

Personalising prevention for breast cancer

Workshop report

B-CAST



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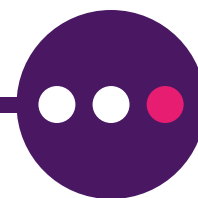
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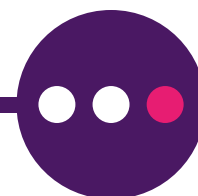
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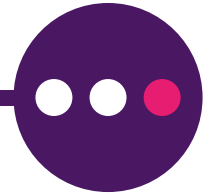


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Executive summary

Breast Cancer Stratification: understanding the determinants of risk and prognosis of molecular subtypes (B-CAST) is a multicentre research study funded by the European Commission. As part of this project, we undertook a preliminary analysis of current approaches to breast cancer prevention and the discourse around personalised breast cancer prevention¹. We then held a multidisciplinary workshop to look at likely future scientific and technological advances and create a vision for future personalised prevention and how it could be achieved. This report provides a summary of the workshop proceedings. Following further policy analysis there will be a subsequent final report, primarily aimed at public health professionals and policy makers to support integration of personalised prevention into wider prevention programmes.

Background

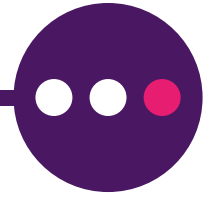
Driven by the convergence of biotechnology and information technology, many government policy documents have embraced the concept of personalised prevention and committed to the development of the relevant supportive technologies and methods. The example of breast cancer has been at the forefront with progress in the identification of genetic risk variants and the development of tools for measuring individual risk. However, despite rapid scientific and technological advances there is little overall vision of how future prevention might change to encompass personalisation and how personalised prevention would be delivered through specific mechanisms within preventive pathways.

Through the workshop we envisaged that the development of such a vision would help in the examination of opportunities for implementation, the identification of issues that would be raised for individuals, health systems and society, and development of potential strategies to achieve optimum benefit. Participants included experts from research, public health, breast screening, primary care, secondary care, tertiary care and the patient viewpoint.

Developments impacting on personalised prevention of breast cancer

Advances in genetics have led to identification of an increasing number of genes that confer moderate/high risk of breast cancer. In addition, progress has been made on the identification of common genetic variants and the development of polygenic risk scores (PRS). This together with developments in measuring mammographic density are contributing to risk prediction.

There are multiple coordinated efforts to improve risk prediction in high risk populations and at the level of the general population based on these advances. Studies indicate that current levels of stratification can be useful. Going forward, it will be crucial to ascertain which parameters and risk factors are most important for accurately refining estimates of breast cancer risk, and that confirmatory studies of clinical utility are conducted.



In early detection, intensive research programmes are underway to identify novel markers such as circulating tumour DNA and its potential to distinguish between benign and malignant lesions. It is feasible that the future use of biomarkers in personalised prevention could extend to *BRCA* mutation testing for all women and annual blood tests for early detection, which could inform personalised, risk-adapted screening approaches and targeted preventative interventions for those in the highest risk groups.

Technologies such as wearable sensors, apps and consumer-facing information systems are also profoundly changing the whole healthcare landscape through the ways in which they configure the digital neighbourhood of individuals. This creates opportunities in the way health care providers interact with individuals. The wider scope of data collection enabled by these technologies may facilitate the move towards a learning health system and alternate models of evidence-based medicine.

How might our approach to prevention change?

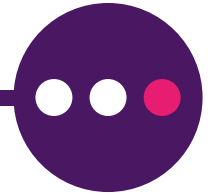
Participants agreed that now and in the future, the approach to personalised prevention of breast cancer should consist of both population wide and risk-based preventative interventions. The science of risk-based stratification is encouraging and going forward consideration is needed on how this would interface with broader public health initiatives.

Risk assessment on the basis of genetic testing or use of risk tools could be incorporated at different stages of the breast cancer prevention pathway. Incorporation of emerging knowledge may have simple or more complex effects on current practice. There may be incremental additions to existing pathways, with risk assessment being used as a tool to assist decision making at static points. Alternatively, a more complex and diverse risk-based prevention pathway was also envisioned.

Generally, the ability to categorise risk has advanced more quickly than the development of evidence of utility for preventive pathways for different levels of risk. Proactive versus reactive assessment of risk was a point of debate given the lack of consensus on which groups would benefit the most from existing preventative interventions. There was no clear evidence that differentiation beyond the current practice of identifying groups eligible for screening (based on age) or those with a family history of breast cancer (based on clinical follow-up of cases or self-identification) had added value. In particular there was currently no clear evidence to support risk assessment for better identification of women who should be offered early detection programmes and, if so, at what age these should be offered.

Implications for health systems

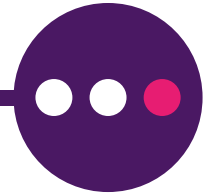
Personalised prevention envisages a future where individuals will access information on their risk of disease or possible early disease in order to take action to improve their health. Discussions throughout the course of the workshop acknowledged the fast evolving and dynamic nature of science and associated technological developments. This has resulted in the ability to accrue data and information using a variety of biomedical and/or digital technologies from diverse sources.



It was clear from the discussions that a move towards personalised prevention pathways provided opportunities to improve and enhance healthcare provision. However, adequate consideration needed to be given to a wide range of often inter-related issues (such as health inequalities, overdiagnosis, regulation and person-centred care), that, if not addressed, could impact on technology implementation or population outcomes. Appropriate management of these issues is important in ensuring the benefits of personalisation outweigh the potential harms. It is clear that these are issues that are unlikely to be resolved easily and will remain important considerations both in the near-term and in the future.

Conclusion

Current scientific knowledge and technologies enable improved risk assessment and population stratification for breast cancer risk based on multiple risk factors, and this landscape is likely to evolve rapidly in the future. While evidence in support of risk-based prevention is currently lacking, we expect to see a more robust evidence base emerging from ongoing trials and new studies. Through this workshop we were able to describe the developments in this field and the likely impact on future prevention pathways.



1 Introduction

Background

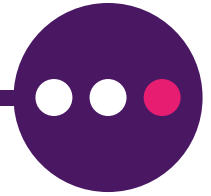
Breast Cancer Stratification: understanding the determinants of risk and prognosis of molecular subtypes (B-CAST) is a multicentre European Commission project. The overall aim of this project is to gain a better understanding of the environmental and biological factors that influence breast cancer development and prognosis. This information can then be used to develop models and tools that will allow more precise identification of individual risk of breast cancer, and, in those with disease, improve assessment of the subtype of breast cancer that is most likely to have developed. The availability of such tools may allow greater individual specific information to be generated, to inform more accurate prevention and treatment strategies.

