



**HAL**  
open science

## Personalized early detection and prevention of breast cancer: ENVISION consensus statement

Nora Pashayan, Antonis Antoniou, Urska Ivanus, Laura Esserman, Douglas Easton, David French, Gaby Sroczynski, Per Hall, Jack Cuzick, D. Gareth Evans, et al.

### ► To cite this version:

Nora Pashayan, Antonis Antoniou, Urska Ivanus, Laura Esserman, Douglas Easton, et al.. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. *Nature Reviews Clinical Oncology*, 2020, 17 (11), pp.687-705. 10.1038/s41571-020-0388-9 . hal-04473637

**HAL Id: hal-04473637**

**<https://hal.science/hal-04473637>**

Submitted on 22 Feb 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

OPEN



## Personalized early detection and prevention of breast cancer: ENVISION consensus statement

Nora Pashayan<sup>1</sup>, Antonis C. Antoniou<sup>2</sup>, Urska Ivanus<sup>3</sup>, Laura J. Esserman<sup>4</sup>, Douglas F. Easton<sup>2</sup>, David French<sup>5</sup>, Gaby Sroczynski<sup>6,7</sup>, Per Hall<sup>8,9</sup>, Jack Cuzick<sup>10</sup>, D. Gareth Evans<sup>11</sup>, Jacques Simard<sup>12</sup>, Montserrat Garcia-Closas<sup>13</sup>, Rita Schmutzler<sup>14</sup>, Odette Wegwarth<sup>15</sup>, Paul Pharoah<sup>16,17</sup>, Sowmiya Moorthie<sup>17</sup>, Sandrine De Montgolfier<sup>18</sup>, Camille Baron<sup>19</sup>, Zdenko Herceg<sup>20</sup>, Clare Turnbull<sup>21</sup>, Corinne Balleyguier<sup>22</sup>, Paolo Giorgi Rossi<sup>23</sup>, Jelle Wesseling<sup>24</sup>, David Ritchie<sup>25</sup>, Marc Tischkowitz<sup>26</sup>, Mireille Broeders<sup>27</sup>, Dan Reisel<sup>28</sup>, Andres Metspalu<sup>29</sup>, Thomas Callender<sup>1</sup>, Harry de Koning<sup>30</sup>, Peter Devilee<sup>31</sup>, Suzette Delaloge<sup>32</sup>, Marjanka K. Schmidt<sup>24</sup> and Martin Widschwendter<sup>28,33,34</sup> ✉

**Abstract** | The European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) brings together several international research consortia working on different aspects of the personalized early detection and prevention of breast cancer. In a consensus conference held in 2019, the members of this network identified research areas requiring development to enable evidence-based personalized interventions that might improve the benefits and reduce the harms of existing breast cancer screening and prevention programmes. The priority areas identified were: 1) breast cancer subtype-specific risk assessment tools applicable to women of all ancestries; 2) intermediate surrogate markers of response to preventive measures; 3) novel non-surgical preventive measures to reduce the incidence of breast cancer of poor prognosis; and 4) hybrid effectiveness–implementation research combined with modelling studies to evaluate the long-term population outcomes of risk-based early detection strategies. The implementation of such programmes would require health-care systems to be open to learning and adapting, the engagement of a diverse range of stakeholders and tailoring to societal norms and values, while also addressing the ethical and legal issues. In this Consensus Statement, we discuss the current state of breast cancer risk prediction, risk-stratified prevention and early detection strategies, and their implementation. Throughout, we highlight priorities for advancing each of these areas.

Worldwide, breast cancer is the second most commonly diagnosed cancer, with approximately 2.1 million new diagnoses and almost 627,000 breast cancer-related deaths estimated to have occurred in 2018 (REF.<sup>1</sup>). Breast cancer is a biologically and clinically heterogeneous disease, with several recognized histotypes and molecular subtypes that have different aetiologies, profiles of risk factors, responses to treatments and prognoses<sup>2–8</sup>. In high-income countries, approximately 75% of breast cancers are diagnosed in postmenopausal women, although around 5–7% are diagnosed in women younger than 40 years of age<sup>9,10</sup>.

The risk of developing breast cancer varies among women. Genetic susceptibility, factors affecting levels of

endogenous hormones (early age at menarche, later age at menopause, nulliparity, late age at first birth, having fewer children and shorter durations of breastfeeding), exogenous hormone intake (hormonal contraceptive use and hormone replacement therapy), lifestyle patterns (high alcohol intake, smoking and physical inactivity), anthropometric characteristics (greater weight, weight gain during adulthood and higher central body fat distribution), a high mammographic breast density and benign breast diseases (non-proliferative disease, proliferative disease without atypia and atypical hyperplasia) are all associated with an increased risk of breast cancer<sup>11–14</sup>. At an individual level, the mechanisms and relative contributions of these different risk

✉e-mail: M.Widschwendter@ucl.ac.uk  
<https://doi.org/10.1038/s41571-020-0388-9>

factors to the development of breast cancer and also to particular subtypes of the disease are increasingly understood<sup>15</sup>.

Women with pathogenic germline mutations in cancer susceptibility genes — that is, in *BRCA1* or *BRCA2* (*BRCA1/2*) — may opt to undergo prophylactic bilateral mastectomy; primary chemoprophylaxis with tamoxifen or other selective oestrogen receptor modulators has also been recommended in this group, albeit the uptake is low<sup>16</sup>. Historically, members of this high-risk

group have been identified on an opportunistic basis following self-referral of women with a family history of breast or ovarian cancer, or on the basis of an ancestry associated with an increased prevalence of clinically significant pathogenic variants of *BRCA1/2* (for example, in those of Jewish descent)<sup>16</sup>. Currently, genetic testing remains somewhat restricted for women with breast cancer; those with triple-negative, bilateral or young-onset disease might be offered a test at diagnosis, but most will be offered testing only if they also have a noted family history of the disease<sup>16</sup>. The 2019 US Preventive Services Task Force recommendations expand the population in which eligibility for genetic testing should be assessed to include women with a personal or family history of breast, ovarian, tubal or peritoneal cancer, in addition to women who have an ancestry associated with pathogenic *BRCA1/2* variants<sup>17</sup>.

At present, the mammographic screening programmes used for early detection of breast cancer in most high-income countries are based on the results of trials conducted at least 20–30 years ago<sup>18–22</sup> and have age as the only entry criterion, although the starting and stopping ages (varying from 40 to 74 years) and the frequency of screens (yearly to triennially) differ between countries. This ‘one-size-fits-all’ approach does not take into account the heterogeneity of the breast cancer subtypes and of the risk in the population. Three decades of mammographic early detection have witnessed an increase in the incidence of early stage cancers with a low-risk tumour biology and an increase in the detection of in situ disease, without a concomitant proportionate decrease in incidence of advanced-stage disease<sup>23,24</sup>. Increasingly, calls have been made for a new approach to early detection with a focus on the identification of more consequential cancers and on avoiding the detection of indolent or ultra-low-risk disease<sup>24,25</sup>.

Personalized approaches to the prevention or early detection of breast cancer have emerged as highly promising strategies<sup>26,27</sup>. These programmes require risk assessment of each woman in the population, stratification of the population into several risk groups, assignment of the individuals to a specific risk group and tailoring of prevention and early detection interventions to each risk group<sup>28</sup> (FIG. 1). Several international research consortia (TABLE 1) are studying ways to better understand, estimate and reduce breast cancer risk<sup>29–32</sup>, to use risk-based stratification to prevent consequential cancers<sup>33,34</sup>, to evaluate the benefit–harm trade-offs of such strategies<sup>35</sup> and to assess the acceptability and feasibility of implementing risk-stratified prevention and early detection programmes<sup>36–38</sup>.

To fulfil the promise of risk-stratified breast cancer prevention and screening, it is important not only to generate evidence on the individual component ‘jigsaw pieces’ of prevention and early detection programmes, but also to bring these pieces together in a complex adaptive system<sup>39</sup>. The European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) comprises leading international research consortia working in this specific field (TABLE 1). In 2019, the ENVISION network organized a consensus conference to identify research priorities and recommend

## Author addresses

<sup>1</sup>Department of Applied Health Research, Institute of Epidemiology and Healthcare, University College London, London, UK.

<sup>2</sup>Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK.

<sup>3</sup>Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia.

<sup>4</sup>Carol Franc Buck Breast Care Center, University of California, San Francisco, CA, USA.

<sup>5</sup>Division of Psychology & Mental Health, School of Health Sciences, University of Manchester, Manchester, UK.

<sup>6</sup>Department of Public Health, Health Services Research and Health Technology Assessment, Institute of Public Health, Medical Decision Making and Health Technology Assessment, UMIT-University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria.

<sup>7</sup>Division of Health Technology Assessment, Oncotyrol — Center for Personalized Cancer Medicine, Innsbruck, Austria.

<sup>8</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.

<sup>9</sup>Department of Oncology, Södersjukhuset, Stockholm, Sweden.

<sup>10</sup>Wolfson Institute of Preventive Medicine, Barts and The London, Centre for Cancer Prevention, Queen Mary University of London, London, UK.

<sup>11</sup>Division of Evolution and Genomic Sciences, University of Manchester, Manchester, UK.

<sup>12</sup>Genomics Center, CHU de Québec — Université Laval Research Center, Québec, Canada.

<sup>13</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA.

<sup>14</sup>Center of Family Breast and Ovarian Cancer, University Hospital Cologne, Cologne, Germany.

<sup>15</sup>Max Planck Institute for Human Development, Center for Adaptive Rationality, Harding Center for Risk Literacy, Berlin, Germany.

<sup>16</sup>Department of Oncology, University of Cambridge, Cambridge, UK.

<sup>17</sup>PHG Foundation, Cambridge, UK.

<sup>18</sup>IRIS Institute for Interdisciplinary Research on Social Issues, Paris, France.

<sup>19</sup>Unicancer, Paris, France.

<sup>20</sup>Epigenetic Group, International Agency for Research on Cancer (IARC), WHO, Lyon, France.

<sup>21</sup>Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK.

<sup>22</sup>Department Medical Imaging, Institut Gustave Roussy, Villejuif, France.

<sup>23</sup>Epidemiology Unit, Azienda USL di Reggio Emilia — IRCCS, Reggio Emilia, Italy.

<sup>24</sup>Division of Molecular Pathology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands.

<sup>25</sup>Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium.

<sup>26</sup>Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK.

<sup>27</sup>Department for Health Evidence, Radboud University Medical Center, Nijmegen, Netherlands.

<sup>28</sup>Department of Women’s Cancer, Institute for Women’s Health, University College London, London, UK.

<sup>29</sup>The Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia.

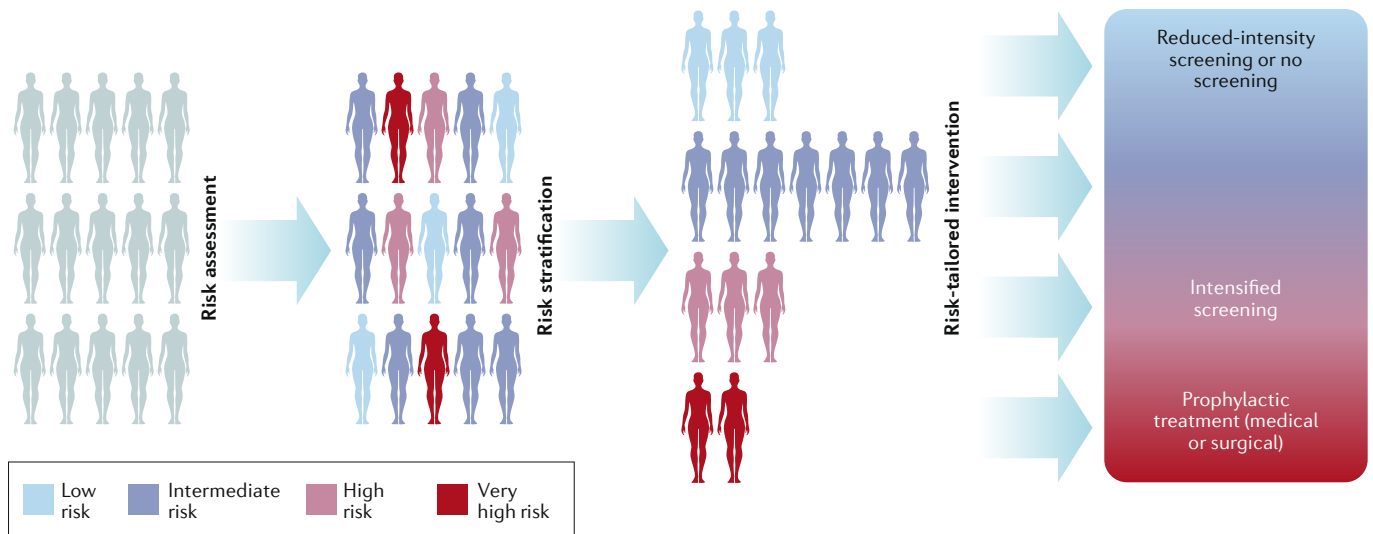
<sup>30</sup>Department of Public Health, Erasmus MC, Rotterdam, Netherlands.

<sup>31</sup>Department of Human Genetics, Department of Pathology, Leiden University Medical Centre, Leiden, Netherlands.

<sup>32</sup>Breast Cancer Department, Gustave Roussy Institute, Paris, France.

<sup>33</sup>Universitat Innsbruck, Innsbruck, Austria.

<sup>34</sup>European Translational Oncology Prevention and Screening (EUTOPS) Institute, Hall in Tirol, Austria.



**Fig. 1 | A schematic outlining a personalized approach to early detection and prevention of breast cancer.** Women entering a personalized early detection programme would initially be assessed using a validated tool to determine their estimated risk of breast cancer. Subsequently, the women would be stratified into appropriate risk groups such that they can receive tailored interventions. This approach might mean that some women start mammographic screening at a younger age, have different screening intervals or have supplemental screening with another imaging modality, such as MRI. Women deemed to be at higher risk of breast cancer could, in addition, be offered prophylactic treatment. A healthy lifestyle would be recommended to all women, independent of risk level.

actions required to enable evidence-based risk-stratified prevention and early detection programmes for breast cancer (BOX 1; Supplementary Table 1).

In this Consensus Statement, we review the current knowledge, explore the barriers and opportunities, and define key areas for the development and implementation of risk assessment, risk-stratified prevention and early detection programmes for breast cancer. As representatives of the ENVISION network, we also present herein the recommendations formulated at the 2019 consensus conference (BOX 2) in the hope that they stimulate and guide such programmes.

