AnteNOR and BRIGHT project consortia

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Guidance for the clinical use of the breast cancer polygenic risk score testing

Breast cancer PRS test - a new necessary standard component for breast cancer risk assessment in personalized risk-based breast cancer prevention.

This guidance endeavours to articulate the scientific evidence underpinning the clinical utility of polygenic risk score in stratifying breast cancer risk, with a particular emphasis on clinical application. It delineates pertinent scenarios wherein its clinical employment is relevant and deliberates on the methodologies through which these principles can be pragmatically instituted within a clinical environment.

Recently the American College of Medical Genetics and Genomics (ACMG) published the statement about the clinical application of polygenic risk scores with points to consider in the clinical application of PRSs (1). Authors state that although being rapidly incorporated into health care, there are currently no clinical guidelines available for the use of this technology.

The current guidance has been created by the AnteNOR and BRIGHT projects developing the clinical use of the breast cancer polygenic risk score and aims to fill this gap.

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Background: Breast Cancer Prevention and Screening

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 (2). Breast cancer morbidity and mortality can be reduced through primary and secondary prevention.

Primary breast cancer prevention involves lifestyle modifications such as a healthy diet, regular exercise, and limiting alcohol intake, alongside medical interventions including hormonal chemprevention, prophylactic surgery in very high risk cases, and prolonged breastfeeding, all tailored to individual risk factors and developed in consultation with healthcare providers(3).

Secondary breast cancer prevention with mammography screening reduces mortality risk from breast cancer by 20-40% (4-6). Current screening guidelines are mostly based on age only and do not support regular screening of women below the age of 50. In most European countries, women aged 50-70 years are invited to breast cancer screening at two-year intervals (7, 8).

Such an approach does not account for the wide variation in individual women's breast cancer risks and disregards younger women with a higher risk, but also women over age 50 with higher risk levels who could benefit from intensified screening. Risk-based screening, in which individualized risk assessment is used to inform screening practices, has been proposed as an alternative to age-based screening (9, 10).

Around one third of the total breast cancer risk has been shown as hereditary (11). Therefore, genetic predisposition and genetic risk assessments are an extremely important component in risk-based, or personalised, breast cancer prevention. Genetic factors include rare monogenic pathogenic variants (MPVs) in high and moderate-risk cancer predisposition genes, having effects large enough to warrant monogenic testing. However, only a fraction (5-10%) of breast cancer cases are caused by these rare MPVs (12). A considerable part of breast cancer risk variation is explained by variants outside these high-risk genes in the form of breast cancer associated common single-nucleotide polymorphisms (SNPs), identified by genome-wide association studies (GWAS) (13, 14). A polygenic risk score (PRS) is the combined effect of individual breast cancer susceptibility SNPs. Although individual associated SNPs may confer only modest disease risk, the combined effect of all known associated SNPs on risk can be substantial. An additional component of genetic susceptibility is also family history without known MPV and PRS data.

Monogenic Breast Cancer Risk

Certain inherited variants (MPVs) in individual genes have a significantly higher predisposition to breast cancer. Recent analyses have specified MPVs in genes *ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, RAD51C, RAD51D, TP53, PTEN, STK11* associated with significantly or moderately higher breast cancer risk levels (15-17).

Testing for MPVs requires panel sequencing of selected genes or sequencing of the entire exome or genome. Indications for MPV testing in healthy individuals are usually defined by international and national guidelines using family cancer history (18-21).

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. The specifics of how carriers are followed can vary based on individual risk factors, family history, and the type of variant.

Polygenic Breast Cancer Risk

A considerable part of breast cancer variation is explained by variants outside high-risk or moderate-risk genes in the form of breast cancer-associated common SNPs (13). PRS in general is an estimate of an individual's susceptibility to develop a specific disorder, based upon the weighted association of single-nucleotide variants (formerly single-nucleotide

polymorphisms) or risk variants identified in genome-wide association studies (22). A breast cancer PRS is the combined effect of individual breast cancer susceptibility variants identified by genome-wide association studies and which have demonstrated their ability to assess individual breast cancer risk levels (14, 23-27).