As part of the B-CAST consortium the PHG Foundation has responsibility for Work Package (WP) 8: *Capacity development for personalised breast cancer prevention and early detection*, which aims to promote the development and integration of personalised breast cancer prevention within national public health programmes.

We began our work by assessing the current prevention and policy landscape of breast cancer prevention through a review of the literature. In our previous report, [Personalised prevention in breast cancer: the policy landscape](#),¹ we set out our analysis of current approaches to breast cancer prevention and the discourse around personalised breast cancer prevention. The analysis focused on primary and secondary prevention programmes i.e. prevention of disease development and early detection. We examined policy and prevention activities at an international level wherever possible, with specific emphasis on three key countries (United Kingdom, Netherlands and Australia) to act as case studies. Although the focus was on breast cancer, it was viewed within the wider context of prevention activities for other chronic diseases.

The findings of our review showed that the scope for personalised prevention of breast cancer continues to be primarily based on an understanding of family history and genetic factors. Environmental and lifestyle factors are currently thought to be either unmodifiable (e.g. reproductive history) or do not provide sufficient risk stratification at the individual level to be able to offer personalised advice (e.g. overweight, high alcohol intake). As these factors are also common to several other chronic diseases, generalised advice is given rather than specifically to breast cancer.

Personalised prevention as a concept seems to be gaining traction, with many government documents committing to develop enabling initiatives. However, our review of the literature found little discussion on specific mechanisms to deliver personalised prevention or a vision for personalised prevention in relation to breast cancer.



The workshop

We based the second phase of the project around an international workshop held 19-21 September 2018 to investigate further the immediate and longer term potential of personalised prevention and risk assessment for breast cancer. PHG Foundation facilitated the workshop which included 22 delegates with expertise in research, public health, breast screening, primary care, secondary care and tertiary care attending from the UK, Netherlands, France, Germany, Sweden and the USA. The delegate list can be found in Appendix 1.

Elements of the workshop included:

- The provision of [background materials](#) (policy review and expert perspectives on the opportunities arising from selected new technologies)
- Presentations to provide delegates with background and context
- Facilitated small group discussions

Objectives:

- Develop a vision for a more personalised prevention pathway for breast cancer for the near term (five years) and the future (20 years)
- Identify health system and other societal requirements for moving towards a more personalised approach to breast cancer prevention now and in the future

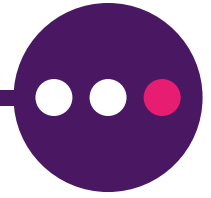
Aims:

- Identify what we can achieve over the next five years given what we know/can do now
- Identify what the landscape of personalised prevention will look like in 20 years for breast cancer
- Describe key technologies (alone and in combination) that have the potential to enable personalised prevention
- Describe the elements of a personalised prevention pathway and issues that will arise for healthcare systems and society as this is developed

Structure of the report

This report provides an account of the workshop proceedings and the key findings. We begin with a summary of the workshop presentations. This is followed by a summary of the feedback and thoughts provided by discussants with backgrounds in different areas of healthcare. Discussants provided their thoughts on how current knowledge could potentially be used to personalise prevention over the next five years. Sections 5 and 6 provide a synthesis of the exchange in the facilitated small group discussions. In the final section we summarise the key conclusions and findings from the workshop.

The results of this workshop will be used to undertake further policy analysis, which will be published along with policy recommendations in 2020.



2 Personalised prevention – setting the context

The first half-day of the workshop comprised a series of talks with the aim of setting the context for subsequent discussions. These talks were designed to provide participants with an overview of currently available interventions, ongoing research activities with regards to breast cancer prevention and future research, gaps and areas for development.

2.1 Personalised breast cancer prevention in the NHS

Professor Anthony Howell (Chair in Breast Oncology, University of Manchester) presented on the current provision of personalised prevention within NHS Risk and Prevention Clinics and the potential for evolving knowledge to inform prevention in these settings as well as at the level of the general population.

Personalised approaches to prevention of breast cancer are already available in European health systems. Most often, this is in the setting of familial cancer clinics where risk assessment is used to inform preventative interventions for those considered at moderate or high risk. It is therefore in this setting that the use of risk tools is most well established. Professor Howell discussed current provision and findings from the PROCAS (Predicting the Risk Of Cancer At Screening) study at the University of Manchester (UK).

Key points

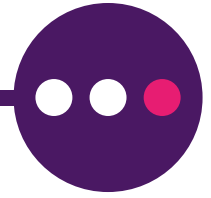
- It is important to ascertain whether risk estimation can be improved
- There is a need to determine how best to use improved risk estimation in primary and secondary prevention
- More focus is needed on women aged under 40 years

Available personalised prevention in the NHS

In the UK, NHS Risk and Prevention Clinics are most frequently accessed by women below 50 years of age who have presented to health services with concerns about their family history of breast cancer, and who have been referred by a clinician in primary or secondary care. Within this familial risk clinic, women receive an estimation of risk using a risk tool and an offer of preventive interventions (lifestyle modification, chemoprevention or surgical prevention) where clinically appropriate.

Extension of personalised prevention – risk and prevention clinics

The risk factors considered and the tools used for risk estimation have evolved over time. It is clear that breast cancer risk can be estimated to some extent through the use of standard models (i.e. those with clinical risk factors) and more recently through inclusion of information on mammographic density (MD) and single nucleotide polymorphisms (SNPs), which enable more refined risk estimates (Figure 1).



However, as evidenced by the PROCAS study, inclusion of MD and information from a panel of 18 SNPs changes the categorisation of lifetime risk (as defined by NICE) in over 50% of women in these clinics². Given that this has an impact on subsequent preventative options, it is crucially important to ascertain which parameters and risk factors are most important for accurately refining estimates of breast cancer risk, and that confirmatory studies of clinical validity and utility are conducted in this population.

Extension of personalised prevention – screening population

Whilst risk-adapted screening is available to younger women known to be at moderate or high risk, there is a notable deficit in clinical services for risk evaluation, risk-adapted screening and preventative interventions in older women eligible for population screening. In order to test approaches to extending personalised prevention for breast cancer to the general population, the PROCAS study invited women attending their first screening mammogram to receive an estimate of their 10-year absolute breast cancer risk.

Comparable risk estimates were generated by the Tyrer-Cuzick model (using standard risk factors), SNP18 (a polygenic risk score (PRS) generated by 18 SNPs), and visually-assessed MD (adjusted for age and BMI) in isolation. Risk estimation using all three parameters in combination revealed higher proportions of women at low and high risk of breast cancer than using conventional models.