### Risk assessment for breast cancer

#### Established risk factors

Breast cancer risk can be predicted using a combination of common genetic variants, mostly single-nucleotide polymorphisms (SNPs); rare coding variants of susceptibility genes, including *BRCA1/2*, *PALB2*, *CHEK2* and *ATM*; mammographic breast density; benign abnormalities in breast biopsy specimens; hormonal, anthropometric and lifestyle factors; family history of the disease; and, potentially, epigenetic markers<sup>11,13,40–43</sup>. Genome-wide association studies (GWAS) have resulted in the identification of >180 independent common genetic variants that together account for ~20% of the familial relative risk of breast cancer and ~40% of the heritability attributed to all common variants on genome-wide SNP arrays<sup>40,41</sup>. Each variant confers a small risk, but their effects can be combined into polygenic risk scores (PRSs) that are predictive of the risk of developing breast cancer, thereby enabling breast cancer risk stratification in the general population<sup>44–46</sup>.

The performance of current PRSs has been thoroughly validated in European populations<sup>44</sup>. The relative

risks associated with individual SNPs and PRSs vary between breast cancer subtypes, with oestrogen receptor-positive (ER<sup>+</sup>) disease being more strongly predicted than other forms of the disease<sup>40,41,44</sup>. The current best performing PRS is based on 313 SNPs (PRS<sub>313</sub>); women in the highest 1% of the risk distribution have an approximately fourfold and threefold greater risk of developing ER<sup>+</sup> and ER<sup>-</sup> breast cancers, respectively, compared with women in the middle quintile (40–60th percentile)<sup>44</sup>. The risk reflected in the PRSs seems to be independent of other established risk factors — that is, the effects are approximately multiplicative<sup>43</sup>. PRS<sub>313</sub> provides the highest level of breast cancer risk stratification in the population, followed by mammographic breast density and the other risk factors<sup>45,47</sup>.

Protein-truncating variants (PTVs) in approximately 12 genes are associated with breast cancer risk<sup>42,48</sup>; for some, the strength of association has been demonstrated to differ between ER<sup>+</sup> and ER<sup>-</sup> disease<sup>49,50</sup>. The risk estimates for PTVs of some genes are, however, very imprecise (TABLE 2). Missense mutations in a subset of these genes have also been associated with an increased risk of breast cancer<sup>42,51–53</sup>. Evidence from in silico and functional studies can help to define this subset of cancers with non-truncating variants<sup>54–56</sup>. For rare individual variants associated with risk, however, the level of risk that they impart remains uncertain. Most genes tested using commercial multigene panels have not been systematically investigated as breast cancer susceptibility genes. The Clinical Genome Resource (ClinGen) framework has assessed the strength of evidence between selected putative susceptibility genes and breast cancer and established definitive clinical validity classifications for only 10 of 31 genes commonly tested when evaluating breast cancer risk<sup>57</sup> (TABLE 2).

# CONSENSUS STATEMENT

Table 1 | Consortia participating in the ENVISION network and endorsing the recommendations herein

Acronym	Consortium	Description and/or aims of the consortium	Funder	Ref.
B-CAST	Breast Cancer Stratification	Define the influence of risk factors, including reproductive history, lifestyle, mammographic breast density and germline genetic variation, on susceptibility to breast cancer overall and for disease subtypes characterized by clinical and molecular markers. Define the influence of risk factors and tumour subtypes on clinical prognosis. Develop, validate and implement breast cancer risk and prognostication models for breast cancer, overall and for different subtypes. Raise awareness; that is, promote the development and integration of personalized breast cancer prevention within national public health programmes	EU Horizon 2020	29
BCAC	Breast Cancer Association Consortium	International consortium of collaborative groups that share data from multiple studies in breast cancer. Identify genes that might be relevant to the risk of breast cancer. Provide a reliable assessment of the risks associated with these genes	Cancer Research UK	81
BRCA-ERC	Understanding cancer development in <i>BRCA1/2</i> pathogenic variant carriers for improved Early detection and Risk Control	Understand cell non-autonomous factors in carriers of <i>BRCA1</i> or <i>BRCA2</i> pathogenic variants that contribute to cancer development. Use cell-free DNA methylation-based markers for early detection of ovarian cancer. Develop new strategies and intermediate surrogate end points for non-surgical prevention of breast cancer	European Research Council	31
BRIDGES	Breast Cancer Risk After Diagnostic Gene Sequencing	Identify breast cancer susceptibility genes. Estimate risks associated with different genetic variants and incorporate into the BOADICEA risk-prediction model to provide individualized risk estimates. Implement individualized risk prediction in clinical settings	EU Horizon 2020	30
EU-TOPIA	Towards Improved Screening for Breast, Cervical and Colorectal Cancer in All of Europe	Develop and validate microsimulation models of breast, cervical and colorectal cancer screening in countries across Europe to assess current screening programmes. To assess inequalities in, and barriers to uptake of, screening. To develop road maps to improve existing screening programmes in Europe	EU Horizon 2020	35
FORECEE	Female Cancer Prediction Using Cervical Omics to Individualise Screening and Prevention	Utilize data on the cervical epigenome, genome and microbiome to develop personalized early detection and prevention strategies for breast, ovarian, endometrial and cervical cancer. Assess the ethical, health-economic, legal and societal aspects of using epigenetic markers for risk prediction. Develop strategies for communicating cancer risk	EU Horizon 2020	32
MyPeBS	My Personalized Breast Screening	Multicountry randomized trial of personalized breast cancer screening comparing risk-based screening to standard screening offered in each participating country among women aged 40–70 years <sup>153</sup> . Assess if individual risk-based screening is non-inferior or superior to the current standard of care in terms of reduction of the incidence of stage II or higher breast cancer	EU Horizon 2020	33
PERSPECTIVE I&I	Personalized Risk Assessment for Prevention and Early detection of Breast cancer: Integration and Implementation	Identification and validation of novel moderate to high risk breast cancer susceptibility genes. Improvement, validation and adaptation of a web-based tool for comprehensive breast cancer risk prediction that is suitable for the Canadian context. Development of a framework to support implementation of a personalized risk-based approach to breast cancer screening within existing mammography centres. Economic analyses for optimal personalized risk-based screening implementation	Canadian Institutes of Health Research, Genome Canada, Genome Quebec, Ontario Research Fund, Quebec Breast Cancer Foundation	36
PROCAS2	Predicting Risk of Cancer at Screening	Assess the feasibility of individualized risk assessment during screening appointments. Assess a range of effects of implementing personalized risk assessment on women, health-care staff and related organizations	National Institute for Health Research UK	37
WISDOM	Women Informed to Screen Depending on Measures of Risk	Multicentre, pragmatic, adaptive, preference-tolerant randomized controlled trial comparing risk-based screening to annual screening of women aged 40–74 years <sup>152</sup> . Determine if personalized breast cancer screening will lead to fewer harms, improve breast cancer prevention and be acceptable to women in comparison with standard annual screening	Patient-Centred Outcomes Research (PCORI)	34

**Box 1 | Process of developing the recommendations of the ENVISION network**

The European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION) network meeting was attended by 119 delegates from 19 countries: 14 countries in Europe (Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Italy, the Netherlands, Slovenia, Spain, Switzerland, Sweden and the UK) as well as Israel, the USA, Canada, Malaysia and Australia. Together, the delegates brought diverse expertise in risk-based breast cancer research and health services (epidemiology, statistics, genetics, epigenetics, oncology, clinical genetics, pathology, gynaecology, radiology, surgery, primary care, public health, psychology, ethics, health economics, policy, screening services and health-care management), with representatives from academia, health-care organizations, industry (information technology support), politics (government representatives) and non-profit organizations (Europa Donna and the Association of European Cancer League).

The meeting was held over 3 days. During the first day, presentations covered the latest evidence ('where we are now') relating to breast cancer risk prediction, risk stratification for prevention, risk stratification for early detection at the population level and the implementation of such strategies. Each presentation was followed by a discussion session for the delegates to identify gaps in research ('where do we want to be'). During the second day, through six workshops (focused on risk assessment, early detection, prevention, engaging stakeholders, health-care organization readiness, and ethical, legal and social implications (ELSI)), the delegates explored how to meet these gaps ('how do we get where we want to be'). During the third day, named delegates, in coordination with the presenters, discussants and the facilitators of the workshops, presented recommendation for each of the 18 areas covered in the ENVISION meeting (genetic risk, epigenetic risk, classical risk factors, risk prediction, breast cancer subtypes, imaging, diagnostic tools for early detection, prevention, specific considerations in high-risk women, outcome, trial logistics, implementation, economic evaluation, communication and decision aids, policy landscape, ELSI, workforce training and health-care organization readiness). The presentation of each recommendation was followed by discussion and checking consensus.

Each delegate who contributed through presenting the evidence, the workshop discussions and the recommendations presented a written summary. After collating these summaries, all 119 delegates were asked for their feedback.

**Emerging risk factors**

The epigenome consists of various 'layers', including non-coding RNAs, histone modification and DNA methylation, and has an essential role in establishing the identity and function of any given cell by determining which genes remain silent and which are transcribed. A plethora of changes in DNA-methylation patterns have been described in breast cancers, and several of these changes are often also present in the non-malignant breast tissue adjacent to the cancer<sup>58</sup>, supporting the principle that an epigenetic field defect renders cells of these tissues susceptible to malignant transformation<sup>59</sup>. In addition to genetic background<sup>60,61</sup>, a large variety of non-genetic factors, including age<sup>62</sup> and endocrine disruption<sup>63,64</sup>, that are known to modulate breast cancer risk also alter patterns of DNA methylation. On the basis of these insights, one might speculate that epigenetic profiles could predict breast cancer risk.

To date, several groups have attempted to develop epigenetic risk classifiers for breast cancer but with only modest success, which could be due to several reasons<sup>65</sup>. First, the vast majority of the studies to date used only blood samples for DNA-methylation analyses. Blood is readily available from participants of several large cohort studies<sup>61,66</sup>, but breast cancer is, by definition, an epithelial disease, and hence immune cells in the blood might not be an appropriate surrogate tissue for those of the breast. Second, unlike in germline genetic analyses, the timing of the sample collection for epigenetic

analyses is crucial. For example, epigenetic analyses using samples obtained from women during cancer treatment are likely to produce results that reflect treatment effects and not cancer predisposition. Third, unlike PRSs, which are established by combining individual SNPs with risk associations that remain statistically significant after multiple test adjustment, epigenetic risk signatures are reflective of cell programmes; therefore, approaches that a priori select a large number of CpGs for inclusion in the epigenetic signatures are more likely to be appropriate. Fourth, the presence of a cancer can modify the epigenome of a particular surrogate tissue. For example, a higher granulocyte to lymphocyte ratio is detected in the blood of patients with ovarian cancer, which subsequently alters the DNA-methylation signature observed when assessing peripheral blood mononuclear cells<sup>67</sup>. Thus, validation of risk-predictive signatures in population-based cohorts is important; however, the majority of the existing cohorts do not have appropriate samples available (owing to non-standardized collection, storage conditions and times, and so on), which makes this validation process prone to producing false-negative results.

Nevertheless, DNA-methylation signatures in easy-to-collect surrogate tissues hold promise, not only in advancing risk-prediction strategies, but also, of equal importance, in providing novel opportunities to monitor the effects of cancer-preventive measures. In addition to epigenetic markers, serum levels of steroid hormones<sup>68–70</sup> and a double-strand DNA break-repair phenotype of peripheral blood cells<sup>71,72</sup> have substantial potential to identify women with a high risk of developing breast cancer.

**Risk-prediction models**

Several breast cancer risk-prediction models are available. Empirical models such as the Gail model<sup>73</sup>, the Breast Cancer Surveillance Consortium (BCSC) risk calculator<sup>74</sup> and the Individualized Coherent Absolute Risk Estimator (iCARE)<sup>75–77</sup> do not consider explicit genetic models of inheritance and are primarily intended for use in women in the general population. By contrast, genetic models such as Tyrer-Cuzick<sup>78</sup> and BOADICEA<sup>45,79</sup> can, in principle, accommodate detailed family history information (including the exact pedigree structure and information on distant relatives) and can, therefore, be applied both at the general population level and in women with a strong family history of breast cancer. These models all vary in terms of the risk factors considered, the study designs and types of data used in their development, and their analytical methods. The validity and clinical utility of these risk-assessment tools must be demonstrated before they are implemented routinely in the clinical setting<sup>80</sup>.

**Validity.** Analytical validity refers to the accuracy of the test in measuring the underlying genotypes (for example, through gene-panel testing or sequencing assay for rare mutations), PRSs (for example, using SNP-genotyping technologies) and other lifestyle and hormonal risk factors (which can be self-reported or available through electronic health records). Importantly, the analytical

## Box 2 | Summary of the key recommendations of the ENVISION

### Assessment of breast cancer risk

- Risk-assessment tools should be validated using prospective cohorts in the context in which they will be used and for each population ancestry.
- Risk-assessment tools that enable better predictions of breast cancer subtype-specific risk and risk in women of non-European descent need to be developed and validated.
- Discovery research to identify additional genetic variants and new markers is required to improve risk stratification.
- The trade-off between the accuracy of comprehensive models and their usability at the population level should be evaluated.
- Algorithm transparency should be ensured, with explicit reporting of the assumptions made.

### Breast cancer prevention

- Ways to better select high-risk women predisposed to breast cancer of poor prognosis need to be developed.
- Clinically relevant surrogate markers (reflecting the field defect in breast tissues) that provide early indications of the effectiveness of the preventive measures in reducing incidence of breast cancer of poor prognosis need to be identified.
- Programmes should incorporate healthy lifestyle recommendations for women at all risk levels.
- Prevention-specific drug doses, schemes and schedules need to be defined, and rational drug repositioning strategies should be explored.
- Better and early assessment of the acceptability of new preventive interventions is required.

### Risk-stratified early detection

- Discovery research is required to identify and validate early detection markers that can differentiate progressive from non-progressive breast cancers.
- Develop risk-stratified early detection strategies underpinned by understanding of how the natural course of breast cancer, sensitivity of the test (for example, mammography) and the probability of overdiagnosis vary according to risk levels.
- Optimize variables related to risk assessment (which risk factors to include, what age to start screening, how often to screen, and so on) and risk stratification (how many risk groups to specify and the risk threshold for each group), thus resulting in a cost-effective, feasible, acceptable and equitably accessible early detection programme.
- Modelling studies can be used to inform on long-term population outcomes and the optimal design of risk-stratified early detection programmes.
- Pragmatic randomized study designs, such as randomized health service studies, should be used to generate evidence on the effectiveness of risk-stratified early detection approaches in a given setting.

