



# Personalising breast cancer prevention:

bridging the gap  
between research  
and policy

### **Personalising breast cancer prevention:** bridging the gap between research and policy

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This report is intended to inform policy makers in national health systems that organise and deliver health services about the possibilities for improving breast cancer prevention and early detection.

It builds on and refers to previous reports from the B-CAST consortium<sup>1,2</sup> to set out key decision points and provide recommendations for policy makers on the development and introduction of personalised breast cancer prevention pathways.

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# Recommendations

# Recommendations

## ■ Breast cancer prevention pathways

### **Agree on population sub-groups for active prevention**

As knowledge of risk evolves there is an opportunity to re-consider broad at-risk populations and distinguish sub-groups who would benefit from more granular risk categorisation to inform offers of specific interventions. The timing (during the life-time) and form of risk assessment for more granular categorisation should be determined.

### **Identify opportunities to address lifestyle modification**

Policy makers and healthcare providers should consider how breast cancer prevention opportunities related to lifestyle modification can be introduced at various points where an individual might interact with the health system.

### **Strengthen delivery of risk-reducing therapies**

Where necessary shared processes should be created between primary, secondary and tertiary care with respect to risk assessment and in supporting uptake of and adherence to risk-reducing therapies.

### **Align early detection strategies**

Early detection strategies applied at the population level and to those at higher risk due to a genetic predisposition can be considered complementary processes. Alignment and consistency across these initiatives is needed so that effective and agreed management strategies are available for individuals across all risk categories.

### **Consider the implications of breast cancer heterogeneity for prevention pathways**

In the future it is likely that the umbrella term 'breast cancer' will contain clear population subgroups at risk for different subtypes of the disease, each with their own specific preventive intervention. This will create further avenues for personalisation of prevention pathways.

### **Create processes that address the gaps in evaluation and regulation of risk tools**

The integration of risk assessment tools for clinical management of breast cancer risk has so far been largely ad hoc and has lacked formal evaluation. As new models and tools are developed, more formalised mechanisms for their external validation, evaluation and integration into practice are needed, ensuring suitability for the intended purpose and context.

### **Develop effective strategies for communicating genetic and non-genetic risk information**

A wider range of services may be involved in providing risk information, based on genetic and non-genetic factors. Resources need to be committed to supporting risk communication strategies and enabling appropriate education and supervision of health professionals who will be involved in delivery at different points in the prevention pathway.

### **■ Prevention in the context of hereditary breast cancer**

#### **Identification and management of hereditary breast cancer should remain a priority**

Some individuals and their relatives are at significantly higher risk of developing breast cancer due to a genetic predisposition because they possess pathogenic variants in particular genes (e.g. BRCA1/2). These individuals are a well-established sub-group who will continue to need specific care pathways and services to manage risk. The integration of evolving knowledge of risk into care pathways for these individuals should continue to be an important focus area.

#### **Policy makers must decide whether to adopt a wider screening approach for individuals with a family history of breast cancer**

There is considerable debate about whether or not to adopt a population-wide screening approach to identifying individuals with a family history of breast cancer. Decisions on this will have an impact on service requirements. If a proactive screening approach is deemed beneficial, services will need to be appropriately configured to enable this and to integrate effectively with existing referral pathways for family cancer clinics.

#### **Consider the various ways in which individuals with rare breast cancer risk variants are identified**

The increasing availability of genetic testing through research or clinical initiatives to embed whole genome sequencing within healthcare, is likely to present another mechanism through which individuals with rare variants will be identified. Therefore, consideration should be given to the various ways in which individuals with rare breast cancer risk variants might be identified either purposefully or incidentally. Suitable pathways should be available for the clinical management of all these patients.

#### **Develop a consensus set of guidelines with respect to genetic testing**

Health systems should develop mechanisms to generate the evidence base for genetic testing. This should be used to inform consensus guidelines on genetic testing for individual health systems to ensure equitable access and consistent quality of testing.

### ■ Prevention in the context of population screening programmes

#### **Consider the evidence, opportunities and potential harms of implementing risk-based stratification approaches in population screening programmes**

Stakeholders in breast cancer screening such as the providers of the service, healthcare professionals, policy makers, payers, advocacy groups, and researchers need to jointly consider the evidence of benefit, harm, cost and acceptability of different approaches to risk stratification. Transparency about decision making on whether to embrace risk stratification, to what extent and in what form, are important in moving this agenda forward.

#### **Identify the appropriate tool to use for early detection programmes**

Implementation of stratified population screening will require agreement on the underlying model to be used and the development of a validated tool that is appropriate for use in this context. Policy makers concerned with the development and delivery of screening programmes should engage early with researchers to ensure that work on risk models and tools is closely aligned with the anticipated needs of all stakeholders involved in screening programmes.

#### **Develop consensus on alternate screening strategies**

Implementation of stratified screening will require that an evidence-based consensus is reached on the programme of interventions for each risk group and that this is found to be acceptable to the public.



A photograph of a female doctor with blonde hair, wearing a patterned V-neck top and a stethoscope, sitting and looking at a tablet. She is smiling and appears to be in a consultation with a patient whose back is to the camera. The patient has long brown hair and is wearing a dark green top. The doctor is also wearing a white lab coat over her patterned top. The background is a bright, modern clinical setting with a lamp and some medical equipment visible. The text "Executive summary" is overlaid in a bold, dark purple font on the right side of the image.

# **Executive summary**



# Executive summary

Breast cancer has been at the forefront of major research programmes over recent years and has been an important exemplar of approaches that seek to personalise medicine. This report forms part of a European research initiative ([B-CAST](#)) focused on the potential to improve prevention and early detection of breast cancer by developing tools that enable more precise risk estimation at the individual level. Alongside the large cohort studies and detailed epidemiological research, our workstream has sought to determine how research findings could be interpreted and incorporated into mainstream preventive practice.