Approximately 16% of women were found to be at moderate or high risk using this model, which increased to approximately 20% when using a PRS generated by 143 SNPs. Women at high risk of breast cancer encountered the highest rates of clinical disease, and were also more likely to have higher grade cancers and oestrogen receptor negative tumours. Conversely, women at low risk who developed breast cancer were observed to have a higher proportion of tumours at low grade or with extremely good prognosis.

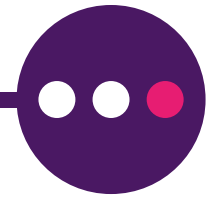
It is pertinent to consider whether information that a woman is at low risk of breast cancer might have the potential to enable reduced screening frequency amongst this cohort.

The future

Within the next 5–10 years, it will be important to ascertain whether risk estimation can be improved, and how best to use emerging knowledge on PRS and MD in primary and secondary prevention (Figure 1).

There is also a need to improve our understanding of the pathophysiology of breast cancer and the relative effects of individual risk factors, how to better determine prognosis, and to improve the effectiveness and delivery of preventative interventions such as chemoprevention and lifestyle advice.

In the PROCAS study, 25% of women at high risk of breast cancer engaged in lifestyle interventions, of which approximately 60% were able to sustain a 5% reduction in body weight. This highlights the potential for introducing lifestyle change into national screening programmes.

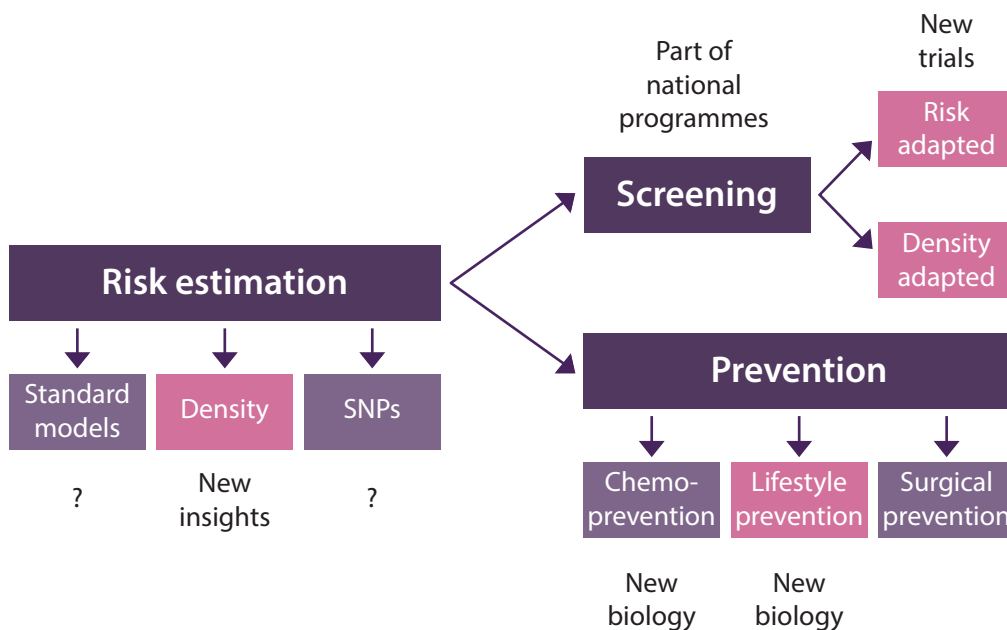


Evidence will be required of the clinical utility of novel approaches to personalised breast cancer prevention. Refinement of screening programmes will be informed by ongoing clinical trials and observational studies investigating risk-adapted mammography. These include the second phase of the PROCAS study, the European MyPeBS (My Personalised Breast Screening) study to assess the effectiveness of risk-adapted screening mammography in detecting stage 2+ breast cancer, and the KARMA study (KARolinska MAMmography Project for Risk Prediction of Breast Cancer) which continues to follow up over 70,000 women undergoing regular screening in Sweden.

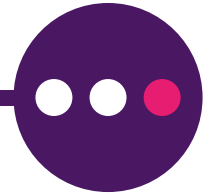
Consideration should also be given to how to facilitate access to risk estimation and preventative interventions, and avoid medicalisation of healthy women. For example, risk models currently operate outside of the health system digital infrastructure and require manual data entry during clinical consultations, which is impeding access to this information.

As part of the second phase of the PROCAS study, improved capabilities have been developed to automatically integrate risk factor data collected through patient-facing online portals and MD data into the Tyrer-Cuzick model.

Figure 1. The changing role of risk assessment over the next 5-10 years.



Considerations include whether risk estimation can be improved with insights from density and SNPs, and how best to use emerging knowledge on polygenic risk score (PRS) and mammographic density (MD) in primary and secondary prevention. New insights can also inform interventions. Source: adapted from slides provided by A.Howell



Summary

■ Improve prediction

Risk prediction is already in use within the context of Risk and Prevention Clinics. However, even in this setting, there is potential for improvement. Going forward, it is crucial to ascertain which parameters and risk factors are most important for accurately refining estimates of breast cancer risk, and that confirmatory studies of clinical utility are conducted. For example, although mammographic density (MD) is an important risk factor, a recent study commissioned by the UK National Screening Committee (NSC) has deemed that currently there is insufficient evidence to support measurement of MD within the NHS Breast Screening Programme.³ The report highlighted the need to assess consistency, reliability and validity of methods applicable to breast density measurement.

■ Improve prevention

Available interventions have varying impact on risk reduction in a familial risk setting, for example, loss of 5% body weight confers an estimated 25% reduction in lifetime breast cancer risk, whereas preventive therapies and surgery decrease risk by 40-50% and by over 90% respectively. Whilst the duration of the preventive effect of tamoxifen is known (five years of therapy is protective for approximately 20 years), further work is required to determine the duration of effectiveness of other forms of chemoprevention (e.g. anastrozole) and the survival advantage conferred by these therapies.

■ More focus on women aged under 40 years

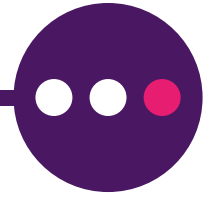
Detailed risk assessment is only available to a minority of women at selected NHS centres, such as Risk and Prevention Clinics at the Manchester University NHS Foundation Trust. It is not known exactly how many women who are eligible for such services utilise them. Experts were of the opinion that in the UK, this mechanism (which is based on self-reporting) results in around half of all women with a significant family history presenting to healthcare services, suggesting that approximately 25% of women below the age of 40 at moderate/high risk are known to health services. A key question is whether active efforts need to be undertaken to ensure a larger proportion of women at this level of risk present to health services.