PRS is the strongest independent risk factor for breast cancer development (28, 29). Breast cancer PRSs identify differences in genetic risks and provide a straightforward basis for designing personalized screening programs by accounting for individual genetic susceptibility (30). Modelling studies have suggested that risk profile informed preventive activities could provide cost savings and health benefits (31, 32). High-risk estimation could be also an indication for the use of hormonal chemoprevention (33).

Assessment of the performance of polygenic risk scores is commonly performed using the hazard ratios (HRsd) or odds ratios (ORsd) for an increment of one standard deviation in the score and the area under the receiver operating characteristic curve (AUC) (34). AUC is the most used statistic for assessing discrimination ability of PRSs, it is defined as the probability that an individual with a disease will be assigned a higher risk than an individual without the disease. AUC of 0.5 indicates no discrimination and 1 indicates perfect discrimination. Breast cancer PRSs alone can be considered to exhibit modest discrimination at around 0.6 - 0.65 (35), however when considering PRS use in clinical context, the added information provided by PRSs has the potential to detect a large portion of the population at increased risk of breast cancer (36).

It is common to report hazard ratios for PRS top quintile, top decile or for top 5%, 2% or 1% percentiles compared to average or low PRS category while modelling breast cancer. In addition, incidence rates of breast cancer in PRS categories are informative. In a landmark study, Mavaddat with colleagues developed several PRSs for breast cancer, from the largest available genome-wide association dataset and empirically validated the PRSs in prospective studies (23). The development dataset comprised 94,075 case subjects and 75,017 control subjects of European ancestry from 69 studies, divided into training and validation sets. Samples were genotyped using genome-wide arrays, and SNPs were selected by stepwise regression or lasso penalised regression. The best performing PRSs were validated in an independent test set comprising 11,428 case subjects and 18,323 control subjects from 10 prospective studies and 190,040 women from UK Biobank (3,215 incident breast cancers). For the best PRSs (313 SNPs), the odds ratio for overall disease per 1 standard deviation in 10 prospective studies was ORsd=1.61 (95%CI: 1.57–1.65) with area under receiver-operator curve (AUC) = 0.630 (95%CI: 0.628–0.651). The lifetime risk of overall breast cancer in the top centile of the PRSs was 32.6%. Compared with women in the middle quintile, those in the highest 1% of risk had 4.37- and 2.78-fold risks, and those in the lowest 1% of risk had 0.16- and 0.27-fold risks, of developing ER-positive and ER-negative disease, respectively. Goodness-of-fit tests indicated that this PRS was well calibrated and predicts disease risk accurately in the tails of the distribution. Authors concluded that breast cancer PRS is a

powerful and reliable predictor of breast cancer risk that may improve prevention programmes (23).

The development of the clinical grade level breast cancer PRS test and the first clinical implementation outside of research settings have been described by Padrik et al. (37).

Authors aimed to develop a clinical-grade PRS test suitable for breast cancer risk-stratified screening with clinical recommendations and implementation in clinical practice. In the first phase of the development, authors gathered previously published PRS models for predicting breast cancer risk from the lit-erature and validated them using the Estonian Biobank and UK Biobank data sets. The best performing model was chosen based on prevalent data and independently validated it in both incident data sets. The best performing PRS included 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. The PRS can stratify individuals with more than a 3-fold risk increase. After that absolute risk simulations were conducted, developed were risk-based recommendations, the test was registerd as a CE-marked in vitro device, and implemented in clinical practice (AnteBC test, manufactured by OÜ Antegenes) (37).

PRSs are distinct from monogenic tests. Single gene or panel tests focus on loci and variants with large effects, whereas PRSs evaluate a cumulative risk of multiple loci. In contrast to monogenic diseases, multifactorial, complex diseases require non-family-based approaches, such as a PRS, because of the lack of population-level genetic segregation. In clinical practice, it is important to consider the impact of both types of genetic predisposition.