Precision public health is seen by many governments as key to improving health and preventing disease. A personalised approach through better risk stratification represents an important component in this endeavour. Nevertheless, personalised prevention is an immense and complex field and there is no agreement as to whether this can be realised for breast cancer at the population level and, if so, when and how.

This report provides policy makers, those working in health promotion, and healthcare providers with a useful interface to engage with findings emerging from research. It includes recommendations for important areas of decision-making and considerations for moving forward with personalising breast cancer prevention pathways.

We have presented the key implications for breast cancer prevention pathways and the more specific considerations that are raised for prevention in the different contexts of hereditary breast cancer and population screening programmes. Our objective is that this will enable policy makers to articulate key evidence gaps and unanswered questions and to make decisions about future practice and policy.

It is essential that research programmes are aligned with policy needs. However, it is important to understand that, given the many uncertainties around the prevention of breast cancer, and due to the heterogeneous nature of the disease, traditional research studies are unlikely to provide all the answers for policy decisions.

Going forward, there will be an increasing need for 'learning health systems' that seek to continually improve and innovate through capturing knowledge and data from routine practice. A learning approach, embedded in routine practice, comparing elements such as current testing intervals, tests or thresholds, could better help address some of the challenges in evidence generation.

Moving from scientific insights to preventive interventions is not easy. It requires careful consideration of the evidence base and how to develop pathways to enable the use of



A woman wearing a grey hijab, a black long-sleeved shirt, a grey scarf with fringe, and colorful patterned leggings stands on a paved path. She is wearing grey and pink sneakers. In the background, there is a body of water, trees with autumn foliage, and a small boat. The text "Improving prevention pathways" is overlaid on the right side of the image in a bold, purple font.

# Improving prevention pathways

emerging knowledge in an effective manner. It also demands a careful balancing act, taking into consideration individual, population and health system needs, benefits and harms. This can only be achieved through engagement across different groups such as individuals, payers and providers.

Engagement is important in articulating the values and preferences of the wider community and building mutual trust, thereby ensuring implementation of accessible and acceptable programmes.

The high population morbidity and mortality from breast cancer make the condition an important target for preventive programmes. Policy makers and healthcare providers should take account of recent research and decide how to capitalise on the opportunities for improved prevention by personalisation of interventions according to risk.



# Improving prevention pathways

Breast cancer is the most common cancer to affect women and is a leading global cause of mortality in women<sup>3</sup>. Reductions in mortality have been achieved through the combination of early detection and treatment, but incidence continues to rise<sup>3</sup>. The substantial associated morbidity and burdens of treatment experienced by individuals and the healthcare system<sup>4</sup> make the search for improvements to primary and secondary prevention important.

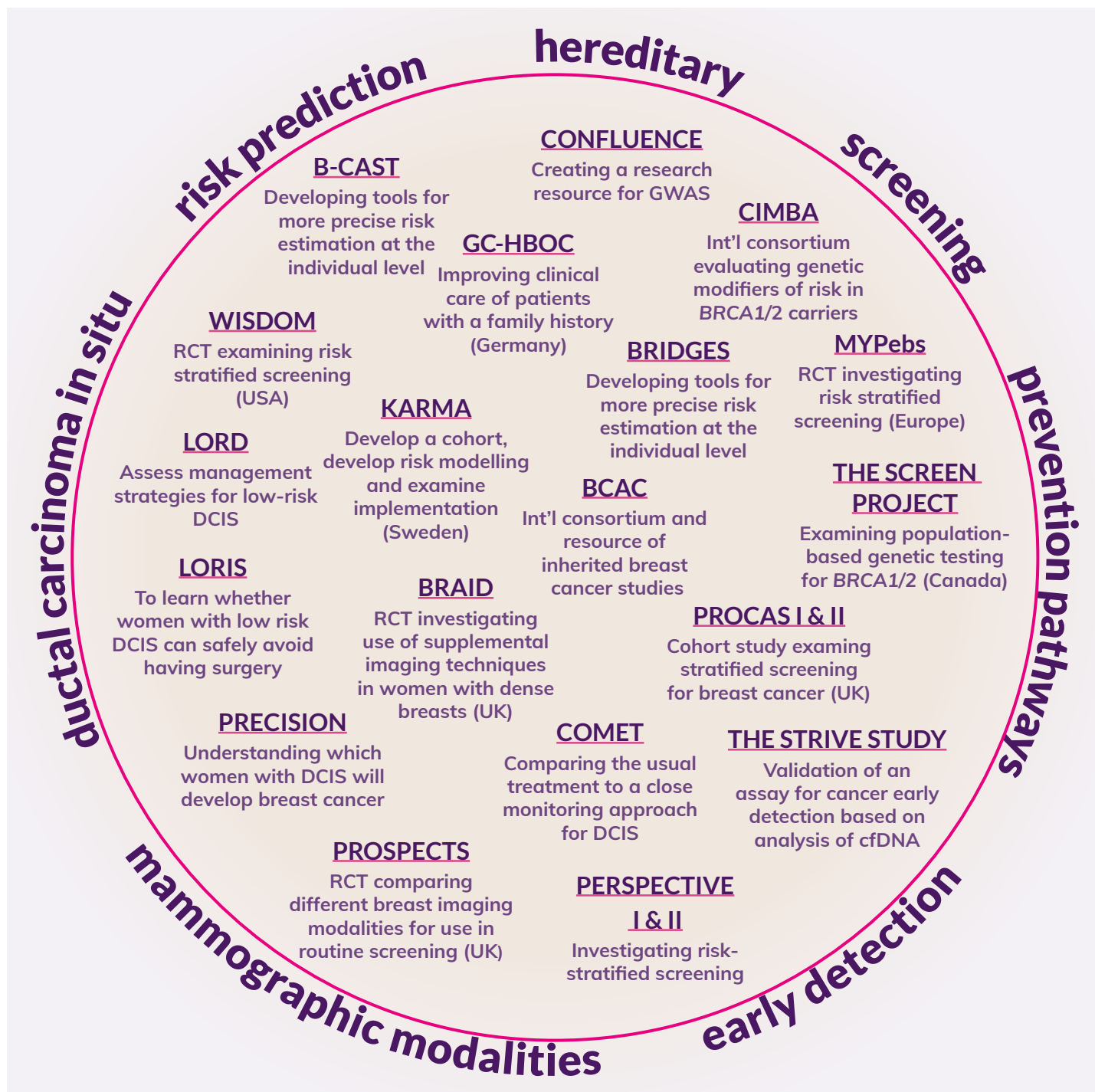
Primary prevention initiatives are currently focused on reducing risk, whilst secondary prevention depends on early detection and treatment of disease. Both may be undertaken for the whole population or by focusing on population sub-groups with substantially increased risk. The potential for personalisation arises through the identification of sub-groups for whom interventions may be tailored to increase benefits and/or reduce harms or costs.