2.2 What do we know about changing health related behaviour?

The (limited) role of personalised risk information, and more promising intervention approaches

Professor David French (Professor of Health Psychology, University of Manchester) explored behaviour change theory, its practical applications and its uses in relation to personalised prevention/breast cancer prevention.

Behaviour change is one approach to health promotion and aims to support and empower individuals to take control of their health. It is a complex intervention and is underpinned by health behaviour change theory. Professor French discussed evidence relating to personalised behaviour change strategies and the role of personalised risk information in motivating behaviour modification in the context of breast cancer.



Key points

- Individual behaviour change is a complex intervention
- Risk communication is important
- Provision of risk information by itself is insufficient

Effects of communicating personalised disease risk on behaviour

Personalised risk information has a role in promoting behaviour change, but it is fairly limited. Many studies have been conducted examining the impact of communicating genetic risk information or personalised disease risk on health related behaviours. These studies demonstrate a lack of evidence in support of personalised disease risk information in encouraging strong, consistent or sustained changes in health-related behaviours such as smoking, alcohol consumption and physical activity.⁴

The way that risk information is communicated can have an impact, for example interventions that provide a numerical risk estimate may have less success than those using a visual representation (e.g. an atherosclerotic artery), due to lack of individual understanding of the information. In the case of genetic-based risk information, it is possible that lack of motivation arises in part from a sense of 'genetic determinism', such that individuals consider their disease risk to be entirely non-modifiable.

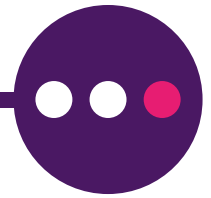
Evidence from studies examining the impact of non-personalised information on behaviour change have yielded some insights.⁵ They suggest that supporting an individual's beliefs in the benefits of behaviour change (response efficacy) and in their ability to achieve behaviour change (self-efficacy) yields the greatest improvements in behavioural intentions and health behaviours. This can be achieved by a set of programmes that facilitate behaviour change and do not solely rely on the communication of risk information by itself.

As such, the impact of using risk information to encourage lifestyle modification may be improved by delivery of interventions to heighten response efficacy, self-efficacy and perception of risk.

Identifying effective behaviour change techniques

Systematic reviews have examined effective interventional techniques for changing self-efficacy in the context of physical activity.⁶ Interventions which include action planning, providing instruction, and reinforcing effort towards behaviour change were most effective in adults under the age of 60. However, studies have shown that not all of these self-regulation intervention techniques will be appropriate and successful in all groups of adults. For example, commonly used behaviour change techniques are associated with lower levels of self-efficacy and physical activity in older adults.⁷ This is probably due to differences in the motivations for behaviour change between different populations.

Among adults above 60 years of age, there is reduced interest in increasing physical activity, except where this may enhance social connections and recreation. Therefore, within the motivational phase of behaviour change interventions, it is important to explore the personal motivations for behaviour change which, in many cases, are not health-related but rather triggered by other factors such as physical appearance and personal enjoyment.



Sustaining behaviour change

Despite initial effectiveness of physical activity interventions, behaviour change in adults is only maintained for approximately 15 months, which is probably due to the effect of other determinants of behaviour such as social, economic and infrastructural factors.⁸ Therefore, within the volitional phase of behaviour change interventions (i.e. when the individual is actively participating), it is important to support the planning, initiation and management of behaviour modification. Factors that may incentivise engagement in interventions include tools that enable self-monitoring and personal behavioural insights, such as pedometers.

Intervening at different levels

It is apparent that individual interventions are unlikely to be sufficient at stimulating long-term behaviour change in isolation, and that these should be integrated within population and community-level behaviour change interventions, as per NICE guidelines.⁹

In order to identify which approaches to behaviour change are most likely to be successful, the Medical Research Council (MRC) Framework¹⁰ for developing and evaluating complex interventions outlines that integral to the design of effective, scalable and maintainable interventions are:

- User input
- Using existing evidence
- Feasibility testing
- Pilot trials and implementation strategies

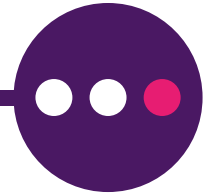
A recent systematic review¹¹ also identified that many academic studies do not effectively perform mediation tests to assess which factors are associated with successful application of behaviour change interventions, including maintenance of altered behaviour. Once an effective intervention has been developed, an additional challenge in its wider implementation is ensuring its effective delivery (intervention fidelity).

The role of personalised risk information for breast cancer

In keeping with evidence that communicating personalised disease risk information in isolation has negligible effect on behaviour change,⁴ no relationship was observed between the level of breast cancer risk and behavioural intentions among women enrolled in the PROCAS study.¹² However, as discussed by Professor Howell, women at higher risk of breast cancer were more likely to engage in a weight loss programme and to maintain their participation in the programme at 12 months.

This data suggests that communicating personalised breast cancer risk information may be most useful for encouraging women to participate in evidence-based programmes that promote and facilitate behaviour modification.

Given the strong evidence that modifiable and non-modifiable factors act together in a multiplicative fashion, it is possible that lifestyle interventions could be targeted at high risk groups in which they will have greatest impact on absolute risk reduction.



Summary

■ Individual behaviour change is a complex intervention

Individual behaviour is influenced by many factors meaning that approaches to behaviour change are complex and need to be considered within a wider framework of interventions aimed at different levels. These include at the level of the community, environment and larger ecosystem. The more of these levels that are targeted, the larger the impact. Often population level interventions embedded in the built and natural environments can have a larger impact on health related behaviours than interventions targeted at the individual. Furthermore, there are many behaviour change techniques that can be applied to different populations, adding complexity to the development and selection of interventions aimed at behaviour change.

■ Risk communication is important

It is important to consider how best to communicate personalised risk information, in order to make the information more understandable and meaningful and to prevent individuals adopting a view that disease is inevitable.

■ Provision of risk information by itself is insufficient

Evidence suggests that supporting an individual's beliefs in the benefits of behaviour change (response efficacy) and in their ability to achieve behaviour change (self-efficacy) yields the greatest improvements in behavioural intentions and health behaviours.⁵ This can be achieved by a set of programmes that facilitate behaviour change, rather than solely relying on the communication of risk information by itself. As such, the impact of using risk information to encourage lifestyle modification may be improved by delivery of interventions to heighten response efficacy, self-efficacy, and perception of risk.

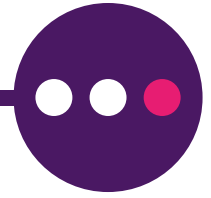
2.3 Clinical utility of preventative interventions aimed at moderate and high risk individuals

Professor Rita Schmutzler (Director at the Center of Familial Breast and Ovarian Cancer in Cologne, Germany) presented an overview of the preventative interventions aimed at moderate and high risk individuals along with evidence of their utility.