Possibilities to Combine Breast Cancer PRS with Other Risk Factors

Several combined risk prediction models incorporate traditional risk factors such as demographics, reproductive history, menopausal status, family history, previous biopsies, mammographic density, and carrier status of MPV and PRS (29, 38-40). For comprehensive breast cancer risk prediction, PRS test information can be used within combined risk models such as CanRisk or Tyrer-Cuzick. In these models, the use of other known risk factors in combination with PRS has been shown to enhance the prediction of combined models (35, 41, 42).

Lee et al. showed that a combined risk by the CanRisk model that includes PRS, family history, breast density and other risk factors is estimated to identify ~13% of the population at moderate or high risk of developing breast cancer (29). Using the Tyrer-Cuzick model this can rise to as high as 20%(41). As expected, the variation in risk is greatest when including all risk factors in the model (29).

PRS alone has been shown to predict the risk of breast cancer in European descent individuals more accurately than current clinical models (43). Van den Broek et al. have assessed the clinical utility of a first-degree breast cancer family history and PRS to inform screening decisions among women aged 30-50 years (44). Results suggested that breast cancer family history and PRS could guide screening decisions before age 50 years among women at

increased risk for breast cancer with the potential to prevent more breast cancer deaths for identifiable groups of women at high risk due to their breast cancer family history and polygenic risk. Analysis by Wolfson et al. concluded that population-wide programs for breast cancer screening that seek to stratify women by their genetic risk should focus first on PRS, not on more highly penetrant but rarer variants, or family history (28). The PRS was most predictive for identifying women at high risk, while family history was the weakest.
The results of the clinically available AnteBC test can be used in the CanRisk combined breast cancer risk assessment model by entering the z-score in the AnteBC test report and the alpha value of 0.437.

Utilising Breast Cancer Polygenic Risk Scores in Clinical Practice

Breast cancer PRSs have become an increasingly relevant tool in the landscape of breast cancer risk-stratified prevention and screening. Here are the primary clinical scenarios where the use of PRS can be particularly impactful:

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 PRS test results combined with other risk factors within combined risk prediction models such as CanRisk (45).

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

1.1. Women with negative breast cancer MPV test findings

Testing of rare pathogenic variants is already standard practice for women with significant breast and ovarian cancer family history or known with diagnosed MPVs in relatives, and with already demonstrated clinical benefit. Approaches in the case of MPVs are summarized in different guidelines and include earlier more intense screening methods (yearly mammography and MRI), hormonal chemoprevention, but also risk-reducing surgeries(19). However, for women in whom MPV testing did not detect the presence of MPVs in them or their families, PRS testing is recommended to fully assess their genetic risk (46-50). PRS identifies women at a genetically high risk of breast cancer who tested negative for monogenic risk genes (51).

A study by Evans et al. demonstrated that PRS gave additional risk modification information for women with familial breast cancer history who received combined risk estimation using the Tyrer-Cuzick model (52). Authors concluded that PRS may be used to refine risk assessment for women at increased familial risk who test negative/have a low likelihood of BRCA1/2 mutations (52).

A study by Dite et al. analysed how much breast cancer risk prediction models can be improved by including information on known susceptibility SNPs. The study showed that for women under the age of 50 according to the population-based Australian Breast Cancer Family Registry data, a 77 SNP-based PRS improved risk prediction by >20% in combined risk prediction models (48).

A study by Li et al. examined the utility of PRS in familial but non-BRCA-associated breast cancer cases, demonstrating that according to their PRS-based predicted risk, management for up to 23% of women could be altered (49).

A study by Mars et al. showed that the PRS improved risk assessment of first-degree relatives of women with breast cancer, with pronounced stratification particularly for family history of early-onset disease (53). Family history is an essential factor guiding screening strategies of family members of breast cancer patients and study results showed that PRS could improve the precision of this assessment (53).

A study by Lakeman et al. showed that including the PRS in the BOADICEA combined risk model for family-based risk prediction changed screening recommendations in up to 27%, 36% and 34% of cases according to breast cancer screening guidelines from the USA, UK and the Netherlands (50).