As many health systems seek to optimise their prevention efforts, personalisation based on better risk assessment and tailored breast cancer prevention pathways is becoming an important consideration. Such approaches must be embedded in current practice, building on existing foundations for risk identification and management, exploiting new risk tools and ensuring integration with broader public health initiatives.

In the long-term, the vision for healthcare providers is to create a system that can effectively, efficiently and equitably manage those at different levels of risk while taking into consideration their individual preferences and circumstances.

## Our approach

The recommendations and considerations put forward in this report are the result of our research and analysis conducted as part of the B-CAST consortium. We began with a



**Figure 1: The breast cancer research landscape**

Globally there are many research efforts underway that aim to improve our understanding of breast cancer and develop better strategies for prevention and early detection. This figure is an illustrative representation of some of the many, often interrelated, initiatives underway. It aims to convey the breadth and depth of research endeavours in this field and is not a comprehensive portrayal of the landscape.



# **Breast cancer prevention pathways**

review of the scientific literature, the various approaches to prevention at individual and population levels and the policy landscape in the UK and internationally.

We then worked with other experts to develop a vision of future personalised prevention, looking at opportunities for implementation, and issues that would arise for individuals, health systems and society. Our work is set out in two reports, which we refer to in this document:

- [Personalised prevention in breast cancer: the policy landscape](#). Moorthie S, Gaynor L, Burton H et al. PHG Foundation. 2017
- [Personalising prevention for breast cancer: workshop report](#). Moorthie S, Gaynor L, Burton H et al. PHG Foundation. 2019

It also builds on our work as part of the EU funded [Collaborative Oncological Gene–environment Study](#) (COGS) consortium and the [European Collaborative on Personalised Early Detection and Prevention of Breast Cancer](#) (ENVISION) Network. As part of COGS we undertook a detailed analysis of the organisational, ethical, legal and social issues in stratified breast cancer screening<sup>5</sup>. The ENVISION Network brought together international research consortia working on different aspects of personalised early detection and prevention of breast cancer.

Following a consensus conference in 2019, the Network identified areas for development to enable evidence-based personalised interventions that could improve the benefits and reduce the harms of existing screening and prevention programmes<sup>6</sup>.

Precision public health is seen by many governments as key to improving health and preventing disease. This development is being driven by the convergence of biotechnology and information technology, which is facilitating novel approaches to personalised healthcare.

Breast cancer has been an important example with a vast amount of EU and international research taking place over many years. This has led to advances in understanding disease epidemiology, pathology and prevention methods, creating opportunities for personalised prevention through better risk stratification (Figure 1). Nevertheless, precision public health is an immense and complex field and there is no agreement as to whether personalised prevention can be introduced at the population level and, if so, when and how.

This report summarises the most important findings emerging from research today. To help policy makers, those working in health promotion, and healthcare providers identify key evidence gaps and to make decisions about future practice and policy, we present the overarching implications for breast cancer prevention pathways. We then

set out specific considerations for the different contexts of hereditary breast cancer and population screening programmes and policy.

## Breast cancer prevention pathways

Our knowledge of breast cancer and the tools we can apply to its prevention are evolving rapidly. A better understanding of risk means that more sophisticated approaches to stratification according to breast cancer risk are becoming possible. These could enable the tailoring of preventive interventions for particular sub-groups. Here we outline the key considerations raised by a greater understanding of risk assessment for breast cancer prevention pathways.

### Identifying population sub-groups for active prevention efforts

#### Recommendation: agree on population sub-groups for active prevention

As knowledge of risk evolves there is an opportunity to re-consider broad at-risk populations and distinguish sub-groups who would benefit from more granular risk categorisation to inform offers of specific interventions. The timing (during the life-time) and form of risk assessment for more granular categorisation should be determined.

All individuals are at risk of developing breast cancer. However, some groups are at an increased risk due to factors such as age, biological sex, ethnicity, family history, genetics and lifestyle. Decision-making for individuals and planning at the population level is based on an understanding of risk profiles, and evidence-based consideration of preventive options together with the capacity of the sub-group with a specified level of risk to benefit. Identifying sub-groups for each preventive initiative is therefore important.