This talk explored currently available interventions for those at moderate and high risk and whether they could be targeted better. Professor Schmutzler began by stating that there was still a gap between risk prediction and the offer of preventative interventions based on risk, in this setting. It is of concern that appropriate preventative interventions are not being effectively delivered to those who have been identified as being at moderate or high risk.

Key points

- There are varying levels of evidence with regards to preventative interventions
- Greater consensus is needed with regards to expansion of genetic testing for breast cancer
- Definitions of risk need to be revisited



Available interventions for *BRCA1/2* mutation carriers and the evidence base

For *BRCA1/2* mutation carriers, available interventions include intensified surveillance, chemoprevention, and bilateral mastectomy with or without bilateral salpingo-oophorectomy (BSO). Intensified surveillance programmes for women with a genetic predisposition to breast cancer includes regular screening by mammography and MRI. Annual dual modality screening is significantly more likely to detect smaller, non-invasive and lymph node negative tumours and significantly improves 10-year survival rates among *BRCA1/2* mutation carriers, compared to those receiving no screening.¹³

Annual screening by MRI and mammography has also been demonstrated to improve 10-year metastasis-free survival in women with *BRCA1* mutations or with a family history.¹⁴ Bilateral mastectomy, with or without BSO, confers a significant reduction in incidence of breast cancer among women with *BRCA1/2* mutations,¹⁵ and improves 10-year survival rates of *BRCA1/2* mutation carriers with a history of primary breast cancer (PBC) independently of BSO.^{13,16}

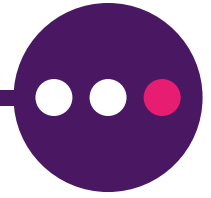
Improvements in overall survival are particularly significant in women with *BRCA1/2* mutations who have undergone both procedures, those diagnosed with PBC before the age of 40 years, and those diagnosed with less aggressive primary tumours.¹³⁻¹⁷

It is important in the clinical management of *BRCA1/2* mutation carriers presenting with PBC that consideration is given to both the risk of progression of the primary tumour and the risk of recurrence. Increasing numbers of women are undergoing prophylactic contralateral mastectomy in order to avoid recurrence of breast cancer, but these women tend to overestimate their recurrence risk and may not seek clarification from their oncologist.

It is apparent that there are distinct challenges in communicating information concerning both primary prevention and recurrence prevention, where estimates of survival also need to be considered.

Whilst the value of BSO and contralateral mastectomy in *BRCA1/2* mutation carriers affected by PBC is clear, data concerning the effectiveness of prophylactic mastectomy on mortality risk in healthy *BRCA1/2* mutation carriers is less convincing.¹⁷ Rigorous data on the effects on survival of preventive interventions in high risk individuals is still awaited.

Data from the German healthcare system indicate that chemoprevention drugs are often offered too late to *BRCA1/2* mutation carriers, to whom risk-reducing surgery is available at the age of 40. Progress is being made in the development of more targeted chemoprevention agents, such as RANK ligand inhibitors (e.g. denosumab) that inhibit progesterone signalling and proliferation of breast epithelial cells harvested from *BRCA1* mutation carriers.¹⁸ Researchers are due to commence a Phase 3 clinical trial investigating the preventive effect of denosumab on breast cancer in women with germline *BRCA1* at the end of 2018.



In summary, we have a good understanding of the prevalence, penetrance, clinical phenotypes, histological subtypes and natural disease course of breast cancer in *BRCA1/2* mutation carriers. However, comprehensive evaluation of *BRCA1/2* testing based on the ACCE framework will not be complete until further evidence of the efficacy of preventive and therapeutic interventions and the survival advantage conferred by them is gathered, and more extensive exploration of the ethical, legal and social issues is conducted. Prospective cohort studies such as MARIBS (MRI for Breast Screening) and MRISC (MRI Screening) should also continue to generate data of cost-effectiveness of intensive surveillance programmes for women at high risk.

The impact of increasing genetic information

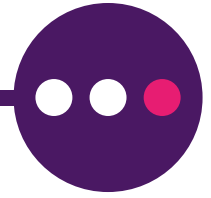
Increased availability of genetic information suggests that breast cancer risk should be considered as a continuum in those at familial risk. Approximately 24% of women who fulfil eligibility criteria for genetic testing are *BRCA1/2* mutation carriers and a further 6% have mutations in *TP53*, *PTEN*, *ATM*, *CHEK2*, *BRIP1* or *PALB2*. However, many genes associated with familial aggregation of breast cancer are not known.

A number of international projects to identify risk genes are underway, including CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*), BCAC (Breast Cancer Association Consortium), PERSPECTIVE (PErsonalised Risk Stratification for Prevention and Early deTeCTIon of breast cancer) and BRIDGES (Breast Cancer Risk after Diagnostic Gene Sequencing), amongst others.^{19–21}

Within the German Consortium for Familial Breast and Ovarian Cancer, the TruRISK® 34 gene panel has been developed which includes 10 'core' high risk genes for breast and/or ovarian cancer, associated genes and candidate genes.²² Information on clinical validity is not available for all these genes. Odds ratios have been estimated for most of these genes, but age-adjusted penetrance data are only available for mutations in *BRCA1/2*, *PALB2* and *CHEK2*.^{23,24}

From a clinical point of view, there is insufficient data for implementation of wider genetic testing into routine clinical care for those who are at familial risk. Evidence of the prevalence, penetrance, clinical phenotypes, histological subtypes and natural disease course in mutation carriers of other genes will be required, as will data on the efficacy and survival advantage of preventive and therapeutic interventions in these women. It is crucial that such data are gathered from prospective cohort studies and deposited within familial tumour registries.

Despite the need for rigorous evidence, there is a sense of urgency for implementation of genetic testing within routine clinical care. The increase both in availability of multi-gene panels to patients within the German healthcare system and of direct-to-consumer (DTC) tests have led to an increase in referrals to clinical services at the Center of Familial Breast and Ovarian Cancer regarding variants of unknown significance. Without expansion in the availability of clinically validated tests, it can be expected that more commercial providers will enter and increase demand within the genetic testing market.



The disparity between availability of clinically validated and commercially available tests is exacerbated by justified criticisms of healthcare providers. Recent data from the National Health Interview Survey of over 47,000 women in the US has revealed that the majority of women with a personal history of PBC and/or ovarian cancer meeting eligibility criteria for genetic testing have never discussed testing with a healthcare provider, and that only 13.8% of these women have undergone this investigation.²⁵

How to implement risk-adjusted care and gain further evidence?