A study by Stiller et al. aimed to assess the clinical value of incorporating a PRS into breast cancer risk calculations in a cohort of German women with suspected hereditary breast and ovarian cancer syndrome (54). The PRS led to changes in risk stratification based on 10-year risk calculations in 13.6% of individuals. Furthermore, the inclusion of the PRS in breast cancer risk predictions resulted in clinically significant changes in 12.0% of cases, impacting the prevention recommendations established by the German Consortium for Hereditary Breast and Ovarian Cancer. These findings support the implementation of the PRS in genetic counselling for personalized breast cancer risk assessment (55).

A study by Tüchler et al. assessed estimated lifetime risks and estimated 10-year risks of 425 cancer-free women with cancer family history using CanRisk model, including germline MPV status, non-genetic risk factors, and a 306 variant-based PRS, analysing impact to the proportions of women changing country-specific European risk categories for intensified breast screening (56). Study findings showed that for women with non-informative MPV status, including PRS and non-genetic risk factors changed clinical recommendations up to 31.0 % of cases, whereas of the women tested negative for a MPV observed in their family, clinical recommendations changed up to 16.7 % of cases. This study provided additional rationale for considering PRS and non-genetic risk factors for individualized breast cancer risk prediction in routine clinical care (56).

This data shows that for women with breast cancer familial history, but with negative findings in MPV testing, individual risk assessments and corresponding clinical recommendations are incomplete without PRS information and are not therefore the most complete clinical practice anymore.

1.2. Women with breast cancer MPV findings

PRSs have been shown in several studies to modify risk associated with MPVs in high- and moderate-risk breast cancer risk genes. Incorporating PRS into genetic testing for MPVs can improve the accuracy of risk estimation and aid risk management decisions for women who are MPV carriers, especially for MPVs in moderate risk genes *ATM* and *CHEK2* (57-60).

A study by Kuchenbaecker et al. showed that breast cancer PRSs were predictive of cancer risk in BRCA1 and BRCA2 MPV carriers (57). Authors conclude that breast cancer PRSs are predictive of cancer risk in BRCA1 and BRCA2 carriers and incorporation of the PRS into risk prediction models has promise to better inform decisions on cancer risk management (57).

A study by Fahed et al. estimated that among carriers of a MPV substantial gradients in disease risk based on the polygenic background has the probability of disease by age 75 years ranged from 13% to 76%, proposing that accounting for the polygenic background is likely to increase the accuracy of risk estimation for individuals who inherit a MPV (58).

A study by Gallagher et al. demonstrated that the 86-SNP PRS was associated with modified risk for carriers of *BRCA1, BRCA2, CHEK2, ATM,* and *PALB2* MPVs (59).

Results from the study by Gao et al. revealed that PRS facilitates the personalization of breast cancer risk among carriers of MPVs in predisposition genes. Incorporating PRS into breast cancer risk estimation may help identify > 30% of *CHEK2* and nearly half of *ATM* carriers below the 20% lifetime risk threshold, suggesting the addition of PRS may prevent overscreening and enable more personalized risk management approaches (60).

A study by Mars et al. analysed how the PRS modifies breast cancer risk in the mutation carriers (53). For both *PALB2* and *CHEK2*, a high PRS further increased the breast cancer risk. In terms of lifetime risk for breast cancer by age 80, women with the *PALB2* mutation and average PRS (10–90th percentile) had a lifetime risk of 55.3% (95% CI 49.4–61.2%), which increased to 83.9% (71.2–96.6%) among women with a high PRS (>90th percentile) and decreased to 49.1% (30.6–67.6%) in women with a low PRS (<10th percentile). Women with *CHEK2* and an average PRS had a lifetime risk of 29.3% (95% CI 26.8–31.8%) which doubled to 59.2% (52.1–66.3%) in women with a high PRS and decreased to 9.3% (4.5–14.1%) in women with low PRS (53).

A study by Lakeman et al. showed that among carriers of MPVs in known moderate breast cancer susceptibility genes, the PRS had the largest impact on *CHEK2* and *ATM* (50).