### Programme implementation

- Adopt hybrid effectiveness–implementation research designs to reduce the time lag between generation of evidence on the effectiveness of a programme and its implementation.
- Shift away from small studies with hypothetical scenarios performed in silos to multidisciplinary research with engagement of all stakeholders to ensure a systems approach to implementation studies in real-world settings.
- A framework for a learning health-care system should be adopted.
- The implementation process in a given setting needs to be aligned with health-care organization readiness for change and the social values, preferences and norms.
- The best ways of communicating risk and supporting behavioural changes in response to risk information need to be identified.

validity of comprehensive breast cancer risk-prediction models also depends on having reliable relative risk estimates for the effects of the various risk factors; having precise risk estimates of the associations with individual rare and common genetic variants; as well as estimates of the joint effects of common genetic variants, the joint effects of common and rare genetic variants, and

the combined effects of genetic and other risk factors, including a family history of cancer. Clinical validity refers to the accuracy of the tool in predicting the occurrence of breast cancer.

Ideally, the individual and combined associations of the various risk factors should be derived from large, well-designed cohort studies that are representative of the population in which the models are intended to be applied. However, cohorts with data that include information on all known risk factors are not widely available; therefore, synthetic mathematical approaches have been developed that combine the risk-factor distributions from separate cohorts<sup>45,75,76</sup>. Data generated by the B-CAST<sup>29</sup>, BRIDGES<sup>30</sup>, BCAC<sup>81</sup> and CIMBA<sup>82</sup> consortia (TABLE 1) provide a platform for estimating the individual and combined risk-factor distributions and breast cancer risk and have been used in the development of the iCARE<sup>77</sup> and BOADICEA<sup>45</sup> breast cancer risk-prediction models. Some empirical models, which are commercially available, have been modified to incorporate breast cancer PRSs, but without accounting for the fact that PRSs explain a large fraction of the familial relative risk of breast cancer. The failure to adjust these models to account for family history of breast cancer results in substantial levels of miscalibration in different risk categories and subsequently compromises the clinical validity of the model<sup>46</sup>.

With regard to clinical validity, several validation studies assessing model calibration (that is, the agreement between the predicted and the observed risk) or discrimination (the ability of a risk score to discriminate between those who will and those who will not develop the disease) in large independent cohorts have been published<sup>83,84</sup>. The interpretation of the literature is challenging, however, because these studies have not necessarily assessed both model calibration and discrimination in the same sample. Moreover, head-to-head comparisons of risk models using the same datasets are lacking. Often the published validation studies have used older versions of the risk models without data on all model components (in particular, mammographic breast density), have limited sample sizes and have varying timescales over which predictions are made, which depend on the follow-up duration of the study.

Ongoing studies by B-CAST<sup>29</sup> and BRIDGES<sup>30</sup> aim to address these issues by evaluating risk-assessment models in multiple prospective cohorts of women initially without breast cancer in diverse settings. Preliminary results indicate that the iCARE<sup>77,85</sup> and BOADICEA<sup>45</sup> models have well calibrated categories of predicted risk and discriminate well between women who develop breast cancer over 5–10 years of follow-up study from those who do not<sup>84</sup>. As such, these models provide valid risk-prediction tools that can be used in clinical practice.

**Clinical utility.** Conceptually, clinical utility refers to the usefulness, benefits and harms of an intervention<sup>86,87</sup>. Clinical utility is a multidimensional construct covering effectiveness and cost-effectiveness, as well as the psychosocial, ethical and legal implications of an intervention<sup>86</sup>. Risk assessment per se does not have

Table 2 | Genes with rare variants associated with an increased breast cancer risk

Gene	PTV associated with breast cancer risk	Missense variants associated with breast cancer risk	Relative risk for PTV (90% CI)	Clinical Genome Resource (ClinGen) definition of clinical relevance
ATM	Yes	Yes	2.8 (2.2–3.7)	Definitive
BARD1	Likely	Unknown	2.1 (1.5–3.0) <sup>48</sup>	Definitive
BRCA1	Yes	Yes	11.4 (NA)	Definitive
BRCA2	Yes	Yes	11.7 (NA)	Definitive
CDH1	Yes	Unknown	6.6 (2.2–19.9)	Definitive
CHEK2	Yes	Yes	3.0 (2.6–3.5)	Definitive
NBN	Yes	Unknown	2.7 (1.9–3.7)	Limited
NF1	Yes	Unknown	2.6 (2.1–3.2)	Not evaluated
PALB2	Yes	Unknown	5.3 (3.0–9.4)	Definitive
PTEN	Yes	Yes	8.8 (2.7–34.4) <sup>48</sup>	Definitive
RAD51D	Likely	Unknown	2.1 (1.2–3.72) <sup>48</sup>	Limited
STK11	Yes	Unknown	No reliable estimate	Definitive
TP53	Yes	Yes	105 (62–165)	Definitive

Data were sourced from Easton et al.<sup>42</sup> and Lee et al.<sup>57</sup>, with risk estimates derived from Easton et al.<sup>42</sup>, except where indicated otherwise. Note that risk estimates calculated by LaDuca et al.<sup>48</sup> come with 95% confidence intervals (CIs) and are derived from a study of individuals referred for testing and, therefore, might not be unbiased estimates of the general population risk. NA, not available; PTV, protein-truncating variants.

inherent clinical utility; the subsequent adoption of a risk-based intervention based on the results of the assessment is what influences the health outcomes<sup>88</sup>. The use of such a strategy depends on whether the risk-based intervention is appropriate, accessible, practicable and acceptable<sup>86</sup>. The interactions of these factors and challenges in assessing them are discussed in more detail in later sections of this article (FIG. 2).

**Future directions in risk prediction**

We have identified several key areas for development in breast cancer risk modelling (BOX 2). These research priorities include models that better predict the risk of specific subtypes of breast cancer and with improved risk stratification of women of all ancestries, particularly non-European ancestries, who have been understudied to date.

Subtyping of breast cancer is currently used routinely in prognostication and treatment, although its use in the context of prevention and early detection of the disease is limited. The ability to predict susceptibility to the typically more aggressive, ER<sup>-</sup> forms of breast cancer would enable selection of women for enhanced surveillance. Better datasets containing both clinical and genetic data are essential to develop and validate models that can more accurately predict subtype-specific risk, pathobiological behaviour and clinical outcomes. For example, B-CAST<sup>29</sup> and BRIDGES<sup>30</sup> are developing such data sources that integrate genetic, epidemiological, pathological and clinical data.

Multiancestry GWAS and targeted DNA-sequencing data from individuals of various ethnicities will enable translation of PRS-based and gene-based risks to

populations of non-European ancestry. Heritability analyses indicate that breast cancer is a highly polygenic disease, with thousands of variants conferring a small effect on risk, and that larger studies would result in new discoveries<sup>89</sup>. The Confluence project<sup>89</sup> aims to build a dataset comprising >300,000 patients with breast cancer and 300,000 individuals without the disease in order to conduct a multiancestry GWAS. This study will enable better understanding of the aetiology of distinct breast cancer subtypes, more powerful modelling of the underlying polygenic risk and improve risk stratification across groups of women with different ancestries.

A large fraction of the unexplained heritability of breast cancer might be attributable to rare variants (allele frequency <0.1%) not captured on SNP arrays<sup>90</sup>. Exome sequencing and replication studies with large cohorts, such as those being conducted by BRIDGES<sup>30</sup> and PERSPECTIVE I&I<sup>36</sup>, should be informative in determining whether additional susceptibility genes, with risk-defining coding variation, exist. For non-protein-coding variants, however, much larger whole-genome sequencing datasets, coupled with genomic risk prediction (genotype imputation), will be required.

Other promising approaches to improve breast cancer risk prediction include imaging and blood-based biomarkers. Improved use of mammography or MRI to predict risk is a particularly attractive area of research<sup>91–93</sup>; parenchymal textual features beyond simple mammographic breast density, such as the co-occurrence matrix and multiresolution spectral features, have been shown to be important<sup>94</sup> and might be independently predictive of the development of breast cancer<sup>92,95,96</sup>. Screening programmes provide longitudinal data that can facilitate studies to identify such imaging biomarkers. Potential blood-based biomarkers include microRNAs, tumour-educated platelets and circulating tumour DNA<sup>97–99</sup>. However, these markers might be more suitable for short-term early detection than long-term risk prediction (since they are perhaps more likely to reflect the presence of cancer rather than cancer susceptibility), and large longitudinal collections of samples will be required to study them.

Comprehensive models incorporating genetic and epidemiological risk factors and mammographic breast density enable more accurate risk stratification in the general population, as well as in carriers of germline pathogenic variants, than is possible with models that consider only PRS<sup>45,47</sup>. Repeat collection of information on the non-genetic risk factors at a population level raises further complexities in the logistics of risk assessment. The feasibility, clinical utility, costs and cost-effectiveness of risk-based programmes using a comprehensive model versus a model with only PRS need to be evaluated.

To enhance the credibility of a given model, and thus confidence in the results, transparency (that is, a clear description of the model structure, equations, parameter values and assumptions) and validation in relevant settings are essential. The challenge lies in having a consensus on the criteria for sufficient evidence to declare a model as ‘valid’ for a particular application<sup>100</sup>.



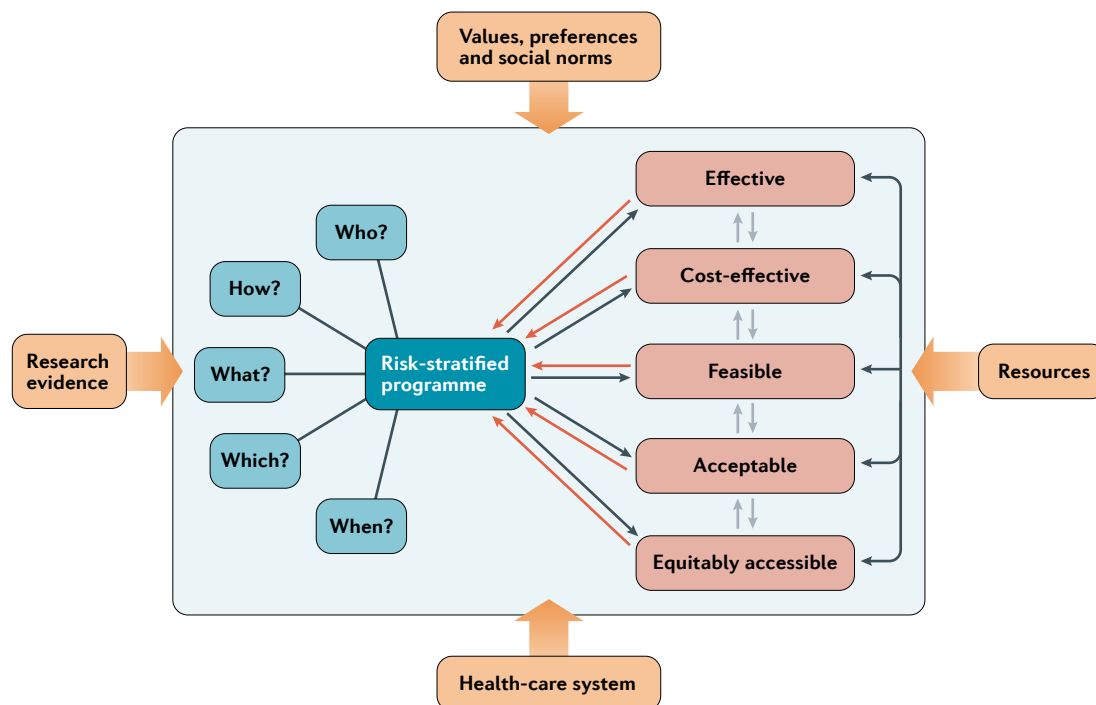


Fig. 2 | **Risk-stratified early detection and prevention programmes as complex adaptive systems.** Various questions will define the risk-stratified programme, including which risk factors to include in risk assessments, what risk threshold to use for risk stratification, how many risk groups to have, when to do risk assessments, how often to screen and to whom screening should be offered, as well as which interventions should be used in individuals deemed to be at high risk. Decision-making regarding these questions will be influenced by the research evidence, the available resources, the health-care setting and societal values, preferences and social norms. The choices made in addressing each of these questions will determine whether the programme will be effective in reducing cancer-specific death and improving the benefit–harm balance of screening and be cost-effective, acceptable, accessible and feasible to implement. Dynamic interactions exist between each of these factors, and thus a change in one factor affects all others. Hence, the importance of a holistic, ‘systems thinking’ approach.

### Risk-stratified prevention

In high-income countries that have implemented strategies to prevent or mitigate cardiovascular disease (CVD), cancer has superseded CVD to become the most common cause of death<sup>101</sup>. In the context of CVD, clinical parameters indicative of risk (for example, blood pressure and serum lipid levels) can be successfully targeted and subsequently used to monitor preventive actions<sup>102</sup>. However, mirroring these concepts in the context of cancer has not been possible to date. Cancer development is a multifactorial process that occurs at various stages of life and sometimes decades in advance of diagnosis. Avoiding certain risk factors for breast cancer (for example, hormone replacement therapy, particularly those containing progesterone<sup>103</sup>), as well as adopting healthier lifestyle patterns (such as limiting alcohol consumption<sup>104,105</sup> and maintaining a healthy weight<sup>106</sup>), can have long-term cancer-preventive effects. Nevertheless, many of the risk factors for breast cancer (including a family history of the disease and genetic predisposition, birthweight, age at menarche, age at first live birth and age at menopause) are not modifiable, and in many cases the biological mechanism underlying the associated increase in breast cancer risk remains unknown. Notwithstanding, several active strategies have been shown to modify breast cancer risk.

### Chemoprevention with anti-oestrogens

The results of prospective randomized controlled trials (RCTs) evaluating primary prevention of breast cancer using selective oestrogen receptor modulators or aromatase inhibitors have consistently shown a reduced incidence in hormone receptor-positive subtypes of the disease<sup>107–119</sup>. However, in order to prevent one breast cancer in the next 20 years, 22 women needed to take tamoxifen daily for 5 years<sup>117</sup>. The considerable adverse effects of anti-oestrogens and the fact that none of these trials has shown any overall or breast cancer-specific survival benefits or a reduction in the incidence of aggressive, hormone receptor-negative forms of breast cancer make it difficult to judge whether treating healthy women with these drugs is a more effective strategy than reserving them for the adjuvant treatment of only those who actually develop breast cancer. Nevertheless, the US Preventive Services Task Force have judged that serious adverse effects, such as thrombosis and endometrial cancer, are uncommon and the more common toxicities, such as vasomotor symptoms, are reversible and were only marginally more frequent in women on active treatment than in those receiving placebo in the aforementioned RCTs<sup>120</sup>. Accordingly, several international guidelines recommend the use of anti-oestrogens as chemopreventives for women at increased risk of breast

cancer<sup>16,121</sup>. Whether improved risk stratification would reduce the number of healthy women who need to take anti-oestrogens in order to achieve the same preventive effect will need to be established in future RCTs.