It is apparent that healthcare systems are currently not equipped to provide wider genetic testing in routine care, which likely reflects a lack of knowledge of genetic testing in primary and secondary care.

To address this, the German Consortium for Familial Breast and Ovarian Cancer has recently expanded to generate networks between 18 specialised centres and 192 cancer centres, which provides remunerated training to clinicians in genetics and genetic counselling, and enables access to multidisciplinary team diagnostic boards. Projects to develop patient-facing genetic testing decision aids and to improve genetic literacy are also underway. Further work is required to consolidate familial tumour registries, which will provide evidence that can be used to inform care by generating insights into the efficacy of therapeutic interventions.

Summary

- There are varying levels of evidence with regards to preventative interventions

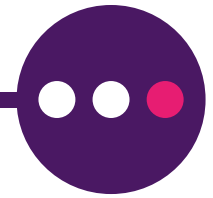
Although *BRCA1/2* carriers have the most defined preventative pathways, robust data are still needed on the effectiveness of prophylactic mastectomy on mortality risk in healthy *BRCA1/2* mutation carriers and more generally on the effects on survival of preventive interventions in high risk individuals.

- Greater consensus is needed with regards to expansion of genetic testing for breast cancer

An increasing number of genes that confer moderate/high risk are being identified; however, clinically validated tests are not being developed in parallel. This is due to the lack of data on the prevalence, penetrance, clinical phenotypes, histological subtypes and natural disease course in mutation carriers. However, it may not be feasible to wait for accumulation of robust evidence. Commercial availability of genetic tests is creating concern for certain health systems, due to managing downstream results of testing and in the quality and delivery of tests that are available. This indicates the need for an agreed course of action that allows individuals to understand the implications of genetic testing.

- Definitions of risk need to be revisited

Definitions such as high risk and moderate risk were set-up normatively prior to widespread genetic testing. Given that increased genetic information has led us to consider breast cancer risk as a continuum in those at familial risk, it is important to revisit these terms so that they better align with preventative care.



2.4 Risk categorisation in breast cancer

Professor Montserrat Garcia-Closas (Deputy Director of the Division of Cancer Epidemiology and Genetics at the NIH National Cancer Institute, USA) on where we are with respect to risk categorisation.

The talk provided an overview of the state of science in terms of being able to stratify individuals and populations into different risk categories.

Key points

- Current levels of risk stratification can be useful
- Model performance is population dependent
- Further model development and validation is needed

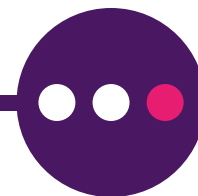
Breast cancer risk models used in clinical practice

Research has identified a number of factors that are associated with risk of developing breast cancer, including lifestyle, reproductive events, MD, benign breast disease (BBD) and genetics. This knowledge has been used to develop risk models that aim to predict risk of future disease in asymptomatic individuals. A variety of risk models have been developed to predict risk in populations identified as having a high risk due to family history, and in the screening or general population (Figure 2). However, in clinical practice, their use is mainly limited to family cancer clinics or clinical genetics settings. An extensive review of this area can be found in an article by Cintolo-Gonzales.²⁶

Figure 2: Breast cancer risk models used in clinical practice

| Risk model | Target population | Reproductive/ lifestyle risk factors | Pedigree level family history | Breast density | BBD histology | Externally evaluated in prospective cohorts |
|---------------------|---------------------|--------------------------------------|-------------------------------|----------------|---------------|---|
| BCRAT (Gail) | Screening | ✓ | X | X | ✓ | ✓✓✓ |
| BCSC-BBD (Tice) | Screening | X | X | ✓ | ✓ | X |
| IBIS (Tyrer-Cuzick) | General & High risk | ✓ | ✓ | ✓ | ✓ | ✓ |
| BRCAPRO | High risk | X | ✓ | X | X | ✓ |
| BOADICEA | High risk | X | ✓ | X | X | ✓ |

Source: adapted from slides provided by M. Garcia-Closas



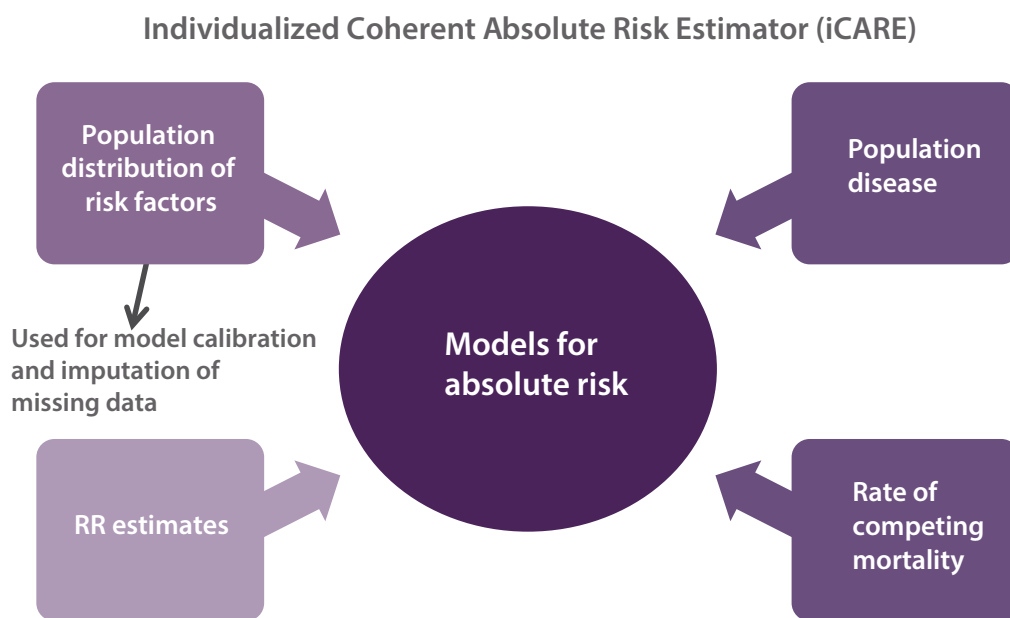
Risk model development and validation

Breast cancer risk models have been externally validated in prospective cohort studies to different extents (Figure 2). The most extensively evaluated is the BCRAT (GAIL) model. As new information on risk factors such as SNPs and breast density become available, an additional consideration is how best to include these within the scope of risk prediction and to understand in which clinical scenarios different sets of information are most suited. Efforts are currently underway to create a user-friendly tool with an underlying comprehensive integrated model that can be used in different clinical scenarios. Key to achieving this will be ensuring that the underlying model is robustly validated.