Study by Schreurs et al. analysed the changes in surveillance category by adding a polygenic risk score based on 311 breast cancer-associated variants (PRS_{311}), questionnaire-based risk factors and breast density on personalized breast cancer risk in unaffected women from

Dutch *CHEK2* c.1100delC families (61). The surveillance advice was reclassified in 20 (34.5%) heterozygotes and 21 (35.6%) non-carriers after adding PRS_{311}. The addition of PRS, questionnaire-based risk factors and breast density to family history resulted in a more personalized breast cancer surveillance advice in *CHEK2*-families, which may lead to more efficient use of surveillance (61).

Summarising the data, we can conclude that the 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*.

2. 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 (41).
Breast cancer individual personalised prevention and screening using the PRS test is implemented currently in Estonian private healthcare (37), but also in different private practices in the UK. The PRS test AnteBC development and preliminary published data about clinical use demonstrate that the PRS test separates different BC risk levels and is feasible to implement in clinical practice (37).

3. Enhancement of systematic public breast cancer screening programmes.

Screening with mammography reduces breast cancer mortality risk by 20-40% (4, 5, 62). Current breast cancer screening programs are based on age only. A major drawback of mammography, however, is its limited specificity which along with the relatively low prevalence of breast cancer among all women, translates into a relatively high number of false positive cases and leads to unwanted overdiagnosis and overtreatment. As a result, current breast cancer screening programs do not support regular screening of women below the age of 50 or 45, where the prevalence is significantly lower. But breast cancer in younger women tends to be more aggressive, with higher rates of metastasis and poorer survival rates

compared to older women with breast cancer. Therefore, early detection and diagnosis are particularly important for this age group.

Thus age-based population screening fails to include younger individuals already at risk-levels exceeding those defined to enter the screening program, e.g., women with higher genetic risk who can develop breast cancer much earlier than the defined age of the screening program. The application of personalized risks is necessary to identify those women who could benefit from an earlier start of the screening. Also, for high-risk women over age 50 current screening with 2-year intervals are not optimal and miss many interval cases that would otherwise be detected earlier. Therefore, breast cancer screening should better be adapted to the individual risk level of a woman.

European guidelines for breast cancer screening recommend for women with an average risk of breast cancer, but in reality, each country has their own programmes (63). Current European guidelines' recommendations for breast cancer screening:

Women aged 40-44: no screening.

Women aged 45-49: screening every 2 or 3 years.

Women aged 50-69: screening every 2 years.

Women aged 70-74: screening every 3 years.

Same time long-term follow-up of the UK Age randomised clinical trial investigating mammographic screening in women from age 40 years showed that annual mammography screening at age 40-49 years conferred a reduction in breast cancer mortality, which was attenuated after 10 years (64).

With the help of the PRS, women can be divided into groups with different levels of risk based on which different recommendations for starting a mammography screening or other preventive measures can be given (41, 42, 65, 66). PRS identifies women at higher genetic risk who reach the threshold for population screening at a younger age, equivalent to risk for a woman at age 50 years who is eligible for population screening.

A study by Wolfson et al. has shown that population-wide programs for breast cancer screening that seek to stratify women by their genetic risk should focus first on PRS, not on more highly penetrant but rarer variants, nor family history (28).

An analysis by Lee et al., demonstrated that PRS is a stronger independent breast cancer risk factor than family history or mammographic density (29).

A thorough analysis by van den Broek et al. has assessed the clinical utility of a first-degree breast cancer family history and PRS to inform screening decisions among women aged 30-50 years (44). Analysis results suggest that breast cancer family history and PRS could guide screening decisions before age 50 years among women at increased risk for breast cancer but expected increases in overdiagnoses and false positives should be expected. Combined use of family history and PRS versus biennial screening from 50 to 74 years had the greatest increase in life-years gained (29%) and breast cancer deaths averted (18%) (44). Benefits increased steeply relative to the USPSTF guideline as polygenic risk increased, so that women with 3 times or higher risk than average could begin screening at age 30 or 35 years, and those