Prevention strategies for most common diseases involve population wide approaches as well as targeting high risk individuals. Even when an intervention, such as a mammography screening programme, is described as 'at population level', there is targeting of broad sub-groups such as those defined by age and/or sex. The purpose of such targeting is to more effectively balance benefits and harms and to be cost-effective. Thus, even at the population level, implementation of preventive initiatives requires agreement on broad at-risk population sub-groups.

Mechanisms are also necessary to classify individuals into more granular risk groups, which would be categorised according to specific thresholds for interventions.

Those with a family history of disease are recognised to be a clear at-risk sub-group,



and specific pathways of care for these people are available in most European countries. Granular risk assessment informs the specific intervention pathways that are offered to this sub-group. However, these individuals only form a small proportion of those who go on to develop disease<sup>7</sup>.

Evolving knowledge of breast cancer risk factors suggests there could be value in identifying other additional higher-risk sub-groups either by single risk factors (e.g. mammographic density or genetics) or by more comprehensive risk estimation, which may include a range of risk factors.

In our previous reports we provided an overview of existing models that enable this sort of increasingly granular risk estimation<sup>1,2</sup>. Research indicates that integrated risk prediction models that bring together classical risk factors, mammographic density and genetic factors are important in identifying women at the extremes of risk (i.e. both high and low)<sup>8</sup>.

The ability to better identify women at increased or low risk has important implications when it comes to considering interventions (such as life-style modification, screening or risk-reducing therapies), especially if the level of risk impacts on the intervention that is offered to these women.

### Primary prevention

#### **Recommendation: identify opportunities to address lifestyle modification**

**Policy makers and healthcare providers should consider how breast cancer prevention opportunities related to lifestyle modification can be introduced at various points where an individual might interact with the health system. Possibilities may be in the contexts of prevention for other chronic diseases, breast screening programmes and related clinical areas such as those for hereditary breast cancer.**

Primary prevention can be described as efforts to avoid exposures that can lead to disease development, to reduce harmful lifestyles and adopt healthy ones. It may be achieved through changes in the environment (e.g. reduction in pollution) or by seeking to influence individual behaviours.

Whilst it is widely recognised that modifiable lifestyle risk factors (diet, weight, alcohol intake and physical activity) can impact on the development of breast cancer<sup>9,10</sup>, efforts primarily and specifically aimed at prevention of this disease in individuals or specific at-risk populations are not usually included in wider population health promotion programmes.

The lack of a specific primary prevention approach to breast cancer contrasts with other programmes such as for diabetes and cardiovascular disease, where both population-wide and individual level health promotion strategies addressing lifestyle risk factors are employed.

Addressing lifestyle factors can have benefits for those across all categories of disease risk and across several chronic diseases<sup>9, 11</sup>. For conditions such as cardiovascular disease or diabetes, preventive interventions are usually based on a life-course approach, with risk factors addressed at various stages. The impact of lifestyle factors on breast cancer risk is also variable across the life course.

As policymakers focus more on prevention and population-wide health promotion activities are developed, it is increasingly important to include mechanisms to personalise and convey risk information for individualised health promotion purposes based on various life stages.

In terms of policy, there are caveats to the development of individual level health promotion that addresses modifiable lifestyle risk factors for breast cancer. These include:

- the overlap with many of the goals of current chronic disease prevention programmes and the lack of evidence for a specific breast cancer risk reduction intervention
- the finding that the relationship of modifiable lifestyle risk factors with breast cancer risk is not straight forward <sup>10,12, 13</sup>, for example, the impact of weight gain may be different in pre- and post-menopausal women.

Nevertheless, addressing these factors through existing avenues is an important prevention opportunity.

### **Recommendation: strengthen delivery of risk-reducing therapies**

**Where necessary shared processes should be created between primary, secondary and tertiary care with respect to risk assessment and in supporting uptake and adherence to risk-reducing therapies for those that need it.**

Primary prevention of breast cancer can also be achieved through active risk-reducing treatments. These include chemoprevention and risk reducing surgery (i.e. mastectomy).

These interventions have significant cost to the individual and to health services, with capacity to do harm as well as provide benefit. They are therefore not used for primary prevention at a population level and recommended only for use in individuals whose risk is above a certain threshold.

Primary prevention through risk-reducing therapies offered at a population level in

a similar way to statins for the prevention of cardiovascular disease could be highly beneficial. However, there are challenges to developing these, such as the long timescale required to show effective prevention and, unlike statins, where cholesterol reduction can be used as an intermediate marker, there are no comparable easily ascertainable markers for breast cancer risk reduction.

Strengthening current efforts to deliver existing therapies are important areas for improvement, along with improved mechanisms for supporting uptake and adherence to risk-reducing therapies. This includes developing consensus on the best mechanisms for objective risk measurement and threshold levels for implementing these therapies.

### Secondary prevention

#### Recommendation: align early detection strategies

**Early detection strategies applied at the population level and to those at higher risk due to a genetic predisposition can be considered complementary processes. Alignment and consistency across these initiatives is needed so that effective and agreed management strategies are available for individuals across all risk categories.**

Secondary prevention involves the early detection and treatment of disease, often at a pre-symptomatic stage, in order to achieve a better outcome.

In breast cancer, the limited opportunities for primary prevention outlined above, together with the increasing success of treatment options if detected early mean that, so far, the focus of prevention efforts has been on early detection. This preventive initiative may be population based – offered to all women of a specific age – or risk based, offered to women who are considered at ‘high’ or ‘moderate’ risk. Individuals at increased risk characteristically receive some form of enhanced surveillance over and above that offered to the population as a whole.