**Surgical prevention**

Prophylactic bilateral mastectomy is certainly the most effective way of preventing breast cancer and reducing breast cancer-specific deaths in the small minority of women (perhaps 3%)<sup>122</sup> with a germline pathogenic *BRCA1/2* variant<sup>123</sup>. Nipple-sparing mastectomies are a safe option for these women, with no known detriment to the risk reduction<sup>124</sup>. General complications include wound dehiscence, infection, implant loss or flap necrosis, asymmetry and capsular contracture<sup>125</sup>. For nipple-sparing mastectomies, the overall complication rate has been reported to be 22.3%, and the rate of nipple necrosis was 5.9%<sup>126</sup>. However, surgery can be associated with other complications and adverse effects, including psychological distress with body image change, and has implications relating to resources. Thus, clinical utility, feasibility and acceptability need to be evaluated in order to set the risk threshold for surgical intervention.

**Other preventive strategies**

In past few years, several new targets of potential preventive interventions for breast cancer have been discovered. In particular, progesterone has an essential role in the development of aggressive breast cancers. A meta-analysis of 58 studies revealed that women receiving a progesterone-containing menopausal hormone therapy not only have a higher incidence of breast cancer than women not receiving such therapy or those receiving oestrogen-only treatments, but also more cancers that had spread beyond the breast<sup>103</sup>. Furthermore, the data indicated that women receiving progesterone-containing therapy are more likely to die from breast cancer than women treated only with oestrogens<sup>127</sup>. Additional evidence for the role of progesterone in breast carcinogenesis comes from the observation that women with germline pathogenic *BRCA1/2* variants have elevated levels of luteal phase progesterone compared with those observed in carriers of non-pathogenic *BRCA1/2* variants<sup>128</sup>. This increase in progesterone levels leads to an increase in receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) levels in the breast<sup>129–133</sup>, as well as reduced levels of the physiological RANKL antagonist osteoprotegerin<sup>129</sup>. These effects in turn lead to an expansion of ER<sup>-</sup> and progesterone receptor-negative mammary stem cells and eventual breast cancer formation<sup>134</sup>. In mouse models, *Brcal/2*-mediated breast cancer formation can be prevented by disrupting the progesterone signalling pathway using the competitive progesterone receptor antagonist mifepristone<sup>135</sup>. In addition, the findings of a case-control study involving women with germline *BRCA1/2* mutations indicate that moderate use of dietary supplements containing folic acid and vitamin B12 can be protective against *BRCA1/2*-associated breast cancer<sup>136</sup>. Other potential risk-reducing chemotherapeutics include aspirin, metformin, statins or other agents<sup>137</sup>.

To date, clinical trial evidence supporting these chemoprevention strategies is lacking. Denosumab, a fully humanized antagonistic monoclonal antibody targeting RANKL, has been shown to reduce breast epithelial cell proliferation in three premenopausal volunteers<sup>134</sup>. In postmenopausal women with breast cancer, however, denosumab does not seem to alter the incidence of contralateral breast cancer<sup>138</sup>. A prevention study of this agent in carriers of pathogenic *BRCA1* variants is underway<sup>139</sup>.

**Future directions in prevention**

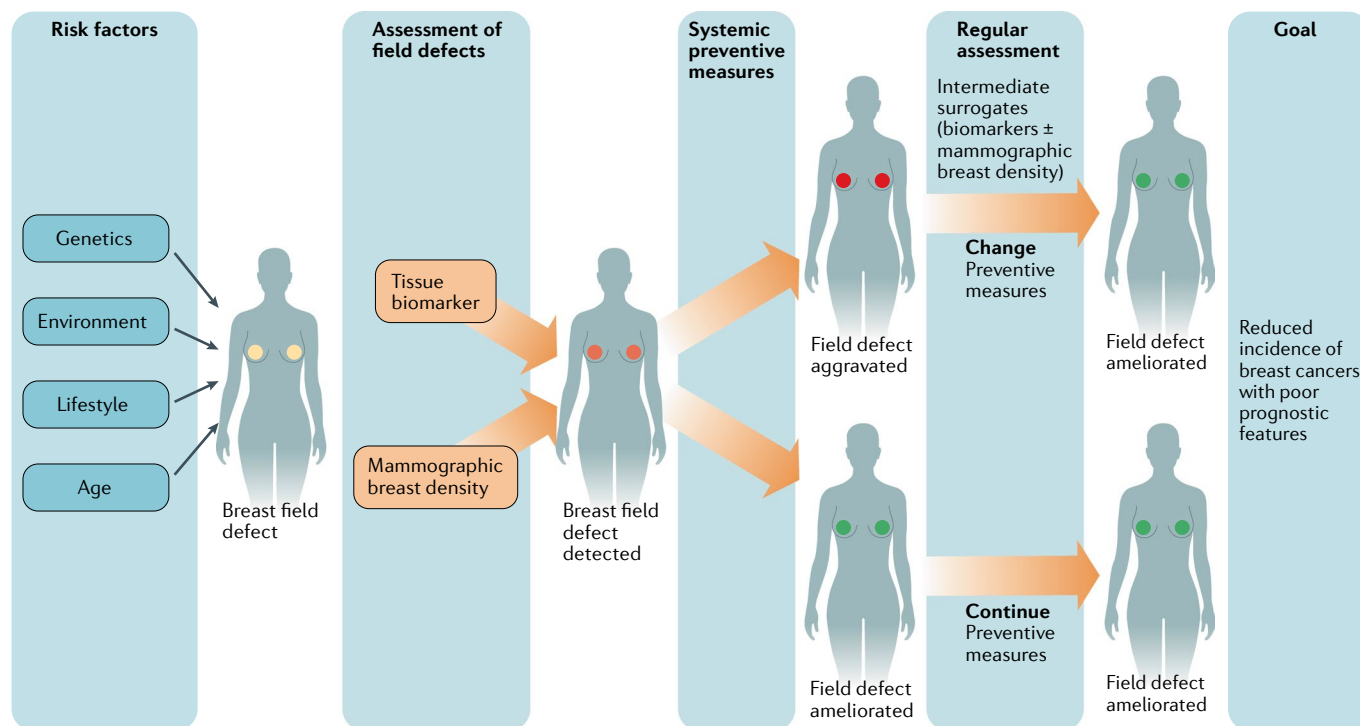
Several challenges need to be addressed to advance the field of breast cancer prevention. First, drugs that can reduce the incidence of aggressive breast cancers, for example, of the triple-negative, HER2<sup>+</sup> or luminal B subtypes, need to be identified.

Second, the required doses and frequency of administration of these potential preventive drugs need to be established. Unlike tamoxifen and aromatase inhibitors, the efficacy and safety of which have been tested in many thousands of women in the adjuvant treatment setting, no such data exist for the most promising novel preventive drugs (that is, progesterone antagonists and denosumab).

Third, efforts are needed to develop an effective approach to selecting women for whom breast cancer primary or secondary prevention measures will provide survival benefits. None of the current risk-prediction models intended to identify women at an increased risk of developing breast cancer in the absence of a familial predisposition (that is, mainly carriers of pathogenic *BRCA1/2* variants) selectively identifies those women at risk of developing an aggressive cancer that, if not prevented, would likely lead to death.

Fourth, surrogate end points are required (BOX 2). Demonstration of a reduction in breast cancer-related mortality is recommended before implementation of any early detection strategy<sup>140</sup> whereas, for prevention strategies, robust evidence of a reduced cancer incidence seems to be sufficient to recommend clinical implementation<sup>141</sup>. The focus should not, however, be a reduction in the incidence of any breast cancer, but rather of breast cancers that hold a poor prognosis. Intermediate surrogate markers are urgently required to enable timely assessment of the efficacy of potential new breast cancer-preventive drugs, particularly in women at high risk of the disease so as not to substantially delay or preclude bilateral mastectomy that is a safe risk-reducing option. A reduction in mammographic breast density has proved to be an excellent predictor of response to tamoxifen in the preventive setting<sup>142</sup>. In addition, molecular biomarkers, assessed directly in breast tissue and reflective of a field defect<sup>58</sup> or indirectly in a surrogate tissue or blood<sup>32</sup>, could potentially provide three essential advantages in prevention strategies for premenopausal women at high risk of breast cancer: 1) they can be measured frequently; 2) the dynamics of the molecular biomarkers in individual volunteers might reflect the cancer risk in real time, and thus individual adjustments to preventive measures could be made ad hoc; and 3) unlike many imaging-based markers, they do not require repeated exposure to x-rays (FIG. 3).

# CONSENSUS STATEMENT



**Fig. 3 | Overview of personalized risk reduction and breast cancer prevention paradigms.** Various risk factors contribute to field defects in breast tissues that favour the development of breast cancer. The presence of such field defects can be assessed using biomarkers and/or imaging to guide personalized prevention strategies, the success of which can be monitored on an ongoing basis through intermediate surrogates (for example, reduction or resolution of the field defect) that reflect the ultimate goal of a decreased incidence of breast cancers with features indicative of a poor prognosis.

Finally, strategies should be developed to increase the acceptability and accessibility of interventions used for breast cancer prevention. Notably, the efficacy of weight loss programmes has been shown to be greater among individuals who are aware of being at high risk of developing breast cancer<sup>143</sup>. Importantly, weight loss<sup>144</sup> and regular exercise<sup>145,146</sup> not only decrease breast cancer risk but also the risks of other cancers and CVDs. Considering the general health benefits, lifestyle interventions could be recommended to women at all levels of breast cancer risk<sup>147</sup>. Thus, developing effective ways to make both lifestyle and chemoprevention options widely available (including within screening programmes), acceptable and better understood by health-care professionals and the public is essential<sup>148</sup> (BOX 2).

### Risk-stratified early detection

The Cancer Control Joint Action European Guide on Quality Improvement in Comprehensive Cancer Control<sup>149</sup> recommends that the benefits (cancer-specific deaths averted and quality-adjusted life years gained), harms (related to false screen findings and subsequent investigations, and overdiagnoses and the associated treatments) and cost-effectiveness of a screening programme should be estimated to guide decisions on implementation. RCTs should be used to generate the primary evidence on the effectiveness of a new screening programme in reducing cancer-specific mortality<sup>149</sup>. When modifying currently running programmes, however, questions remain regarding what

constitutes supportive evidence (that is, the required level of evidence and study design)<sup>150</sup> and how complete the evidence needs to be before recommendations for implementation can be made<sup>151</sup>.

### Effectiveness

Two short-term RCTs evaluating the effectiveness of risk-stratified screening for breast cancer are currently ongoing: WISDOM in the USA<sup>152</sup> and MyPeBS in Europe<sup>153</sup>. While the two trials share a similar design, with intermediate outcome measures (such as stage distribution) as end points, their protocols are adapted to the local health-care settings.

WISDOM<sup>152</sup> is a multicentre, pragmatic, adaptive, preference-tolerant RCT comparing risk-based screening to annual screening in women aged 40–74 years. WISDOM is designed to determine whether risk-based screening is as safe as annual mammographic screening (number of stage  $\geq$ IIB cancers is no higher than that observed with annual screening), but with less morbidity (measured according to the number of breast biopsies performed) as well as greater acceptability, conductivity to preventive interventions and health-care value<sup>152</sup>. Women in the risk-based screening arm are receiving a personal risk assessment based on the BCSC risk calculator integrated with a PRS (which has been adapted during the course of the trial) and testing of a panel of nine susceptibility genes<sup>154</sup>. Those women are being stratified into four risk groups: highest risk, elevated risk, average risk and lowest risk. Each group is recommended

a screening strategy that varies in starting age and the frequency and modality of screening — annual mammography with adjunctive MRI, annual mammography, biennial mammography and deferred screening until the age of 50 years (in the lowest risk group comprising women aged 40–49 years with 5-year absolute risk <1.3%), respectively<sup>155</sup>.

MyPeBS<sup>153</sup> is a pragmatic, multicentre RCT that is being performed in five countries (Belgium, France, Israel, Italy and the UK) to determine if risk-based screening of women aged 40–70 years is non-inferior, in terms of the 4-year incidence of stage  $\geq$ II breast cancer, to the standard screening programme currently offered in each participating country (screening every 2–3 years beginning at 40–50 years of age and ending at 69–74 years of age). In MyPeBS, the frequency and modality of screening vary according to the level of risk predicted using PRS<sub>313</sub> combined with the BCSC<sup>74</sup> or the Tyrer–Cuzick<sup>78</sup> risk calculator. The latter calculator is used only in women with more than one first-degree relative with a history of breast or ovarian cancer. In MyPeBS, women are also being classified into four risk groups<sup>153</sup>, although the risk thresholds differ from those used in WISDOM. However, the lead investigators of both trials are ensuring that data are collected in a similar way and have committed to pooling the data to improve the ability to learn from each study.

RCTs of screening interventions provide the strongest evidence of efficacy, although they have certain limitations. In particular, lifetime health effects cannot be observed in RCTs with limited follow-up durations. Thus, the observed benefit–harm trade-offs might not accurately reflect those expected with long-term population screening<sup>156</sup>. Moreover, the outcomes of screening depend on the screening strategy (including the choice of risk-assessment tool, risk thresholds, screening modalities, screen intervals and starting and stopping ages) and variables relating to the setting (such as the available infrastructure, levels of adherence and population preferences)<sup>149</sup>. Variations in any of these elements can alter the benefit–harm trade-offs. Finding the optimum strategy for a given population requires comparisons of several alternative screening strategies; however, RCTs — particularly of screening strategies that require very large cohorts and long follow-up durations — are inherently limited in their ability to compare more than a few approaches (typically two or three).

Simulations using natural history models and decision analysis models constitute useful tools to study the long-term benefits and harms as well as the cost-effectiveness of various screening strategies<sup>157–159</sup>. Such modelling studies can precede or follow RCTs of screening interventions. Lifetime health effects can be modelled using empirical data — for example, from RCTs of different approaches to screening, long-term observational studies and clinical registries<sup>160</sup>. Modelling studies that incorporate data on the population structure and preferences, the natural history and prevalence of disease, life expectancy, the available resources and costs can provide an indication of which screening strategies are likely to be optimal in a given setting<sup>160</sup>. Thereafter, the most promising strategies could be

tested in RCTs. Thus, modelling studies can inform population-screening policies by extrapolating evidence beyond the time horizon of prospective trials and enabling the translation of evidence from one study population to another.

To date, evidence on the effectiveness of risk-stratified screening has come from model-based studies<sup>26,27,161</sup>. Modelling approaches have limitations, however. Models present a simplified representation of disease progression and intervention outcomes. Moreover, the accuracy of the results of modelling is dependent on the underlying assumptions and the degree of uncertainty in the input parameters<sup>162</sup>. Estimating overdiagnosis through simulations is particularly challenging<sup>163</sup> and more so in the absence of data on the rates of disease progression for different risk groups.