with greater than average risk (but <3 times the risk) could initiate screening at age 40 years. In addition, the lowest risk group could be screened triennially from ages 50 to 74 years (44).
Mars et al. evaluated PRS, family history, and MPVs for stratified screening (67). Using FinnGen data (N = 117,252), linked to the Mass Screening Registry for breast cancer, authors assessed the screening performance of a breast cancer PRS and compared its performance with family history of breast cancer and MPVs in moderate- (*CHEK2*)- to high-risk (*PALB2*) susceptibility genes. A high PRS conferred an elevated risk of interval breast cancers and women with a low PRS had a low risk for both interval- and screen-detected breast cancers. Using real-life screening data, this study demonstrates the effectiveness of a breast cancer PRS for risk stratification, alone and combined with family history and MPVs (67).
A modelling analysis by Huntley et al. has shown that under favourable assumptions PRS use in UK cancer screening suggests modest potential efficiency gain in breast cancer case detection and deaths averted (68).
Personalized breast cancer screening based on hereditary risks for women at age 35-49 has been tested in the Estonian branch of the BRIGHT project using the family cancer history questionnaire, PRS test AnteBC risk estimates for all women, and MPV testing based on family cancer history (69). Amongst 800 participants aged 35–49, 72 had MPVs tested after consultations by clinical geneticists, resulting in 5 MPV diagnoses. PRS testing for all identified 124 women at higher risk than the average 50-year-old. The BRIGHT study demonstrated the feasibility of genetics-based precision prevention, facilitating earlier BC screening for younger women with elevated genetic risks. The predominantly digital service minimised the burden on healthcare personnel (69).
The BRIGHT study assessed also the cost-effectiveness of risk-stratified breast cancer screening in Estonia for women starting at age 35 versus standard mammography screening for ages 50-69, focusing on the PRS test's isolated impact (70). Risk-stratified screening led to a redistribution of breast cancer stages, with more early (0-I) and fewer advanced stages (II-IV) and averted 1.5 breast cancer deaths per 1,000 women screened. Risk-stratified screening resulted in larger net costs of €145,235 (mainly related to PRS test and counselling costs), and a gain of 3.85 QALYs, with an ICER of €37,755 per QALY gained (70). The conclusion was that a PRS-tailored breast cancer screening has clinical benefit and is potentially cost-effective in Estonia.

Clinical Recommendations for Personalised Prevention and Screening of Breast Cancer Based on Polygenic Risk Score Results

There are three foundations for the implementation of clinical recommendations based on polygenic risk scores.

1. 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 (or 45, or 40 accordingly). Then it is logical to start screening at a younger age for women if their PRS risk level achieves same level or is higher than average risk at age 50. This is according to principles of equitability and equivalence of risks.
This approach is used in the WISDOM study for women aged 40 to 49 years, where screening is recommended when women' five-year risk equals or exceeds that of the average woman aged 50 years (71). WISDOM study uses thresholds on five-year risk given that screening and prevention are most impactful in those at immediate risk of cancer, and five-year risk thresholds are standardly used to guide chemoprevention. The 5-year risk estimate in the WISDOM study for women aged 50 was 1.3%.

2. Another basis for clinical recommendations is comparison with similar risk monogenic pathogenic variants (MPVs).
Similar to elevated PRS risk, moderately elevated risk level (lifetime risks 25-30%) is in the case of MPVs in genes *ATM* and *CHEK2* (19). Accordingly, on the same PRS risk level, we can give similar clinical recommendations 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% (72). A similar approach is feasible for women on the same risk level as a polygenic risk score.
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 (73): 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.

3. The third basis for clinical recommendations is the 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.

Guidelines for breast risk-stratified screening and surveillance in different countries

Guidelines in the United Kingdom

UK National Institute for Health and Care Excellence (NICE) guidelines for the management of familial define breast cancer risk categories using the following thresholds (74), Table 1 below:

Table 1: Breast cancer risk categories by NICE guidelines

	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%

https://www.nice.org.uk/guidance/cg164/chapter/recommendations#terms-used-in-this-guideline

The NICE guideline refers to three levels of risk for developing breast: general population risk, moderate risk, and high risk. Women whose risk is the same as the general population have about an 11% chance of developing breast cancer in their lifetime. Women with a moderate risk have a lifetime risk of developing breast cancer of greater than 17% but less than 30%. Women with a high risk have a 30% or greater chance of developing breast cancer in 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 (37):

- 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 in different ages, recommending annual mammography from age 40 for increased risk groups.

