarily based on the current practice of the authors of the article.

Current guidelines in the United Kingdom

UK National Institute for Health and Care Excellence (NICE) guidelines for the management of women with familial breast cancer risk are using thresholds for risk categories (22), Table 1.

Table 1. Breast cancer risk categories by the UK NICE guidelines (22), corresponding relative risks added based on average lifetime risk data (1).

	Breast cancer risk category		
	Near population risk	Moderate risk	High risk
Lifetime risk from age 20	Less than 17%	17% or greater but less than 30%	30% or greater
Risk between ages 40 and 50	Less than 3%	3-8%	Greater than 8%

Corresponding relative risk	Less than 1.5	1.5-2.7	Greater than 2.7

The NICE guidelines classify breast cancer risk into three categories: general population risk, moderate risk, and high risk (22). Women at general population risk have an estimated lifetime breast cancer risk of approximately 11% (1). Those at moderate risk have a lifetime risk exceeding 17% but below 30%, while women at high risk have a 30% or greater likelihood of developing breast cancer over their lifetime. Accordingly, the UK NICE Guidelines have defined a moderate risk as 1.5 to 2.7 times higher than average risk, and a high risk as more than 2.7 times higher than average.

Breast cancer PRS can allocate risk groups based on this accordingly (15):

- general population risk: 1.–79. percentiles;
- moderate risk: 80.–97. percentiles;
- high risk: 98.–99. percentiles.

The NICE guideline also gives recommendations on surveillance for high- and moderate-risk groups of different ages, recommending annual mammography from age 40 for increased-risk groups.

This Personalised Breast Cancer Prevention service takes all of the above aspects into account when providing clinical recommendations based on its breast cancer PRS.

Possibilities to Combine Breast Cancer PRS with Other Risk Factors

Several integrated risk prediction models combine traditional risk factors, including demographic characteristics, reproductive history, menopausal status, family history, prior biopsies, mammographic density, and carrier status of MPVs and PRSs (13-17). For comprehensive breast cancer risk predictions, PRS test information can be used within combined risk models such as CanRisk or Tyrer-Cuzick (15, 18). In these models, the use of other known risk factors in combination with PRS has been shown to enhance the prediction of combined models (19-21).

PRS alone has been shown to predict breast cancer risk more accurately than existing clinical models (23). Van den Broek et al. evaluated the clinical utility of PRS alongside a first-degree family history of breast cancer to guide screening decisions for women aged 30–50 years (24). Their findings suggested that incorporating PRS and family history help refine screening strategies before the age of 50, reducing breast cancer mortality among women at high risk due to genetic susceptibility. Additionally, an analysis by Wolfson et al. concluded that population-wide breast cancer screening programmes aiming to stratify women by genetic risk should prioritise PRS over rarer but highly penetrant variants or family history (25).

The results of the clinically available AnteBC test (PRS2803, Antegenes Ltd.) can be used in the CanRisk combined breast cancer risk assessment model by entering the z-score from the AnteBC test report and the alpha value of 0.437 or in Tyrer-Cuzick using the non-logarithmic OR.

The Current Service of Personalised Breast Cancer Prevention

Personalised Breast Cancer Prevention is an up-to-date solution aimed at minimizing the potential impact of breast cancer by tailoring it to a woman's genetic risk level (23, 24).
It begins with polygenic risk score testing (AnteBC test), as polygenic risk score is the strongest independent risk factor for breast cancer. Based on the test results, women receive personalised medical plans for screening and prevention. This guidance includes when and how to initiate breast cancer screening and other effective strategies (hormonal medical prevention, health behaviour changes) to reduce personal risks. The service also includes a family history questionnaire for breast cancer, based on which it is determined whether the woman requires additional testing for rare monogenic pathogenic variants (in genes such as *BRCA1*, *BRCA2*, etc.). Armed with scientifically backed and well-documented medical advice, women can take preventive measures within their local healthcare system to protect their health proactively.

To whom? Recommended for women aged 30-75.
The service includes:

- Polygenic risk assessment of breast cancer (AnteBC test) combined with age, population background and ethnic information.
- Medical plans with clinical recommendations based on personal polygenic risk level for breast cancer prevention and early detection.
- Family cancer history questionnaire to assess the need for monogenic pathogenic variant (MPV) testing; if indicated, recommendations for a medical geneticist consultation and MPV testing. Based on family history criteria for breast cancer, women can also undergo MPV testing through their GP within the NHS system. The current service determines the need for this.
- Following possibilities to implement breast cancer prevention and control according to personalised medical plans (relevant information is provided in these personalised medical plans).
- Optional: possibilities for additional verbal counselling and consultations with medical professionals.
- As next steps, it is possible for women in breast clinics and through GPs to complement their genetic risk assessment with additional information based on mammographic breast density following mammography, as well as using combined risk assessment models (such as the CanRisk and Tyrer-Cuzick models). Based on family history criteria for breast cancer, women may undergo MPV testing through their GP within the NHS system.
- Optional: if a combined breast cancer risk assessment model (as the CanRisk or Tyrer-Cuzick model) is used in clinical practice, the AnteBC test result can be integrated into the model to provide the more accurate and regulatory compliant information for clinical practice.

Additional information:

Members of the Personalised Breast Cancer Prevention Consortium are among the leading experts who have developed and published international clinical guidelines for the clinical use of the breast cancer polygenic risk scores in personalised breast cancer prevention:

- Padrik P, Tõnisson N, Hovda T, Sahlberg KK, Hovig E, Costa L, et al. Guidance for the Clinical Use of the Breast Cancer Polygenic Risk Scores. Cancers. 2025;17(7):1056.
- First international clinical guidance on breast cancer polygenic risk scores published.
- Groundbreaking Global Guidelines Released on Breast Cancer Polygenic Risk Scores.

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