### Cost-effectiveness

Thus far, few studies have evaluated the cost-effectiveness and benefit–harm trade-offs of risk-stratified screening for breast cancer. Vilaprinio et al.<sup>161</sup> risk stratified women using several combinations of risk factors and showed that quinquennial or triennial screening for the low-risk or moderate-risk groups and annual screening for the high-risk group, from 50–74 years of age, would reduce costs, the number of false-positive findings and overdiagnosis, while averting the same number of deaths as biennial screening between the ages of 50 and 69 years. Trentham-Dietz et al.<sup>27</sup> used a combination of mammographic breast density and four exemplar relative risk levels for risk stratification and showed that triennial screening of average-risk women with low breast density, starting at 50 years of age, and annual screening of higher-risk women of the same age with high breast density would be cost-effective at a threshold of \$100,000 per quality-adjusted-life years gained and would maintain a similar or better balance of benefits and harms than biennial screening of average-risk women. Pashayan et al.<sup>26</sup> used the distribution of polygenic risk in the population combined with other risk factors for stratification and showed that, compared with screening women from age 50–69 years triennially, not screening women at lower risk of developing breast cancer would improve the cost-effectiveness and benefit to harm ratio of the breast-screening programme.

### Policy implications

When modifying an existing breast cancer screening programme, several considerations need to be taken into account. In particular, agreement should be reached on the framework of expected changes and acceptable trade-offs, whether in benefits, harms, net benefit, equity, cost or opportunity cost, in order to facilitate decisions on whether the evidence is supportive of the adapted programme. The ultimate aim is to implement risk-stratified screening that is justifiable from ethical, legal and societal viewpoints.

The policy priorities should be explicit: is the priority to maximize the return on investment or maximize the benefits of screening? That is, will the total number of screens and/or the budget allocated to the screening programme stay the same, but be utilized in a different

way to maximize the benefits by focusing on higher-risk groups; or will the screening efforts and resources be increased to enable tailoring of screening to the risk level of each individual?

### **Future directions in early detection**

We have identified several key areas for future research to improve early breast cancer detection (BOX 2). The evidence from modelling studies indicates that risk-stratified screening approaches could potentially improve the efficiency and the benefit–harm balance of breast cancer screening programmes. Further data are required, however, on how the natural course of breast cancer, the sensitivity and specificity of mammography, as well as the probability of overdiagnosis vary according to the underlying risk of the disease. This information is needed to minimize the assumptions and uncertainties in the estimates used in models of risk-tailored screening strategies.

To have confidence in the validity of the outputs of modelling studies, the models have to be well calibrated, the structural assumptions and parameter estimates should be reported clearly and explicitly and the effects of alternative assumptions should be assessed in sensitivity analyses<sup>100,164–166</sup>. Having the code made open-source and easily accessible will enhance the transparency of the model<sup>158</sup>.

In countries with existing breast cancer screening programmes, randomized health service trial designs could be used to evaluate risk-based screening in routine health-care settings. Such trials enable the comparison of a new policy or intervention to the current standard approach within the context of an existing health service<sup>167</sup>. Indeed, although modelling, routine monitoring and observational studies can provide helpful evidence, they are not a replacement for randomized health service studies<sup>167</sup>.

Trading off benefits and harms of different screening strategies is a fundamentally value-laden activity. Discrete choice experiments (DCEs) provide a quantitative approach to eliciting women's preferences<sup>168</sup>. In a DCE, participants are asked to choose between a series of alternative hypothetical scenarios described in terms of characteristics (or attributes) of the approach and associated levels of, for example, benefit and/or harm. In making these choices, participants are trading off between preferred and less preferred attributes presented in each alternative scenario. Incorporating the choice probability derived from DCEs for each screening approach into decision analytical modelling might facilitate the identification of optimal screening strategies.

In addition to cost-effectiveness analyses, budget-impact analyses will be needed to assess the affordability of a risk-stratified screening programme in a given setting<sup>169</sup>. Finally, although risk-stratified screening could potentially reduce overdiagnosis, a major need remains for tests that can differentiate, at diagnosis, tumours with progressive potential in order to reduce overtreatment. At present, no test is available for such differentiation at diagnosis. Biomarker-driven decisions regarding adjuvant therapy have, however, been incorporated into guidelines for the management of women

with certain types of breast cancer<sup>170</sup>, which suggests that such an approach might be viable at diagnosis.

### **Implementation**

Before risk-stratified prevention and early detection programmes for breast cancer can be implemented, health-care providers and policymakers would need to plan the resources, build the infrastructure for population-wide risk assessment, develop policies and regulations to protect the public from stigmatization and discrimination, and provide support for informed decision-making of individual women regarding whether or not to participate in the screening programme. Ultimately, these actions are needed to ensure the feasibility and affordability of providing a high-quality risk-stratified screening programme that is accessible to all and is aligned with public values and preferences. There will not be a single predefined way of organizing and delivering such programmes. The optimal approach will be context-specific to account for the idiosyncrasies of the health-care system, as well as the social, economic, cultural and political context (FIG. 4). Here, we are not dealing with a mathematical or technical problem; the implementation of risk-adapted breast cancer prevention and screening strategies does not constitute a simple change that has a simple solution, but rather necessitates complex adaptive changes that require all stakeholders, scientists, health-care professionals, the lay public and policymakers to work together.

### **Health-care organization readiness**

Organizational readiness for systems change is widely recognized as being necessary for the successful implementation of complex changes in health-care settings<sup>171</sup>. This state reflects the extent to which those involved in implementing the new approach are primed, motivated and capable of achieving the required changes<sup>172</sup>. Organizational readiness is a dynamic process with pull and push factors between what is possible owing to constant emergence of new technological opportunities and what resources are available<sup>173</sup>.

To address the challenge of a constantly changing environment, health-care organizations should embrace an evolutionary approach, rather than espouse a sudden dramatic shift, by adopting a learning organizational culture and building on existing infrastructure<sup>65</sup>. In keeping with this concept, the adaptive design of WISDOM enables learning and adaptation of the risk-assessment model and the screening recommendations accordingly over the course of the trial, instead of waiting for certain new discoveries to emerge before starting the trial, or excluding participants of non-European ancestry (for whom limited relevant data are currently available)<sup>152</sup>. The coverage with evidence development (CED) model<sup>174</sup> is a way of developing a 'learning-based health-care system'. CED provides a mechanism for promising but unproven health technologies to enter practice sooner, through time-limited reimbursement that is conditional on a specific requirement for generation of further evidence on the performance of the new technology.

Readiness for change requires the commitment and engagement of all stakeholders, resources (including

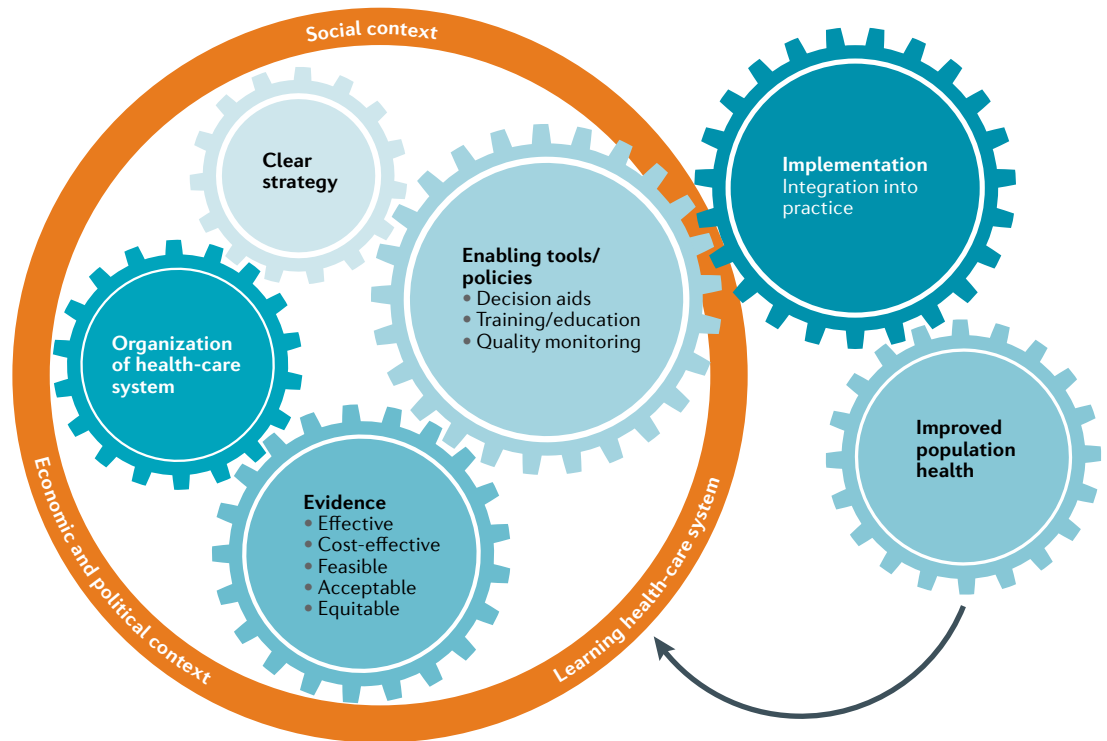


Fig. 4 | **Implementation of risk-stratified early detection and prevention programmes in a learning health-care system.** The schematic illustrates the various multilevel interactions between the different components needed for the implementation of risk-stratified programmes for the early detection and prevention of cancer. The ultimate goal is an improvement in population health outcomes. To achieve this goal, the process has to be iterative within a learning health-care system.

knowledge, skills, time, money and infrastructure) and governance<sup>171</sup>. To ensure the commitment of health-care organizations, the need for a change should be recognized and embedded in a shared vision, with leadership and coalition of all stakeholders<sup>171,175</sup>. To achieve a shared vision, the stakeholders have to agree on a framework of values that are aligned with those of the health-care organization. For example, health-care organizations value time-efficiency; therefore, successful implementation would require time-respecting strategies and tools, such as having one test to predict multiple cancers (which is a goal that FORECEE<sup>32</sup> aims to achieve). Overall, vision, skills, incentives, resources and action plans are needed to achieve the systems change that will be required for implementation of risk-stratified prevention and early detection programmes for breast cancer<sup>176</sup>.

#### Stakeholder engagement

Given the diverse opinions on breast cancer screening among key stakeholders at present and the specific challenges of risk-stratified screening, engagement of all stakeholders is crucial to implementation of new programmes. A stakeholder is a person, group or organization involved in or affected by a decision<sup>177</sup>. Key stakeholders in breast cancer prevention and screening include the users and the providers of the service, health-care professionals, policymakers, payers, advocacy groups, researchers and others. Stakeholder engagement would enable the identification of potential misunderstandings among the various stakeholders regarding opposition to, and perspectives on, the

implementation of a risk-stratified programme<sup>178</sup>. Using a multistakeholder approach to reach agreement on what would constitute sufficient evidence to change practice and on guidelines would increase the chances of implementing the research findings within the health-care system<sup>152</sup>. Such an approach would also help to articulate the values and preferences of the wider community and to build mutual trust, thereby facilitating the implementation of a programme that is accessible and acceptable. Stakeholder analysis<sup>179</sup> would be useful to not only identify the key stakeholders, but also their interests and influences, and the level of involvement of each (whether it be provision of information, consultation, deliberation, participatory decision-making or delegated decisions)<sup>177</sup>.

#### Risk communication and its impact

Many women overestimate their risk of developing breast cancer<sup>180</sup> and thus perceive screening as ‘almost always a good idea’<sup>181</sup>. This attitude is attributable to suboptimal levels of risk literacy among both patients and doctors as well as the limited transparency in the reporting of risks in the media and patient brochures<sup>182</sup>. Importantly, therefore, women should be transparently informed — for example, using fact boxes<sup>183,184</sup> — about their baseline risks and the benefit to harm ratio of risk-based screening as compared to the existing options of a universal screening approach or no screening<sup>185</sup>. The development of risk-stratified programmes will need to include consideration of how to update risk assessments as risk-prediction models improve and how to communicate these changes to individuals.

Communicating information on breast cancer risk alone is unlikely to result in changes in health-related behaviours, such as smoking or low levels of physical activity<sup>148,186,187</sup>. Indeed, a methodical review of nine systematic reviews, encompassing at total of 36 unique studies, revealed no evidence that providing risk information would have strong, consistent or sustained effects on behaviour<sup>186</sup>. Changes in health-related behaviour can, however, be facilitated by including elements of interventions to alter the behaviour in question<sup>143</sup>.

Importantly, the available evidence suggests that providing women with their breast cancer risk estimates is unlikely to produce elevated distress<sup>188</sup>. Nevertheless, knowledge of whether providing risk estimates will promote informed choices regarding screening attendance is lacking, although the evidence base is starting to increase<sup>148</sup>. More definitive conclusions regarding the behavioural and emotional effects of receiving risk estimates require studies specifically designed to assess these questions (for example, PROCAS2 (REF.<sup>37</sup>), MyPeBS<sup>153</sup> and PERSPECTIVE I&I<sup>36</sup>).

### Acceptability

Acceptability is a complex and poorly defined concept<sup>189</sup>. The level of uptake is one index of the acceptability of a risk assessment. Many studies have addressed the issue of acceptability of risk-stratified screening for breast cancer from the perspective of women<sup>38,190</sup> and of health-care professionals and policymakers<sup>191</sup>. The available evidence suggests that risk-stratified screening is broadly acceptable to women if it involves the potential for more frequent screening for those deemed to be at high risk<sup>192,193</sup>.

By contrast, a number of concerns exist among professionals working in this area, not least regarding costs and the available evidence base<sup>38</sup>. Similarly, major reservations surrounding the appropriateness of reducing the frequency of screening for women deemed to be at low risk have been expressed by health-care professionals, policymakers and women themselves<sup>194</sup>. A few high-quality ongoing studies<sup>36,37</sup> are examining these issues empirically, rather than discussing the issues as hypothetical possibilities<sup>195</sup>. Further research is needed to determine the feasibility of risk-stratified screening, particularly studies on implementation of screening in a research context, such as PERSPECTIVE I&I<sup>36</sup> and PROCAS2 (REF.<sup>37</sup>).

### Workforce training

Effective delivery of risk-stratified prevention and screening services requires health-care professionals to be competent in the use of a risk tool, in interpreting and applying the risk scores and in communicating risk scores effectively to each individual, including discussion of the accuracy of the risk prediction and its future implications<sup>196</sup>. Risk-stratified approaches entail (epi)genetic testing for risk assessment. Health-care professionals need not become geneticists to effectively use the (epi)genomic information obtained<sup>197</sup>; however, they need to be sufficiently versed in (epi)genomics — for example, in understanding the contribution of common and rare coding variants to risk prediction, gene-panel

testing and DNA-sequencing modalities and the implications of identifying pathogenic variants with poorly defined cancer risks or genetic variants of uncertain significance (VUS)<sup>198</sup>. Health-care systems should develop clear guidance related to the reporting of VUS in order to aid health-care professionals in the management of these variants, including descriptions of how patients with VUS should be informed if and when variants are found to confer an additional risk.