Guidelines in Germany

German guidelines for breast cancer management, including screening are characterized in "Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms" (75).
The current German breast cancer guidelines recommend that women aged 40-49 undergo a mammogram screening every two years, but the guidelines suggest that the decision to

undergo mammography screening in this age group should be based on an individual assessment of the potential benefits and harms, taking into account the woman's personal risk factors for breast cancer and her preferences (75).
There are in place principles and guidelines for "Breast Cancer Risk, Genetics and Prevention" by Arbaitsgemeinschaft Gynäkologische Onkologie (AGO) (76).
In Germany, genetic testing for breast cancer is primarily offered to individuals with a personal or family history of breast or ovarian cancer. The current guidelines for genetic testing in Germany are based on recommendations from the German Society of Human Genetics (GfH) and the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) - Deutsches Konsortium Familiärer Brust- und Eierstockkrebs (77) German Consortium for Hereditary Breast and Ovarian Cancer recommends for moderate MPV carriers' annual clinical examination, breast ultrasonography and MRI from age 30 and mammography annually or biannually from age 40.

Guidelines in Norway

In Norway, there are in place national guidelines and recommendations for risk-stratified BC prevention where the inclusion of PRS information can give possibilities for more systematic implementation of risk-stratified prevention and screening (78). Women with increased risk assessed based on family history - this applies to women who have undergone a risk assessment by a clinical geneticist, where the conclusion is that there is an increased risk of breast cancer based on family history (without a proven highly penetrant gene defect). These women should be offered annual 2-plane mammography from the age of 40-60. In families with cases of breast cancer before the age of 40, it may be considered to start mammography checks from the age of 30 (78).

The regulatory and legal status of breast cancer risk estimation tools in the European Union in the context of polygenic risk score testing

Explanation

Polygenic risk score (PRS) tests are regulated under the EU In Vitro Diagnostic Regulation (IVDR) 2017/746 because they are considered in vitro diagnostic (IVD) medical devices (79). According to the regulation, an IVD medical device is any device which, whether used alone or in combination, is intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information on a physiological or pathological state, or a congenital abnormality, or to monitor therapeutic measures.

Summary about current European Union regulations regarding PRS testing:

Polygenic Risk Score (PRS) Tests under EU IVDR 2017/746 (79):

PRS tests are classified as in vitro diagnostic (IVD) medical devices and must comply with the EU's IVDR 2017/746.
These tests must demonstrate clinical validity and utility, with a clear demonstration of performance characteristics and safety.
They are subject to pre-market scrutiny and must fulfil post-market surveillance obligations.
Providers must ensure the tests are not discriminatory and take into account the diversity of the population, including genetic variations across different ancestries.

Laboratory Developed Tests (LDTs) under EU IVDR 2017/746:
The IVDR imposes more stringent requirements on LDTs than the previous directive, aiming to align their safety and performance standards with commercially available IVDs.
There is a health institution exemption under Article 5(5), but it requires LDTs to be justified, documented, and notified to national competent authorities.
LDTs must be manufactured and used within the same EU member state health institution, under a quality management system.
Performance evaluations and compliance with the general safety and performance requirements are mandatory.
These regulations ensure a high standard of quality and safety for diagnostic tests, including PRS tests, whether they are commercial kits or developed in-house within EU health institutions.
The EU Regulation 2017/746 on vitro diagnostic medical devices states (79):
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.
The EU Regulation 2017/746 states also conditions for lab-developed tests (79):
the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:
(a) the devices are not transferred to another legal entity;

(b) manufacture and use of the devices occur under appropriate quality management systems;
(c) the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;
(d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met or cannot be met at the appropriate level of performance by an equivalent device available on the market.
This paragraph shall not apply to devices that are manufactured on an industrial scale.

In conclusion:
Lab-developed tests cannot be used for public screening programs (on an industrial scale). Tests reporting breast cancer PRS for clinical use must be preferably CE-marked in vitro medical devices.

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