The breast cancer screening test is largely undertaken through imaging, primarily mammography. Other imaging modalities such as digital breast tomosynthesis, whole breast ultrasound, magnetic resonance imaging (MRI) and contrast enhanced spectral mammography may be offered to specific sub-groups of the population, such as those considered at high or moderate risk<sup>3</sup>.

We have previously summarised the extensive debate about the benefits of existing population-based early detection strategies and concerns about the level of overdiagnosis<sup>1,2</sup>. Modelling studies suggest risk stratified screening could improve efficiency and benefit-harm ratio of existing programmes<sup>14</sup>, with cohort and randomised trials underway to examine this approach.

The recognition that mammography is not a perfect screening test, and the advances being made in imaging technologies, means that mechanisms to identify sub-groups of the population that would benefit from alternate imaging tests are also in progress.

Clear strategies are in place for women at high risk due to a family history of breast cancer. For these women, annual rather than biennial or triennial mammography is often recommended and screening modalities, such as MRI, are offered to optimise early detection. Practice is more variable when a woman's family history indicates moderate risk.

Across these sub-groups knowledge of risk can have implications for the choice of imaging modality, use of risk-reducing therapies, age at which to begin and stop screening, and frequency of screening. For example, MRI is a better imaging modality in younger women and in those who have dense breast tissue. Therefore, the ability to better stratify according to risk and offer tailored screening interventions is integral to optimisation of early detection. This also requires knowledge of risk to be used more consistently to inform the screening test or regime offered.

### Breast cancer as a heterogeneous disease

#### **Recommendation: consider the implications of breast cancer heterogeneity for prevention pathways**

**In the future it is likely that the umbrella term 'breast cancer' will contain clear population subgroups at risk for different subtypes of the disease, each with their own specific preventive intervention. This will create further avenues for personalisation of prevention pathways.**

Breast cancer is not one single entity, but an umbrella term for a number of subtypes, characterised on the basis of molecular profiles, morphology and expression of biomarkers such as the oestrogen receptor<sup>2</sup>. This heterogeneity must be accommodated within disease prognosis.

Research within B-CAST has focused on the differential relationships of the various risk factors with particular disease subtypes, with an emphasis on the potential to identify risk groups who may be more (or less) amenable to preventive therapies, those who are likely to progress to the more aggressive forms of cancer or those with increased likelihood of mortality.

At present it is not possible to accurately differentiate risk for these subtypes and therefore to differentiate between women who will develop aggressive or fatal breast

cancers and those who will not. There is thus, at present, one uniform approach to breast cancer prevention and early detection<sup>15</sup>.

However, as more is learned about different subtypes of disease, it is becoming increasingly important to recognise that a more nuanced approach to prevention may be needed that takes into consideration risk of breast cancer overall as well as risk of developing a particular sub-type.

### **Integrating risk assessment into breast cancer management**

#### **Recommendation: create processes that address the gaps in evaluation and regulation of risk tools**

The integration of risk assessment tools for clinical management of breast cancer has so far been largely ad hoc and has lacked formal evaluation. As new models and tools are developed, more formalised mechanisms for their external validation, evaluation and integration into practice are needed, ensuring suitability for the intended purpose and context.

Breast cancer risk prediction models bring together a varied set of risk factor information to give an overall estimation of the likelihood of future disease. Risk tools are a mechanism through which risk models are used to enable individual level testing and scoring<sup>16</sup>.

Risk tools enable users to easily collate model input parameters, apply an algorithm based on a prediction model to these parameters, and produce an output. As set out in our first report on the landscape<sup>2</sup> and discussed further in our workshop report<sup>1</sup> various tools include different inputs – for example the inclusion of family history, reproductive or lifestyle risk information or measurements such as breast density – and have been validated to varying degrees<sup>1</sup>. Breast cancer risk tools are thought to be useful in clinical practice; their main use currently is in family cancer or clinical genetics settings.

Potential users of risk information will vary and include various healthcare professionals and citizens. The information may also be used to answer different questions.

For example, primary care professionals consider risk in the context of whether to refer patients to specialist services, such as family cancer clinics. Family cancer clinics consider risk in the context of deciding on predictive or mutation (genetic) testing, appropriate surveillance strategies and risk reducing medical or surgical strategies.

Differing information such as short-term risk (i.e. over the next five years) or life-time risk may be required for these different contexts and, for all of them, the most appropriate risk tool must be selected.



Advances in knowledge about risk factors and development of more sophisticated risk tools that combine all these risk factors can impact on prevention pathways now and in the future through:

- improving accuracy of risk estimation

Risk estimation is important to aid decision making when deciding on preventive interventions. Improving the accuracy of risk estimation should lead to more effective targeting.

- creating novel approaches and opportunities for prevention through enabling risk estimation in a wider variety of populations than currently possible

In our [policy landscape report](#), we provided a summary of some existing tools used in clinical practice<sup>2</sup>. There is variation in the extent to which existing models have progressed to become tools and been integrated into clinical practice. Furthermore, there is variation in the extent to which both models and tools have been evaluated for clinical use. Whilst some guidance exists on the use of risk prediction tools, it is not clear which are the best tools to use and how best to use them<sup>17</sup>.

This is important, as the use of tools to stratify individuals by risk, and to provide personalised risk assessments is undergoing increased regulatory scrutiny. Tools qualifying as medical devices or in vitro diagnostic medical devices must meet the requirements of new EU Regulations, including, amongst other things, for clinical performance, transparency, and quality standards<sup>18,19</sup>.

### Risk communication

#### **Recommendation: develop effective strategies for communicating genetic and non-genetic risk information**

A wider range of services may be involved in providing risk information, based on both genetic and non-genetic factors. Resources need to be committed to supporting risk communication strategies, and to enable appropriate education and supervision of health professionals who will be involved in delivery at different points in the prevention pathway.