To engage with a new prevention and/or early detection scheme, the health-care professionals involved need to have a clear understanding of the rationale for risk stratification and risk-tailored interventions<sup>196</sup>, and have adequate knowledge of screening risk literacy<sup>199</sup> and risk-communication skills; they should also have access to structured referral pathways for those women who need more detailed counselling. Accordingly, aspects of genomics and risk-stratified interventions should be integrated across the continuum of training for health-care professionals, from undergraduate education to broad specialty training to continuous professional development programmes. Educational-needs assessments should inform the educational requirements of each medical specialty<sup>200</sup>.

### Ethical, legal and social implications

Ethical, legal and social issues need to be considered at every step of implementation of risk-based interventions, from health-service planning, invitation of participants and consent and sample collection, to risk calculation, communication of results and storage of data<sup>201,202</sup>. Some of the issues associated with risk-stratified screening will be dependent on the methods by which a programme is implemented<sup>202</sup>.

The four principles of bio-ethics promulgated by Beauchamp and Childress<sup>203</sup> — autonomy, beneficence, non-maleficence and justice — provide a useful framework to understand the potential implications of risk-based screening, although these principles are more commonly applied to the doctor–patient relationship in the clinical context. Respecting autonomy requires that an individual has adequate knowledge and understanding to decide whether they wish to opt for a given intervention. The capacity of the individual to independently make an informed decision will depend on the information content, the communication tools used and the adequacy of workforce training in conveying the relevant information. Optimizing the balance between providing benefit (beneficence) and the potential for harm (maleficence) with a risk-based screening programme requires rigorous evaluation. This balance also requires consideration and mitigation of potential unintended harms of such programmes. These unintended harms might include the negative consequences of risk assessment for individuals (such as anxiety and breaches of confidential genetic and other personal data) or at a society level (stigmatization of and discrimination against some individuals because of their risk level and non-participation of some individuals in the programme, for example, because they perceive that health care is being rationed for those for whom less screening is recommended<sup>202</sup>). Finally, justice relates

to the fairness of a programme. Screening programmes have the potential to increase health inequalities, owing to differences in the level of uptake between socioeconomic groups, including those covered under universal health systems<sup>204–206</sup>. Risk-based screening programmes might exacerbate these differences<sup>201</sup>, given their additional complexity and inherent selectivity relative to universal screening. Efforts are needed to mitigate this possibility, for example, through ‘proportionate universalism’<sup>207</sup>, whereby social inequalities are considered and programme resources are targeted commensurately<sup>208</sup>. Communication relating to screening and risk assessment has to be accessible and congruent to the literacy and numeracy level of the recipients while also accurately presenting both the potential benefits and risks<sup>209</sup>. Meeting these requirements will not only avoid misinterpretation of the information provided and subsequent inequitable use of screening services, but also enable each individual to make an informed decision<sup>201</sup>. In addition, robust legislation is necessary to prevent discrimination and stigmatization, in particular, by insurers and employers. Current approaches vary by country, but can be broadly divided into four categories: moratoria, industry self-regulation, legal limitations to the use of genetic information, and legal bans<sup>210,211</sup>. As an example, in the UK, an open-ended code of practice between insurers and the government exists, prohibiting the use of predictive genetic tests except in defined circumstances<sup>212</sup>.

**Future directions for implementation**

The time is right to perform implementation research in a real-world setting of risk-stratified prevention and screening for breast cancer, with clearly defined criteria for success (for example, relating to the extent of adoption, appropriateness, acceptability, sustainability, cost implications and effectiveness of the programme). The research should be designed and conducted together with all stakeholder groups, taking into account the ethical, legal and social context as well as factors that affect implementation (such as the idiosyncrasies of the health-care system and organizational readiness). The process has to be iterative in a health-care system conducive to learning and adaptation<sup>213</sup>.

To reduce the time lag between obtaining evidence on the effectiveness of a programme and its implementation, studies with hybrid effectiveness–implementation design could be used<sup>214</sup> (BOX 2). WISDOM<sup>152</sup> and MyPeBS<sup>153</sup> are examples of studies with hybrid designs primarily focused on effectiveness while also exploring the ‘implementability’ of the intervention. Several strategies adopted in WISDOM, such as the adaptive design, multistakeholder approach<sup>215</sup> and CED model<sup>174</sup>, will

accelerate implementation of the findings. By contrast, PERSPECTIVE I&I<sup>36</sup> has a hybrid design focused primarily on implementation outcomes (including the acceptability and feasibility of risk-based screening, uptake of genetic testing for risk assessment and screening behaviours); however, data on effectiveness (that is, screening outcomes of different risk groups) are also being collected, and simulation modelling is being performed to assess the efficiency, resource use, costs and cost-effectiveness of risk-based screening at a population level using real-world administrative data. A third type of hybrid design involves the simultaneous study of effectiveness and implementation strategies. This approach enables the demonstration of which implementation strategies work in a given context, as opposed to demonstrating the effects of a particular implementation strategy on the adoption or uptake of an intervention<sup>214</sup>.

The model of evidence-generating health care could be adopted to study the clinical utility of risk stratification in the prevention of breast cancer among carriers of pathogenic *BRCA1/2* variants. This approach would require linking of genetic profiles and the outcomes of preventive interventions to cancer registries, training of treating physicians to develop a working knowledge of cancer risk and genetics, and the development of decision aids for patients.

Women with a family history of breast cancer constitute a ‘high-impact’ group in which to first pilot national level application of integrated breast cancer risk assessment. In this group, the intervention might not only substantially improve clinical management, but also provide valuable information on how risk-stratified programmes might perform in the general population. Thus, the results of this pilot approach could form the basis on which to build subsequent population-level risk-based interventions.

**Conclusions**

Substantial progress has been made in research focused on estimating an individual woman’s risk of developing breast cancer, applying risk stratification in breast cancer prevention studies, modelling the benefit–harm balance of risk-stratified early detection approaches, and assessing the acceptability and feasibility of implementing risk-based prevention and screening programmes. To translate this progress into improvements in population health outcomes, a systems approach to the evaluation of risk-based programmes is necessary, taking into account the health-care organization’s readiness for change, its openness to learning and adapting, the social context and the need for engagement of all stakeholders.

Published online 18 June 2020

<p>1. Bray, F. et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. <i>CA Cancer J. Clin.</i> <b>68</b>, 394–424 (2018).</p> <p>2. Sorlie, T. et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. <i>Proc. Natl Acad. Sci. USA</i> <b>98</b>, 10869–10874 (2001).</p> <p>3. Blows, F. M. et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long</p>	<p>term survival: a collaborative analysis of data for 10,159 cases from 12 studies. <i>PLoS Med.</i> <b>7</b>, e1000279 (2010).</p> <p>4. Curtis, C. et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. <i>Nature</i> <b>486</b>, 346–352 (2012).</p> <p>5. Yang, X. R. et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. <i>J. Natl Cancer Inst.</i> <b>103</b>, 250–263 (2011).</p>	<p>6. Broeks, A. et al. Low penetrance breast cancer susceptibility loci are associated with specific breast tumor subtypes: findings from the Breast Cancer Association Consortium. <i>Hum. Mol. Genet.</i> <b>20</b>, 3289–3303 (2011).</p> <p>7. Turkoz, F. P. et al. Association between common risk factors and molecular subtypes in breast cancer patients. <i>Breast</i> <b>22</b>, 344–350 (2013).</p> <p>8. Waks, A. G. &amp; Winer, E. P. Breast cancer treatment: a review. <i>JAMA</i> <b>321</b>, 288–300 (2019).</p>
---	---	---



9. Cancer Research UK. Breast cancer incidence by age <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive> (2019).
10. Netherlands Cancer Registry. Incidence of cancer in the Netherlands <http://www.dutchcancerfigures.nl/> (2019).
11. Nelson, H. D. et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann. Intern. Med.* **156**, 635–648 (2012).
12. Brinton, L., Gaudet, M. & Gierach, G. in *Cancer Epidemiology Prevention* (eds Thun, M., Linet, M., Cerhan, J., Haiman, C. & Schottenfeld, D.) 861–888 (Oxford University Press, 2018).
13. Winters, S., Martin, C., Murphy, D. & Shokar, N. K. Breast cancer epidemiology, prevention and screening. *Prog. Mol. Biol. Transl. Sci.* **151**, 1–32 (2017).
14. Hartmann, L. C. et al. Benign breast disease and the risk of breast cancer. *N. Engl. J. Med.* **353**, 229–237 (2005).
15. Moorthie, S. et al. *Personalised Prevention in Breast Cancer: the Policy Landscape* (University of Cambridge, 2017).
16. NICE. *Familial Breast Cancer: Classification, Care and Managing Breast Cancer and Related Risks in People with A Family History of Breast Cancer* (NICE, 2013).
17. Owens, D. K. et al. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer. *JAMA* **322**, 652 (2019).
18. Alexander, F. E. et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet* **353**, 1903–1908 (1999).
19. Habbema, J. D., van Oortmarssen, G. J., van Putten, D. J., Lubbe, J. T. & van der Maas, P. J. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. *J. Natl Cancer Inst.* **77**, 317–320 (1986).
20. Nystrom, L. et al. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* **359**, 909–919 (2002).
21. Miller, A. B., To, T., Baines, C. J. & Wall, C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann. Intern. Med.* **137**, 305–312 (2002).
22. Moss, S. M. et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* **368**, 2053–2060 (2006).
23. Welch, H. G., Prorok, P. C., O'Malley, A. J. & Kramer, B. S. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. *N. Engl. J. Med.* **375**, 1438–1447 (2016).
24. Drukker, C. A. et al. Mammographic screening detects low-risk tumor biology breast cancers. *Breast Cancer Res. Treat.* **144**, 103–111 (2014).
25. Esserman, L., Shieh, Y. & Thompson, I. Rethinking screening for breast cancer and prostate cancer. *JAMA* **302**, 1685–1692 (2009).
26. Pashayan, N., Morris, S., Gilbert, F. J. & Pharoah, P. D. P. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer a life-table model. *JAMA Oncol.* **4**, 1–7 (2018).
27. Trentham-Dietz, A. et al. Tailoring breast cancer screening intervals by breast density and risk for women aged 50 years or older: collaborative modeling of screening outcomes. *Ann. Intern. Med.* **165**, 700 (2016).
28. Burton, H. et al. Public health implications from COGS and potential for risk stratification and screening. *Nat. Genet.* **45**, 349–351 (2013).
29. Horizon 2020. B-CAST. *Breast cancer stratification: understanding the determinants of risk and prognosis of molecular subtypes* <https://cordis.europa.eu/project/rcn/193256/factsheet/en> (2020).
30. Horizon 2020. BRIDGES. *Breast cancer risk after diagnostic gene sequencing* <https://cordis.europa.eu/project/rcn/193315/factsheet/en> (2019).
31. European Research Council. BRCA-ERC. *Understanding cancer development in BRCA1/2 mutation carriers for improved Early detection and Risk Control* <https://cordis.europa.eu/project/rcn/210990/factsheet/en> (2017).
32. Horizon 2020. FORECEE. *Female cancer prediction using cervical omics to individualise screening and prevention* <https://cordis.europa.eu/project/rcn/193298/factsheet/en> (2019).
33. Horizon 2020. MyPeBS. *International randomized study comparing personalized, risk-stratified to standard breast cancer screening in women aged 40-70* <https://cordis.europa.eu/project/rcn/212694/factsheet/en> (2019).
34. WISDOM. The WISDOM study <https://wisdom.secure.force.com/portal/> (2020).
35. Horizon 2020. EU-TOPIA. *EU-TOPIA: towards improved screening for breast, cervical and colorectal cancer in all of Europe* <https://cordis.europa.eu/project/rcn/193304/factsheet/en> (2019).
36. GenomeQuebec. PERSPECTIVE I&I. *Personalized risk assessment for prevention and early detection of breast cancer: integration and implementation* <http://www.genomequebec.com/211-en/project/personalized-risk-assessment-for-prevention-and-early-detection-of-breast-cancer-integration-and-implementation/> (2020).
37. Prevent Breast Cancer. PROCAS 2. Predicting the risk of cancer at screening 2nd stage <https://preventbreastcancer.org.uk/breast-cancer-research/research-projects/early-detection-screening/procas/> (2016).
38. Rainey, L. et al. Are we ready for the challenge of implementing risk-based breast cancer screening and primary prevention? *Breast* **39**, 24–32 (2018).
39. The Health Foundation. *Evidence Scan: Complex Adaptive Systems* (The Health Foundation, 2010).
40. Michailidou, K. et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* **551**, 92–94 (2017).
41. Milne, R. L. et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat. Genet.* **49**, 1767–1778 (2017).
42. Easton, D. F. et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N. Engl. J. Med.* **372**, 2243–2257 (2015).
43. Rudolph, A. et al. Joint associations of a polygenic risk score and environmental risk factors for breast cancer in the Breast Cancer Association Consortium. *Int. J. Epidemiol.* **47**, 526–536 (2018).
44. Mavaddat, N. et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am. J. Hum. Genet.* **104**, 21–34 (2019).
45. Lee, A. et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet. Med.* **21**, 1708–1718 (2019).
46. Läll, K. et al. Polygenic prediction of breast cancer: comparison of genetic predictors and implications for risk stratification. *BMC Cancer* **19**, 557 (2019).
47. Choudhury, P. P. et al. Comparative validation of breast cancer risk prediction models and projections for future risk stratification. *J. Natl Cancer Inst.* **112**, 278–285 (2020).
48. LaDuca, H. et al. A clinical guide to hereditary cancer panel testing: evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. *Genet. Med.* **22**, 407–415 (2020).
49. Schmidt, M. K. et al. Age- and tumor subtype-specific breast cancer risk estimates for CHEK2\*1100delC carriers. *J. Clin. Oncol.* **34**, 2750–2760 (2016).
50. Foulkes, W. D. et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer. *Clin. Cancer Res.* **10**, 2029–2034 (2004).
51. Fletcher, O. et al. Missense variants in ATM in 26,101 breast cancer cases and 29,842 controls. *Cancer Epidemiol. Biomarkers Prev.* **19**, 2143–2151 (2010).
52. Gao, P., Ma, N., Li, M., Tian, Q.-B. & Liu, D.-W. Functional variants in NBS1 and cancer risk: evidence from a meta-analysis of 60 publications with 111 individual studies. *Mutagenesis* **28**, 685–697 (2013).
53. Weitzel, J. N. et al. Pathogenic and likely pathogenic variants in PALB2, CHEK2, and other known breast cancer susceptibility genes among 1054 BRCA negative Hispanics with breast cancer. *Cancer* **125**, 2829–2836 (2019).
54. Parsons, M. T. et al. Large scale multifactorial likelihood quantitative analysis of BRCA1 and BRCA2 variants: an ENIGMA resource to support clinical variant classification. *Hum. Mutat.* **40**, 1557–1578 (2019).
55. Kleiblova, P. et al. Identification of deleterious germline CHEK2 mutations and their association with breast and ovarian cancer. *Int. J. Cancer* **145**, ijc.32385 (2019).
56. Boonen, R. A. C. M. et al. Functional analysis of genetic variants in the high-risk breast cancer susceptibility gene PALB2. *Nat. Commun.* **10**, 5296 (2019).
57. Lee, K. et al. Clinical validity assessment of genes frequently tested on hereditary breast and ovarian cancer susceptibility sequencing panels. *Genet. Med.* **21**, 1497–1506 (2019).
58. Teschendorff, A. E. et al. DNA methylation outliers in normal breast tissue identify field defects that are enriched in cancer. *Nat. Commun.* **7**, 10478 (2016).
59. Curtius, K., Wright, N. A. & Graham, T. A. An evolutionary perspective on field cancerization. *Nat. Rev. Cancer* **18**, 19–32 (2018).
60. Yang, Y. et al. Genetically predicted levels of DNA methylation biomarkers and breast cancer risk: data from 228,951 women of European descent. *J. Natl Cancer Inst.* **112**, 295–304 (2020).
61. Xu, Z., Sandler, D. P. & Taylor, J. A. Blood DNA methylation and breast cancer: a prospective case-cohort analysis in the Sister study. *J. Natl Cancer Inst.* **112**, 87–94 (2020).
62. Teschendorff, A. E. et al. Age-dependent DNA methylation of genes that are suppressed in stem cells is a hallmark of cancer. *Genome Res.* **20**, 440–446 (2010).
63. Knowler, K. C., To, S. O., Leung, Y.-K., Ho, S.-M. & Clyne, C. D. Endocrine disruption of the epigenome: a breast cancer link. *Endocr. Relat. Cancer* **21**, T33–T55 (2014).
64. Levine, M. E. et al. Menopause accelerates biological aging. *Proc. Natl Acad. Sci. USA* **113**, 9327–9332 (2016).
65. Widschwendter, M. et al. Epigenome-based cancer risk prediction: rationale, opportunities and challenges. *Nat. Rev. Clin. Oncol.* **15**, 292–309 (2018).
66. Bodelon, C. et al. Blood DNA methylation and breast cancer risk: a meta-analysis of four prospective cohort studies. *Breast Cancer Res.* **21**, 62 (2019).
67. Teschendorff, A. E. et al. An epigenetic signature in peripheral blood predicts active ovarian cancer. *PLoS One* **4**, e8274 (2009).
68. Key, T. J. et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol.* **14**, 1009–1019 (2013).
69. Key, T. J. et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J. Natl Cancer Inst.* **95**, 1218–1226 (2003).
70. Fourkala, E.-O. et al. Association of serum sex steroid receptor bioactivity and sex steroid hormones with breast cancer risk in postmenopausal women. *Endocr. Relat. Cancer* **19**, 137–147 (2012).
71. Bau, D.-T., Mau, Y.-C., Ding, S.-L., Wu, P.-E. & Shen, C.-Y. DNA double-strand break repair capacity and risk of breast cancer. *Carcinogenesis* **28**, 1726–1730 (2007).
72. Machella, N. et al. Double-strand breaks repair in lymphoblastoid cell lines from sisters discordant for breast cancer from the New York site of the BCFR. *Carcinogenesis* **29**, 1367–1372 (2008).
73. Gail, M. H. et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J. Natl Cancer Inst.* **81**, 1879–1886 (1989).
74. Tice, J. A. et al. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann. Intern. Med.* **148**, 337–347 (2008).
75. Garcia-Closas, M., Gunsoy, N. B. & Chatterjee, N. Combined associations of genetic and environmental risk factors: implications for prevention of breast cancer. *J. Natl Cancer Inst.* **106**, 1–6 (2014).
76. Maas, P. et al. Breast cancer risk from modifiable and nonmodifiable risk factors among white women in the United States. *JAMA Oncol.* **2**, 1295–1302 (2016).
77. Chatterjee, N., Shi, J. & Garcia-Closas, M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat. Rev. Genet.* **17**, 392–406 (2016).
78. Tyrer, J., Duffy, S. W. & Cuzick, J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat. Med.* **23**, 1111–1130 (2004).
79. Antoniou, A. C. et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br. J. Cancer* **98**, 1457–1466 (2008).