Development and validation of an integrated risk model

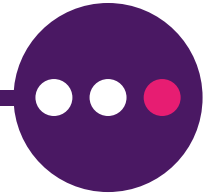
The Individualized Coherent Absolute Risk Estimation (iCARE) tool provides a flexible risk model-building tool that can be used to build a synthetic risk model for prediction of cancer risk in the general population.²⁷ The main inputs for this tool are estimates of relative risk (RR), population risk distribution, age specific incidence rates, and rates of competing mortality. By compartmentalising input parameters, it enables researchers to incorporate the best available information on key model parameters, to update models as new information becomes available, and examine impact in particular populations (Figure 3). This tool also handles for missing data on risk factors.

Figure 3: Individualized Coherent Absolute Risk Estimation (iCARE). Flexible tool to develop and validate absolute risk models



Choudhury et al
www.biorxiv.org/content/early/2018/08/23/079954

Source: adapted from slides provided by M.Garcia-Closas



In addition, the tool has a validation component that can be used to calibrate models, and therefore provides a standardised methodology and evaluation platform for model development. It has been used to develop two novel models using RRs from the literature review for women of all ages, and using RRs from a multivariate model fitted using data from eight US cohorts (BPC3) of women aged over 50 years, iCARE-Lit and iCARE-BPC3, respectively, and validate their performance against existing models – BCRAT and IBIS. This has enabled identification of classical risk factor information that can be integrated along with PRS and MD into BOADICEA to develop a comprehensive model which can consider classical risk factors, SNPs and pedigree information.

How well can we categorise populations into different risk categories?

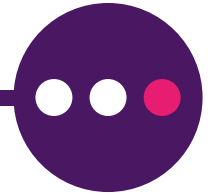
The iCARE platform has been used to examine the relative and absolute risk calibration and discrimination of the risk of above models across 11 different cohorts. These multiple evaluations need to be done in order to evaluate the robustness of the models across different populations.

A summary of the findings are:

- Using a combination of classical risk factors and PRS improves calibration and AUC (i.e. discriminatory capacity)
- There is consistent miscalibration in the top decile with all models overestimating risk, but the magnitude varies across models. The implications of this for clinical care need to be examined further
- Differences in model performance with regards to calibration across validation populations could be due to study design or underlying differences in risk factor distribution
- The initial findings indicate good calibration of the BOADICEA model including classical risk factors and PRS in a UK cohort study
- Integrated models identify a higher percentage of women at low and high risk in comparison to models that are based only on classical risk factors
- Models that integrate MD and PRS are yet to be validated in prospective cohorts

Efforts to improve risk prediction

There are multiple coordinated efforts to improve risk prediction models, including B-CAST which is focussing on sub-type specific risk prediction. Initiatives such as BRIDGES and PERSPECTIVE I & II are working to identify rare variants, while the Confluence Project, a new breast cancer genome-wide association study, is working to improve polygenic risk prediction across ethnic groups and breast cancer subtypes.



Summary

- Current levels of risk stratification can be useful

Integrated models, i.e. those that bring together classical risk factors, MD and genetic risk factors, are important for identifying women at the extremes of risk distribution. PRS contributes substantially to the ability to stratify women according to risk. This information can be applied at the general population level to identify a larger proportion of women at low and high risk. This can be potentially useful in identifying those most likely to benefit from risk-reducing interventions. However, models that integrate MD and PRS are yet to be prospectively validated.

- Model performance is population dependent

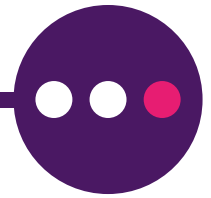
Interpretation of model performance will be impacted by differences in validation population, including underlying differences in age distribution and incidence. As such, it is important to evaluate models across different populations, particularly those populations in which models are going to be used.

- Further model development and validation is needed

There are multiple different efforts underway to integrate and better predict risk with respect to breast cancer, all of which require model performance to be examined and validated prior to clinical implementation. However, there is uncertainty regarding what is required with respect to model validation.

Factors that impact on ability to validate were touched upon and include the availability of appropriate validation cohorts that contain comprehensive risk factor information so that validation is possible, and obtaining information on the distribution of risk factors for the target population where the models will be used. This is easier for genetic factors than classical risk factors. It is also important to validate models in a population similar to the one stratification is going to be applied to.

An additional consideration in examining model performance, especially with respect to stratification, is examining the impact that stratification has on thresholds set for classification as high/moderate/low risk.



3 The evolving landscape of breast cancer prevention

The future of personalised prevention for breast cancer will be very different in light of evolving knowledge of biomarkers that give information on risk. Digital and information technologies are also contributing to our ability to harness knowledge from biomarkers. Risk information and interventions are likely to be offered from many different healthcare providers and the commercial sector, employing a range of technologies. There may be greater availability of increasingly tailored interventions, including digital (e.g. apps), to provide support for lifestyle change. This series of talks covers particular technology areas, giving an overview of anticipated future developments, visualising their impact on healthcare and their potential use in breast cancer prevention

3.1 The future outlook

Professor Paul Pharoah (Professor of Cancer Epidemiology at the University of Cambridge) outlined where we are in terms of scientific understanding of breast cancer and likely future progress with respect to developments in risk stratification, primary prevention and secondary prevention.

Key points

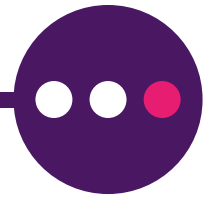
- Current knowledge contributes to risk stratification
- There will be limits to our ability to stratify by risk
- Developments in prevention are needed

Developments in risk stratification

Information with respect to the relative impact of different lifestyle factors could be useful in assessing risk and identifying mechanisms for risk reduction. However, the major risk factors for breast cancer have been known for many years and it is unlikely that this knowledge will change substantially over the next five to 20 years. This is because many factors are difficult to study epidemiologically, mainly due to difficulties in measuring complex exposures that have small effects on risk.

The early hopes for nutritional epidemiology have not been realised as a result of these difficulties. There is some potential for novel biomarkers to be identified using proteomics and metabolomics approaches, but these studies are technically demanding to conduct and, as yet, have not been proven to be useful.

In addition, although lifestyle risk factors are useful in risk stratification they may not always be useful in informing risk reduction. In contrast to many other risk factors the study of germline genetic variation and breast cancer risk is comparatively easy. This genetic variation is stable within an individual and comparatively cheap and easy to measure.