If health systems adopt more systematic use of risk tools and incorporation of other novel biomarkers such as mammographic density and polygenic scores, there could be implications for services and resources, e.g. radiographers, infrastructure for genetic testing. In addition, a wider range of services may be involved in providing risk

information, both genetic and non-genetic.

Currently, a risk assessment is mostly used in family cancer clinics, with a focus on communicating genetic risk. It is likely that even in this setting, there will be a need to integrate risk factors beyond genetics into risk communication.

If risk assessment is to become part of screening programmes with a move to stratified screening, then communication of risk to individuals must be clear, objective and transparent to enable them to make informed decisions about the available options for preventive interventions.

Clear understanding of risk levels is needed, particularly for individuals in low risk categories who should understand that there is some residual risk and know what to do in the event of clinical symptoms arising. The development of effective risk communication will require detailed planning, including:

- the amount and type of information that will be imparted
- optimal methods of presentation
- the variations and adaptations that can be made to tailor the information according to the recipient's background, understanding, preferences, and interests
- appropriateness to different cultural or social backgrounds and provision made for those with special needs or vulnerabilities

Significant resources will be necessary to develop and support such risk communication strategies, including the education and supervision of health professionals.

### Summary

Many of these challenges and considerations relating to breast cancer prevention arise from the fact that our ability to assess risk has progressed much further than our ability to provide effective interventions based on that risk. This is mainly through the development of mechanisms for risk assessment. Breast cancer risk tools are established for managing those with a family history of breast cancer. As models and tools continue to be developed, they will likely add value in other areas of clinical and public health practice. Understanding the different contexts where risk assessment might need to be integrated in the breast cancer prevention pathway is important.

Emerging scientific knowledge, technological innovation, and social and demographic shifts have led to an emphasis on personalised and preventive medicine where individuals are able to access more information and have a greater understanding of their own health and risk of disease. This is shifting the relationship between citizens and the health system, generating new challenges and opportunities for individuals and society that will affect the optimal use of new technologies. Breast cancer prevention

A photograph of three women of different ages looking out over a beach. The woman in the foreground is older, with visible wrinkles and a slight smile. Behind her are two younger women, one with reddish hair and another partially visible. They are all looking towards the right side of the frame. The background shows a sandy beach and a hazy horizon.

# **Prevention in hereditary breast cancer**

must be viewed against this changing backdrop and the wider health care context.

There is a growing market for direct-to-consumer testing whereby individuals pay to access genetic testing from commercial providers on an individual basis, irrespective of their family history or risk status. The increasing popularity of such tests suggests the interface between these and health system provision is likely to become more important.

## Prevention in hereditary breast cancer

Family cancer clinics are set up within most health services to manage people who are or may be at high risk due to a family history of cancer. Prevention for these individuals can be either primary via chemoprevention or risk reducing surgery, or secondary via the various forms of early detection as described in the previous section. Here we outline the impact of evolving knowledge for these services.

### Improving risk stratification for family cancer clinics

#### Recommendation: continue a focus on hereditary breast cancer

Some individuals and their relatives are at increased risk of breast cancer due to a genetic predisposition because they possess variants that confer a high risk for breast cancer (e.g. *BRCA1/2* pathogenic variant carriers). These individuals are a well-established sub-group who will continue to need specific care pathways and services to manage risk. The integration of evolving knowledge of risk into care pathways for these individuals should continue to be an important focus area.

Clinical pathways for women being managed through family cancer clinics rely on an estimation of breast cancer risk. This is followed by the opportunity to make a personal decision on whether to adopt a preventive option that weighs risk against the inconvenience and possible harms and side effects of options such as frequent screening, risk reducing surgery and/or risk-reducing therapies. In this context, opportunities for improving current pathways arise largely from more accurate risk estimation. Whilst these women are all classified as high risk, there can be substantial variation in the risk profiles of women presenting at family cancer clinics.

Granular risk assessment can lead to more precise risk classification. Risk may vary for example because of differing patterns of family history and on the basis of knowledge of pathogenic variants.

Testing for pathogenic variants in the *BRCA1/2* genes and interpreting this information with consideration of other risk factors is established practice in many countries. Testing for pathogenic variants that are moderately associated with disease (e.g. in *RAD51C*, *CHEK2* genes) is becoming more feasible and can inform risk estimation. However, there is variation in practice with respect to the genes that are examined. As described below, this is largely due to uncertainties around testing for variants in these genes. Furthermore, for some individuals, this information may be incomplete; for example,



the pathogenic variants driving risk may not be identified. Incorporating knowledge of common risk variants in the form of a polygenic score can also alter the risk estimation based on knowledge of pathogenic variants or other risk factors<sup>20,21</sup>.

Mammographic density is another key risk factor, as well as an important parameter in influencing decisions about modality of screening<sup>22</sup>. As mechanisms for automated collection of breast density data are being developed, it is becoming more feasible to incorporate this information into risk estimation as well as using it to make clinical decisions on the mode of screening. As techniques for image analysis advance, other features from breast imaging such as calcifications are also being considered as parameters that could inform clinical decision making.

### Proactive or reactive approach to hereditary breast cancer

#### **Recommendation: policy decisions on how to proactively to screen for individuals with a family history of breast cancer are needed**

There is considerable debate about whether or not to adopt a wider screening approach to identifying individuals with a family history of breast cancer. Decisions on this will have an impact on service requirements. If a proactive screening approach is deemed beneficial, services will need to be appropriately configured to enable this and integrate effectively with existing referral pathways for family history and hereditary cancer clinics.