80. Zimmern, R. L. & Kroese, M. The evaluation of genetic tests. *J. Public Health* **29**, 246–250 (2007).

81. University of Cambridge. BCAC — *The Breast Cancer Association Consortium* <http://bcac.ccge.medschl.cam.ac.uk/> (2020).

82. University of Cambridge. Centre for Cancer Genetic Epidemiology. CIMBA — *Consortium of Investigators of Modifiers of BRCA1/2* <http://cimba.ccge.medschl.cam.ac.uk/> (2020).

83. Louro, J. et al. A systematic review and quality assessment of individualised breast cancer risk prediction models. *Br. J. Cancer* **121**, 76–85 (2019).

84. Terry, M. B. et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol.* **20**, 504–517 (2019).

85. Choudhury, P. P. et al. iCARE: An R package to build, validate and apply absolute risk models. *PLoS One* **5**, e0228198 (2020).

86. Smart, A. A multi-dimensional model of clinical utility. *Int. J. Qual. Health Care* **18**, 377–382 (2006).

87. Sanderson, S. et al. How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. *Genet. Med.* **7**, 495–500 (2005).

88. Grosse, S. D. & Khoury, M. J. What is the clinical utility of genetic testing? *Genet. Med.* **8**, 448–450 (2006).

89. Garcia-Closas, M. et al. Confluence: uncovering breast cancer genetics <https://dceg.cancer.gov/research/cancer-types/breast-cancer/confluence-study-project.pdf> (2019).

90. Wainschtein, P. et al. Recovery of trait heritability from whole genome sequence data. *bioRxiv* <https://doi.org/10.1101/588020> (2019).

91. Yala, A., Lehman, C., Schuster, T., Portnoi, T. & Barzilay, R. A deep learning mammography-based model for improved breast cancer risk prediction. *Radiology* **292**, 60–66 (2019).

92. Arasu, V. A. et al. Population-based assessment of the association between magnetic resonance imaging background parenchymal enhancement and future primary breast cancer risk. *J. Clin. Oncol.* **37**, 954–963 (2019).

93. Malkov, S. et al. Mammographic texture and risk of breast cancer by tumor type and estrogen receptor status. *Breast Cancer Res.* **18**, 122 (2016).

94. Gastounioti, A., Conant, E. F. & Kontos, D. Beyond breast density: a review on the advancing role of parenchymal texture analysis in breast cancer risk assessment. *Breast Cancer Res.* **18**, 91 (2016).

95. Wang, C. et al. A novel and fully automated mammographic texture analysis for risk prediction: results from two case-control studies. *Breast Cancer Res.* **19**, 114 (2017).

96. Nguyen, T. L. et al. Predicting interval and screen-detected breast cancers from mammographic density defined by different brightness thresholds. *Breast Cancer Res.* **20**, 152 (2018).

97. Cohen, J. D. et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* **359**, 926–930 (2018).

98. Wan, J. C. M. et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat. Rev. Cancer* **17**, 223–238 (2017).

99. Best, M. G. et al. RNA-Seq of tumor-educated platelets enables blood-based pan-cancer, multiclass, and molecular pathway cancer diagnostics. *Cancer Cell* **28**, 666–676 (2015).

100. Eddy, D. M. et al. Model transparency and validation: a report of the ISPOR-SMDM modeling good research practices task force — 7. *Value Health* **15**, 843–850 (2012).

101. Dagenais, G. R. et al. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* **395**, 785–794 (2020).

102. Fulcher, J. et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet* **385**, 1397–1405 (2015).

103. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* **394**, 1159–1168 (2019).

104. Hamajima, N. et al. Alcohol, tobacco and breast cancer — collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer* **87**, 1234–1245 (2002).

105. Bagnardi, V. et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose–response meta-analysis. *Br. J. Cancer* **112**, 580–593 (2015).

106. Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569–578 (2008).

107. Cuzick, J. Progress in preventive therapy for cancer: a reminiscence and personal viewpoint. *Br. J. Cancer* **118**, 1155–1161 (2018).

108. Fisher, B. et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J. Natl Cancer Inst.* **90**, 1371–1388 (1998).

109. Cuzick, J. Aromatase inhibitors for breast cancer prevention. *J. Clin. Oncol.* **23**, 1636–1643 (2005).

110. Cuzick, J. et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet* **383**, 1041–1048 (2014).

111. Goss, P. E. et al. Exemestane for breast-cancer prevention in postmenopausal women. *N. Engl. J. Med.* **364**, 2381–2391 (2011).

112. Cuzick, J. et al. First results from the International Breast Cancer Intervention Study (IBIS-II): a randomised prevention trial. *Lancet* **360**, 817–824 (2002).

113. Cuzick, J. et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet* **361**, 296–300 (2003).

114. Powles, T. et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet* **352**, 98–101 (1998).

115. Veronesi, U. et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* **352**, 93–97 (1998).

116. Powles, T. J., Ashley, S., Tidy, A., Smith, I. E. & Dowsett, M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. *J. Natl Cancer Inst.* **99**, 283–290 (2007).

117. Cuzick, J. et al. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. *Lancet Oncol.* **16**, 67–75 (2015).

118. Vogel, V. G. et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA* **295**, 2727–2741 (2006).

119. Vogel, V. G. et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev. Res.* **3**, 696–706 (2010).

120. Nelson, H. D., Smith, M. E. B., Griffin, J. C. & Fu, R. Use of medications to reduce risk for primary breast cancer: a systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* **158**, 604 (2013).

121. Owens, D. K. et al. Medication use to reduce risk of breast cancer: US Preventive Services Task Force recommendation statement. *JAMA* **322**, 857–867 (2019).

122. Armstrong, N., Ryder, S., Forbes, C., Ross, J. & Quek, R. G. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin. Epidemiol.* **11**, 543–561 (2019).

123. Heemskerk-Gerritsen, B. A. M. et al. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res. Treat.* **177**, 723–733 (2019).

124. Jakub, J. W. et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with BRCA mutations. *JAMA Surg.* **153**, 123 (2018).

125. Mota, B. S. et al. Nipple- and areola-sparing mastectomy for the treatment of breast cancer. *Cochrane Database Syst. Rev.* **11**, CD008932 (2016).

126. Headon, H. L., Kasem, A. & Mokbel, K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch. Plast. Surg.* **43**, 328–338 (2016).

127. Beral, V., Peto, R., Pirie, K. & Reeves, G. Menopausal hormone therapy and 20-year breast cancer mortality. *Lancet* **394**, 1139 (2019).

128. Widschwendter, M. et al. The sex hormone system in carriers of BRCA1/2 mutations: a case-control study. *Lancet Oncol.* **14**, 1226–1232 (2013).

129. Widschwendter, M. et al. Osteoprotegerin (OPG), the endogenous inhibitor of receptor activator of NF-kappaB ligand (RANKL), is dysregulated in BRCA mutation carriers. *EBioMedicine* **2**, 1331–1339 (2015).

130. Schramek, D. et al. Osteoclast differentiation factor RANKL controls development of progesterin-driven mammary cancer. *Nature* **468**, 98–102 (2010).

131. Joshi, P. A. et al. Progesterone induces adult mammary stem cell expansion. *Nature* **465**, 803–807 (2010).

132. Gonzalez-Suarez, E. et al. RANK ligand mediates progesterin-induced mammary epithelial proliferation and carcinogenesis. *Nature* **468**, 103–107 (2010).

133. Tanos, T. et al. Progesterone/RANKL is a major regulatory axis in the human breast. *Sci. Transl. Med.* **5**, 182ra55 (2013).

134. Nolan, E. et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. *Nat. Med.* **22**, 933–939 (2016).

135. Poole, A. J. et al. Prevention of Brca1-mediated mammary tumorigenesis in mice by a progesterone antagonist. *Science* **314**, 1467–1470 (2006).

136. Kim, S. J. et al. Folic acid supplement use and breast cancer risk in BRCA1 and BRCA2 mutation carriers: a case-control study. *Breast Cancer Res. Treat.* **174**, 741–748 (2019).

137. Evans, D. G., Howell, S. J. & Howell, A. Personalized prevention in high risk individuals: managing hormones and beyond. *Breast* **39**, 139–147 (2018).

138. Gnant, M. et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **20**, 339–351 (2019).

139. European Medicines Agency. *European Union Clinical Trials Register* <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002505-35/AT> (2018).

140. Sasieni, P. D., Duffy, S. W. & Cuzick, J. Ovarian cancer screening: UKTOCS trial. *Lancet* **387**, 2602 (2016).

141. Curtis, H. J., Walker, A. J. & Goldacre, B. Impact of NICE guidance on tamoxifen prescribing in England 2011–2017: an interrupted time series analysis. *Br. J. Cancer* **118**, 1268–1275 (2018).

142. Cuzick, J. et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J. Natl Cancer Inst.* **103**, 744–752 (2011).

143. Harvie, M. et al. Breast cancer risk status influences uptake, retention and efficacy of a weight loss programme amongst breast cancer screening attendees: two randomised controlled feasibility trials. *BMC Cancer* **19**, 1089 (2019).

144. Teras, L. R. et al. Sustained weight loss and risk of breast cancer in women ≥50 years: a pooled analysis of prospective data. *J. Natl Cancer Inst.* <https://doi.org/10.1093/jnci/djz226> (2019).

145. Kyu, H. H. et al. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ* **354**, i3857 (2016).

146. Guo, W., Fensom, G. K., Reeves, G. K. & Key, T. J. Physical activity and breast cancer risk: results from the UK Biobank prospective cohort. *Br. J. Cancer* **122**, 726–732 (2020).

147. Rainey, L. et al. The impact of alcohol consumption and physical activity on breast cancer: the role of breast cancer risk. *Int. J. Cancer* <https://doi.org/10.1002/ijc.32846> (2020).

148. French, D. P., Howell, A. & Evans, D. G. Psychosocial issues of a population approach to high genetic risk identification: behavioural, emotional and informed choice issues. *Breast* **37**, 148–153 (2018).