Family history is a well understood component of breast cancer risk and can be a key driver to identify at-risk individuals for whom there are established care pathways. For these women, early detection must be deployed at the right time; those with a family history of breast cancer are more likely to develop disease at a younger age compared to the general population. This means they are more likely to develop disease before they would characteristically engage with the population screening programme.

Proactive identification of individuals with a family history for breast cancer would probably be in the form of family history screening. In most countries, this is not established practice, due to concerns about the relative benefits and harms of this approach, as well as the practical methods to deliver a proactive approach. The lack of a proactive approach may lead to a larger proportion of those who would (otherwise) be eligible and benefit from current risk-based management not being identified<sup>23</sup>.

Whilst the systematic collection of family history information could enable identification of high-risk individuals who could then access existing prevention programmes, it is not a simple task and is further complicated by the fact that this information may change over time, for example as family members are diagnosed with the disease. Verification

of cancer types in family members, particularly in the older generations, further complicates the process.

Several research programmes are attempting to improve the use of family history for breast cancer. A variety of electronic tools that collect family history on multiple conditions exist but require further assessment<sup>24</sup>. There are also attempts to simplify the process through the development of integrated risk assessment tools that also consider a wide range of risk factors together and include family history<sup>25, 26</sup>.

### **Harnessing knowledge on rare variants**

#### **Recommendation: consider the various ways in which individuals with rare breast cancer risk variants are identified**

Consideration should be given to the various ways in which individuals with rare breast cancer risk variants might be identified either purposefully or incidentally. Suitable pathways should be available for the clinical management of all these patients.

The complexity of collecting high quality family history information, smaller families (which limit the potential value of a family history, for example if there are few first degree relatives), and the falling cost of genome analysis are contributing to the debate around DNA-based population screening to identify individuals with rare pathogenic variants such as those in *BRCA1/2*<sup>27</sup>.

Uncertainty about the penetrance of high and moderate risk genes in the general population (people without a family history) and interpretation of variants of unknown significance pose challenges to this approach. Such limitations are compounded by ethical concerns about the implementation of widespread genetic testing, including establishing what constitutes informed consent in this context, maintaining privacy and confidentiality, ensuring equitable access, genetic responsibility and fears around genetic discrimination.

Nevertheless, the increasing availability of genetic testing through direct-to-consumer testing and initiatives to embed whole genome sequencing within healthcare, are likely to present another mechanism through which individuals with rare variants may be identified. Likely contexts will include cancer care or during clinical testing for rare disease, where these are characterised as additional findings.

Identification of rare variants in one individual in a clinical context may also lead to proactive testing of family members (cascade testing) with a view to offering preventive options. The impact of increasing genetic testing on identification of those with rare variants related to breast cancer risk needs to be recognised along with its impact on prevention pathways.

A large, dense crowd of people walking, with a woman in a yellow dress in the foreground. The image is slightly blurred, emphasizing the sheer number of people. The text 'Population screening programmes' is overlaid in a bold, purple font.

# **Population screening programmes**

### Developing consensus on genetic testing

#### Recommendation: develop a consensus set of guidelines with respect to genetic testing

Health systems should develop mechanisms to generate the evidence base for genetic testing. This should be used to inform consensus guidelines on genetic testing for individual health systems to ensure equitable access and consistency in the quality of testing.

Genetic information is becoming more available to participants through research and to the public via direct-to-consumer companies. The extent of genetic testing provided by national health systems and via research or private initiatives can differ. There needs to be greater consensus on the extent of genetic testing to be provided by national health systems in the context of hereditary breast cancer. This is particularly necessary to increase certainty around the impact of variants that confer 'moderate' risk, where there is a lot of clinical uncertainty as to how best to manage these individuals.

Collaborative translational research initiatives such as CanGene-CanVar in the UK and the network created by the German Consortium for Familial Breast and Ovarian Cancer with specialised centres, provide examples of mechanisms by which researchers are working with clinical experts and services to generate and implement evidence about variant interpretation, genetic testing and decision support.

Decision makers will be compelled to decide the extent of genetic testing for breast cancer that a health system can provide. Greater consensus and transparency with respect to the extent of genetic testing is important for improving clarity of communication to individuals who are referred to family cancer clinics.

#### Summary

Those with a family history of breast cancer are a well-established sub-group of individuals who will continue to need specific care pathways and services to manage risk. The care of this group can and should improve.

Emerging science and technology enable us to strengthen existing efforts and to create a strong foundation for preventive services through more accurate risk estimation. Incorporating new knowledge will lead to fine-tuning of risk categories; this will lead to more precise and accurate measures of risk, rather than a wholesale alteration of risk management in family cancer clinics.

Ensuring that best practice for individuals with hereditary breast cancer is deployed effectively is an important cornerstone in building personalised pathways for other sub-

groups. Such efforts are essential as the scope of a risk-based approach is widened to incorporate additional populations.

# Population screening programmes

Risk-stratified screening has been widely discussed as a potential mechanism to improve existing screening programmes. The organisational, ethical, legal and social implications of risk-stratified screening have been previously examined and recommendations developed as part of the COGS project<sup>28</sup>. However, little progress has been made towards implementation; the main findings of the COGS project and the associated recommendations still stand. Here we outline other key considerations in moving towards implementation of risk-stratified screening.

## Moving towards risk-stratified screening

### **Recommendation: consider the evidence, opportunities and potential harms of implementing risk-based stratification approaches as part of population screening programmes**

Stakeholders in breast cancer screening such as the providers of the service, healthcare professionals, policy makers, payers, advocacy groups, and researchers need to jointly consider the evidence of benefit, harm, cost and acceptability of different approaches to risk stratification. Transparency with respect to decision making on whether to embrace risk stratification, to what extent and in what form, is important in moving the agenda forward.