149. Alhbert, T., Kiasuwa, R. & van den Bulcke, M. European guide on quality improvement in

- comprehensive cancer control [https://cancercontrol.eu/archived/uploads/images/Guide/pdf/CanCon\\_Guide\\_FINAL\\_Web.pdf](https://cancercontrol.eu/archived/uploads/images/Guide/pdf/CanCon_Guide_FINAL_Web.pdf) (2017)
150. Lesko, L. J., Zineh, I. & Huang, S.-M. What is clinical utility and why should we care? *Clin. Pharmacol. Ther.* **88**, 729–733 (2010).
  151. Rychetnik, L., Frommer, M., Hawe, P. & Shiell, A. Criteria for evaluating evidence on public health interventions. *J. Epidemiol. Community Health* **56**, 119–127 (2002).
  152. Esserman, L. J. et al. The WISDOM study: breaking the deadlock in the breast cancer screening debate. *NPJ Breast Cancer* **3**, 4 (2017).
  153. US National Library of Medicine. *Clinicaltrials.gov* <https://clinicaltrials.gov/ct2/show/NCT03672331> (2020)
  154. Vachon, C. M. et al. The contributions of breast density and common genetic variation to breast cancer risk. *J. Natl Cancer Inst.* **107**, dju397 (2015).
  155. Shieh, Y. et al. Breast cancer screening in the precision medicine era: risk-based screening in a population-based trial. *J. Natl Cancer Inst.* **109**, djw290 (2017).
  156. Etzioni, R. D. & Thompson, I. M. What do the screening trials really tell us and where do we go from here? *Urol. Clin. North Am.* **41**, 225–228 (2014).
  157. Getaneh, A. M., Heijnsdijk, E. A. & de Koning, H. J. The role of modelling in the policy decision making process for cancer screening: example of prostate specific antigen screening. *Public Health Res. Pract.* **29**, 2921912 (2019).
  158. Karlsson, A. et al. A natural history model for planning prostate cancer testing: calibration and validation using Swedish registry data. *PLoS One* **14**, e0211918 (2019).
  159. Lew, J.-B. et al. Benefits, harms and cost-effectiveness of cancer screening in Australia: an overview of modelling estimates. *Public Health Res. Pract.* **29**, 29121913 (2019).
  160. Siebert, U. When should decision-analytic modeling be used in the economic evaluation of health care? *Eur. J. Health Econ.* **4**, 143–150 (2003).
  161. Vilapriño, E. et al. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. *PLoS One* **9**, e86858 (2014).
  162. Etzioni, R. et al. Limitations of basing screening policies on screening trials. *Med. Care* **51**, 295–300 (2013).
  163. Etzioni, R. & Gulati, R. Recognizing the limitations of cancer overdiagnosis studies: a first step towards overcoming them. *J. Natl Cancer Inst.* **108**, djv345 (2015).
  164. Weinstein, M. C. et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices — modeling studies. *Value Health* **6**, 9–17 (2003).
  165. Caro, J. J., Briggs, A. H., Siebert, U. & Kuntz, K. M. Modeling good research practices — overview. *Med. Decis. Making* **32**, 667–677 (2012).
  166. Briggs, A. H. et al. Model parameter estimation and uncertainty analysis. *Med. Decis. Making* **32**, 722–732 (2012).
  167. Hakama, M., Malila, N. & Dilner, J. Randomised health services studies. *Int. J. Cancer* **131**, 2898–2902 (2012).
  168. Ryan, M., Bate, A., Eastmond, C. J. & Ludbrook, A. Use of discrete choice experiments to elicit preferences. *Qual. Saf. Health Care* **10**, i55–i60 (2001).
  169. Mauskopf, J. A. et al. Principles of good practice for budget impact analysis: report of the ISPOR Task force on good research practices — budget impact analysis. *Value Health* **10**, 336–347 (2007).
  170. Krop, I. et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J. Clin. Oncol.* **35**, 2838–2847 (2017).
  171. Weiner, B. J. A theory of organizational readiness for change. *Implement. Sci.* **4**, 67 (2009).
  172. Holt, D. T., Helfrich, C. D., Hall, C. G. & Weiner, B. J. Are you ready? How health professionals can comprehensively conceptualize readiness for change. *J. Gen. Intern. Med.* **25**, 50–55 (2010).
  173. Andermann, A. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull. World Health Organ.* **86**, 317–319 (2008).
  174. Rosenberg-Wohl, S. et al. Private payer participation in coverage with evidence development: a case study. *Health Affairs Blog* <https://www.healthaffairs.org/doi/10.1377/hlbg20170314.059181/full> (2017).
  175. Kotter, J. *Leading Change* (Harvard Business Press, 1996).
  176. Knoster, T., Villa, R. & Thousand, J. in *Restructuring for Caring and Effective Education: Piecing the Puzzle together* (eds Villa, R. & Thousands, J.) 93–128 (Paul H. Brookes, 2000).
  177. Lemke, A. A. & Harris-Wai, J. N. Stakeholder engagement in policy development: challenges and opportunities for human genomics. *Genet. Med.* **17**, 949–957 (2015).
  178. Puzhko, S. et al. Health professionals' perspectives on breast cancer risk stratification: understanding evaluation of risk versus screening for disease. *Public Health Rev.* **40**, 2 (2019).
  179. Schmeer, K. *Stakeholder analysis guidelines* <https://www.who.int/workforcealliance/knowledge/toolkit/33.pdf> (2019).
  180. Wegwarth, O. et al. What do European women know about their female cancer risks and cancer screening? A cross-sectional online intervention survey in five European countries. *BMJ Open* **8**, e023789 (2018).
  181. Waller, J., Osborne, K. & Wardle, J. Enthusiasm for cancer screening in Great Britain: a general population survey. *Br. J. Cancer* **112**, 562–566 (2015).
  182. Wegwarth, O. & Gigerenzer, G. Improving evidence-based practices through health literacy — reply. *JAMA Intern. Med.* **174**, 1413 (2014).
  183. McDowell, M., Rebitschek, F. G., Gigerenzer, G. & Wegwarth, O. A simple tool for communicating the benefits and harms of health interventions: a guide for creating a fact box. *MDM Policy Pract.* **1**, 1–10 (2016).
  184. McDowell, M., Gigerenzer, G., Wegwarth, O. & Rebitschek, F. G. Effect of tabular and icon fact box formats on comprehension of benefits and harms of prostate cancer screening: a randomized trial. *Med. Decis. Making* **39**, 41–56 (2018).
  185. Steckelberg, A., Berger, B., Kopke, S., Heesen, C. & Muhlhauser, I. Criteria for evidence-based patient information. *Z. Arztl. Fortbild. Qualitatssich.* **99**, 343–351 (2005).
  186. French, D. P., Cameron, E., Benton, J. S., Deaton, C. & Harvie, M. Can Communicating personalised disease risk promote healthy behaviour change? A systematic review of systematic reviews. *Ann. Behav. Med.* **51**, 718–729 (2017).
  187. Hollands, G. J. et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ* **352**, i1102 (2016).
  188. French, D. P. et al. Psychological impact of providing women with personalised 10-year breast cancer risk estimates. *Br. J. Cancer* **118**, 1648–1657 (2018).
  189. Sekhon, M., Cartwright, M. & Francis, J. J. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Serv. Res.* **17**, 88 (2017).
  190. Evans, D. G. et al. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS breast screening programme and family history clinics: a dual cohort study. *Program. Grants Appl. Res.* <https://doi.org/10.3310/pgfar04110> (2016).
  191. Rainey, L. et al. Women's perceptions of personalized risk-based breast cancer screening and prevention: an international focus group study. *Psychooncology.* **28**, 1056–1062 (2019).
  192. Meisel, S. F. et al. Adjusting the frequency of mammography screening on the basis of genetic risk: attitudes among women in the UK. *Breast* **24**, 237–241 (2015).
  193. Chanouni, A. et al. Attitudes towards risk-stratified breast cancer screening among women in England: a cross-sectional survey. *J. Med. Screen.* <https://doi.org/10.1177/0969141319883662> (2019).
  194. Keogh, L. A. et al. Consumer and clinician perspectives on personalising breast cancer prevention information. *Breast* **43**, 39–47 (2019).
  195. Lévesque, E., Hagan, J., Knoppers, B. M. & Simard, J. Organizational challenges to equity in the delivery of services within a new personalized risk-based approach to breast cancer screening. *N. Genet. Soc.* **38**, 38–59 (2019).
  196. Chowdhury, S. et al. Do health professionals need additional competencies for stratified cancer prevention based on genetic risk profiling? *J. Pers. Med.* **5**, 191–212 (2015).
  197. Feero, W. G. & Green, E. D. Genomics education for health care professionals in the 21st century. *JAMA* **306**, 989–990 (2011).
  198. Kurian, A. W. et al. Gaps in incorporating germline genetic testing into treatment decision-making for early-stage breast cancer. *J. Clin. Oncol.* **35**, 2232–2239 (2017).
  199. Wegwarth, O., Schwartz, L. M., Woloshin, S., Gaissmaier, W. & Gigerenzer, G. Do physicians understand cancer screening statistics? A national survey of primary care physicians in the United States. *Ann. Intern. Med.* **156**, 340–349 (2012).
  200. Slade, I. & Burton, H. Preparing clinicians for genomic medicine. *Postgrad. Med. J.* **92**, 369–371 (2016).
  201. Lévesque, E. et al. Ethical, legal, and regulatory issues for the implementation of omics-based risk prediction of women's cancer: points to consider. *Public Health Genomics* **21**, 37–44 (2018).
  202. Hall, A. E. et al. Implementing risk-stratified screening for common cancers: a review of potential ethical, legal and social issues. *J. Public Health* **36**, 285–291 (2014).
  203. Beauchamp, T. & Childress, J. *Principles of Biomedical Ethics*. (Oxford University Press, 2013)
  204. Maheswaran, R., Pearson, T., Jordan, H. & Black, D. Socioeconomic deprivation, travel distance, location of service, and uptake of breast cancer screening in north Derbyshire, UK. *J. Epidemiol. Community Health* **60**, 208–212 (2006).
  205. Morris, M. et al. Ethnicity, deprivation and screening: survival from breast cancer among screening-eligible women in the West Midlands diagnosed from 1989 to 2011. *Br. J. Cancer* **113**, 548–555 (2015).
  206. Moutel, G. et al. Women's participation in breast cancer screening in France — an ethical approach. *BMC Med. Ethics* **15**, 64 (2014).
  207. Marmot, M. Fair society, healthy lives: the marmot review: strategic review of health inequalities in England post-2010 <http://www.instituteofhealthequity.org/resources-reports/fair-society-healthy-lives-the-marmot-review/fair-society-healthy-lives-full-report-pdf.pdf> (2010).
  208. Darquy, S., Moutel, G., Jullian, O., Barré, S. & Duchange, N. Towards equity in organised cancer screening: the case of cervical cancer screening in France. *BMC Womens Health* **18**, 192 (2018).
  209. Hersch, J. et al. Use of a decision aid including information on over-detection to support informed choice about breast cancer screening: a randomised controlled trial. *Lancet* **385**, 1642–1652 (2015).
  210. Prince, A. E. R. Comparative perspectives: regulating insurer use of genetic information. *Eur. J. Hum. Genet.* **27**, 340–348 (2019).
  211. Joly, Y., Feze, I. N., Song, L. & Knoppers, B. M. Comparative approaches to genetic discrimination: chasing shadows? *Trends Genet.* **33**, 299–302 (2017).
  212. HM Government and Association of British Insurers. *Code on Genetic Testing and Insurance*. (HM Government and Association of British Insurers, 2018).
  213. Lu, C. Y. et al. A proposed approach to accelerate evidence generation for genomic-based technologies in the context of a learning health system. *Genet. Med.* **20**, 390–396 (2018).
  214. Landes, S. J., McBain, S. A. & Curran, G. M. An introduction to effectiveness-implementation hybrid designs. *Psychiatry Res.* **280**, 112513 (2019).
  215. D'Aunno, T., Hearld, L. & Alexander, J. A. Sustaining multistakeholder alliances. *Health Care Manage Rev.* **44**, 183–194 (2019).

## Acknowledgements

The ENVISION Conference was funded by a European Research Council (ERC) Advanced Grant (BRCA-ERC) and the following European Union Horizon 2020 (H2020) Programme (H2020/2014-2020) consortia: FORECEE, BRIDGES, B-CAST, EU-TOPIA and MyPeBS. N.P., G.S., O.W., D.R. and M.W. have received research funding from H2020 FORECEE (grant agreement number 634570) and The Eve Appeal charity. M.W. has also received support from the ERC Advanced Grant BRCA-ERC (grant agreement number 742432). D.F.E., P.H., J.S., R.S. and P.D. have received

support from H2020 BRIDGES (grant agreement number 634935). A.C.A., D.F.E., P.H., M.G.-C., P.P., S.M. and M.K.S. have received support from H2020 B-CAST (grant agreement number 633784). U.I. and H.d.K. have received support from H2020 EU-TOPIA (grant agreement number 634753). D.F., D.G.E., S.D.M., C. Baron, C. Balleyguier, P.G.R., D. Ritchie and S.D. have received support from H2020 MyPeBS (grant agreement number 755394). The ENVISION Conference 2019 received additional funding from the Tirolean Government and was supported by UMIT — University for Health Sciences, Medical Informatics and Technology.

### Author contributions

M.W., P.D., S.D., M.S., H.d.K. and N.P. organized the ENVISION Conference 2019. N.P. and M.W. led the drafting of this manuscript. All authors contributed to the content through presentations at the Conference and draft sections, and edited and reviewed the manuscript before submission.

### Competing interests

P.G.R. is the Principal Investigator and research project data owner of an independent study, funded by the Italian Ministry of Health, and conducted negotiations with Becton Dickinson, Hologic and Roche to obtain reagents at a reduced price or for free; he is member of the MyPeBS steering committee. The other authors declare no competing interests.

### Disclaimer

The work of D.F. and D.G.E. is supported by the National Institute for Health Research (NIHR); the views expressed are those of the authors and not necessarily those of the UK National Health Service (NHS), the NIHR or the UK Department of Health. Z.H. is a member of the International Agency for Research on Cancer (IARC) and the following disclaimer applies: "Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization." The work of M.G.-C. work is supported by Intramural Funds of the US National Cancer Institute. The work of Z.H. is supported by the Institut National du Cancer and EU Translational Cancer Research (TRANSCAN) Framework and the Fondation ARC pour la Recherche sur le Cancer.

### Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

### Reviewer information

*Nature Reviews Clinical Oncology* thanks Nehmat Houssami, Kala Visvanatha and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

### Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41571-020-0388-9>.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

### RELATED LINKS

**BOADICEA:** <https://canrisk.org>

**ClinGen:** <https://clinicalgenome.org/>

**Tyrer–Cuzick IBIS Breast Cancer Risk Evaluation Tool:**

<http://www.ems-trials.org/riskevaluator/>

© The Author(s) 2020