Experts agree that a move from 'one size fits all' to a stratified screening approach for breast cancer is likely to be beneficial. This approach requires those participating in a screening programme to undergo risk assessment.

Potential advantages to offering stratified screening – i.e. different screening regimes according to the estimated risk of the participant are:

- fewer people needing the screening test to achieve the same preventive impact
- achieving a better balance between benefits and harms by using different screening approaches for people with different risks

Whether these advantages are achievable depends on the extent to which the addition of extra information on risk permits the screening test to be targeted at those more likely to have the disease. But it also depends on how the new approach is implemented and whether it is acceptable to populations and individuals.

Therefore, any changes to an existing screening programme will need to balance population health goals with the individual choices of those who are offered screening.

This will be influenced by the ways in which the screening pathways might be reconfigured. It will also be important to consider the options for women who opt out of risk assessment but would still like to participate in a screening programme.

Engagement across different groups (citizens, individuals, payers, providers) is important to identify and address the differing perspectives on the implementation of a risk-stratified programme. It also would help to articulate the values and preferences of the wider community and build mutual trust, thereby ensuring implementation of an accessible and acceptable programme.

There are many different approaches that can be applied to population stratification. These range from basing stratification on a single variable such as age, polygenic score or mammographic density, to more integrated risk assessment that takes into consideration a range of variables such as family history, reproductive history, genetics and lifestyle factors.

There are advantages to each of these approaches. For example, basing stratification on a polygenic score may be perceived as being easier and more objective than requiring participants to provide a wider range of information. Obtaining a detailed, accurate family history is a skilled and time-consuming undertaking and lifestyle information such as smoking or diet is notoriously difficult to gather accurately and objectively. The feasibility and acceptability of different approaches to stratification may vary in health systems across Europe.

It is important that due consideration is given to the approach used in stratification, as this will determine the mechanisms and tools that are utilised for this purpose.

For example, if polygenic score alone is the approach chosen, this will require infrastructure for the collection of genomic data for this purpose. If integrated risk assessment is the approach chosen, it will require development, evaluation and deployment of an appropriate risk tool.

### **What risk assessment tool to use**

#### **Recommendation: identify the appropriate tool to use for early detection programmes**

Implementation of stratified population screening will require agreement on the underlying model to be used and the development of a validated tool that is appropriate for use in this context. Policy makers concerned with the development and delivery of screening programmes should engage early with researchers to ensure that work on risk models and tools is closely aligned with the anticipated needs of all stakeholders involved in screening programmes.



The background of the slide features a close-up, shallow depth-of-field shot of several light-colored wooden puzzle pieces. The pieces are scattered across a smooth, light-colored surface, with some in sharp focus in the foreground and others blurred in the background, creating a sense of depth and texture. The lighting is warm and soft, highlighting the natural grain of the wood.

# Conclusions

Assessment of risk is usually undertaken using tools based on an underlying risk prediction model. Models and tools are discussed above. In population screening programmes, risk estimation can facilitate decisions on the screening intervention that should be offered.

Breast cancer risk prediction tools are currently available via two main routes: either in a clinical encounter where advice is given to an individual concerned about risk, for example in the context of family history; or as a commercial product for consumers interested in their risk.

It should be noted that none of the current tools are developed for use in the general population to support decision making about screening.

### Consensus on alternate screening test strategies

#### Recommendation: develop consensus on alternate screening strategies

**Implementation of stratified screening will require that an evidence-based consensus is reached on the programme of interventions for each risk group and that this is found to be acceptable to the public.**

Preventive interventions have the potential to do harm as well as provide benefit and all entail some cost to the individual (e.g. travel, time off work or anxiety waiting for the result) and the service provider. The purpose of stratified prevention is to target the offer of more intensive screening tests - these are likely to be more costly, whilst possibly offering greater potential for both benefit and harm - to those at higher risk; and to offer less costly, less intensive screening tests to those at lower risk.

Higher intensity screening strategies could include starting at a younger age, more frequent mammography, and/or using a more sensitive modality of screening test. Lower intensity might mean starting at an older age, longer intervals between mammography, or even no screening. The selection of interventions should be based on good evidence of clinical effectiveness, including a favourable balance of benefit and harm for the different risk groups and consideration of the associated costs.

It is unlikely that intermediate disease markers or the ability to differentiate fatal breast cancers will become a reality in the short-term. This means that the metrics available for measuring the performance of different tools and screening approaches are likely to be limited, presenting a challenge for researchers in developing the necessary evidence. Hence agreement on the outcome measures that are acceptable and measurable in determining the clinical utility of specific approaches is needed.

A lack of evidence and therefore consensus on which interventions to provide to

particular risk groups is a barrier to implementation of stratified screening for breast cancer.

### Summary

Modelling studies indicate that a risk-based approach to screening may be more beneficial and cost effective than existing screening strategies. Ongoing clinical trials and cohort studies are expected to provide further evidence in favour of risk-based screening (Figure 1). In theory, the addition of risk information should permit screening to be targeted to those most likely to develop disease. Whether this can be achieved in screening programmes will depend on how these approaches are implemented.

Current research is unlikely to answer all the important outstanding questions and, going forward, a wide group of stakeholders will be required to address public and professional acceptability, pragmatic and organisational considerations and ethical, legal and social implications.

The logistical and financial impact of a move towards a substantially different approach, as well as the one that incorporates an additional stage of risk assessment, is likely to be significant and will require careful assessment, commitment and planning.

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