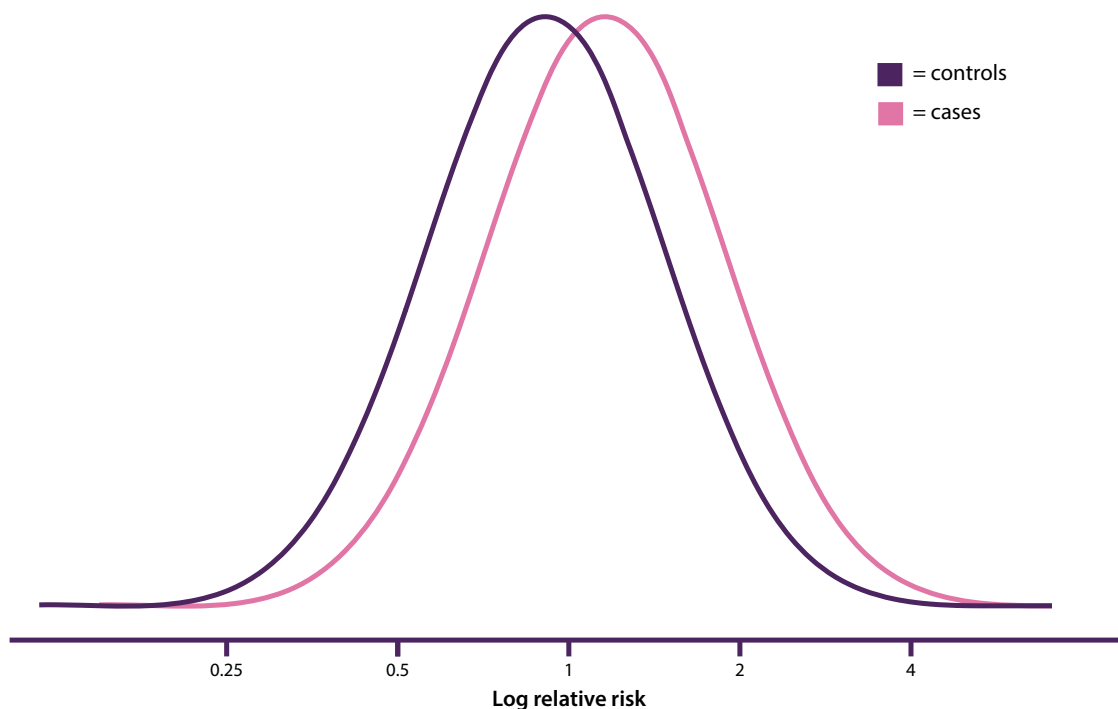
The future outlook with respect to breast cancer genetics

We have made considerable progress in our understanding of the basis for inherited susceptibility to breast cancer, but still have much to learn. Over 160 common SNPs associated with breast cancer risk have now been identified at very stringent levels of statistical significance. At less stringent levels over 300 variants have been shown to be associated with risk. Together with known moderate and high risk genes, these common SNPs explain approximately 45% of the breast cancer risk.

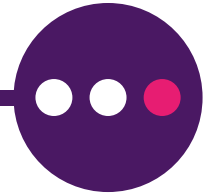
Risk scores are evaluated using several metrics, although none of them are ideal. The most commonly used evaluation method is discrimination i.e. the ability of a risk score to discriminate between those who will or will not develop the disease. The risk follows a normal distribution in cases and controls (Figure 4), with cases having a higher average risk than controls.

Nevertheless, some people at high risk will not develop the disease and it is likely that some at low risk will develop the disease. The separation between these two curves indicates ability to discriminate between future cases and controls. This is measured by the area under the receiver operating curve (AUC). The receiver operator curve (ROC) presents sensitivity (true positive rate) against 1- specificity (false positive rate), for different risk thresholds. This is useful as clinical decisions are often made in categorical or dichotomous ways and have thresholds, hence it can be useful to know the number of people above or below particular thresholds. As the variance of the risk distribution defines its spread, it is a key determinant of performance.

Figure 4: Discrimination is a measure of separation of risk in cases and controls and is measured by area under the receiver operator curve.



Source: adapted from slides provided by P. Pharoah



Polygenic risk scores: current state and future prospects

Recently, the predictive ability of a polygenic risk score using 313 SNPs has been evaluated.²⁸ The AUC was 0.63, meaning that for any given case-control pair of the same age, there is a 63% chance that the case will have a higher PRS.

Polygenic risk is approximately normally distributed on the log relative risk scale in the population. At the 99th centile of the risk distribution the relative risk compared to the population average risk is 2.7. This means that the 1% of the population at highest polygenic risk have a relative risk of 2.7 or above. These individuals account for 3.2% of breast cancer cases. The 20% of the population with the highest polygenic risk have a relative risk of 1.3 or above and account for 36% of all cases.

In the future, as we identify more variants, the predictive ability of PRS will improve. It is important to consider the maximum achievable capabilities in prediction. For example if all risk-associated common variants were known, the AUC would improve to around 0.68. This would improve to 0.7 by including lifestyle factors. Furthermore, whether this degree of discrimination would have clinical utility is debatable – any potential utility of a polygenic risk score will depend on the benefits and harms of interventions to reduce risks.

Developments in primary and secondary prevention

Currently primary prevention for cancer in the form of drug therapies is limited. In the future, prophylactic interventions that are taken for a short time with long-lasting benefits would be desirable. Over the next five to ten years we are likely to accrue greater knowledge about the impact of our ability to stratify for secondary prevention i.e. screening. Modelling studies have been conducted on the costs and outcomes of stratified mammographic screening and trials such as PROCAS, WISDOM and MyPeBS are evaluating differing screening strategies/modalities of screening integrated with risk stratification.

Summary

- Current knowledge contributes to risk stratification

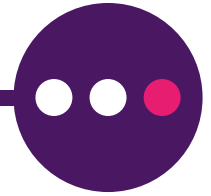
Lifestyle factors have been used to stratify populations for some time. Polygenic risk scores are another biomarker that can be used for population stratification.

- There will be limits to our ability to stratify by risk

The predictive ability of PRS could be improved as we identify more variants associated with disease. However, there are likely to be limits to prediction capabilities. It is unclear at this stage to what extent development in other 'omics technologies will contribute.

- Developments in prevention are needed

The ideal goal is a future where there is more certainty with respect to screening resulting in better identification of lesions that will lead to fatal disease and a reduction in over-diagnosis.



3.2 Biomarkers in personalised breast cancer prevention

Dr. Esther Lips (Associate Staff Scientist from the Netherlands Cancer Institute) presented an overview of the biomarkers currently used in the context of breast cancer, how developments in biomarkers might contribute to personalised breast cancer prevention in 20 years' time, and the challenges in technology development that need to be overcome for these to be implemented.

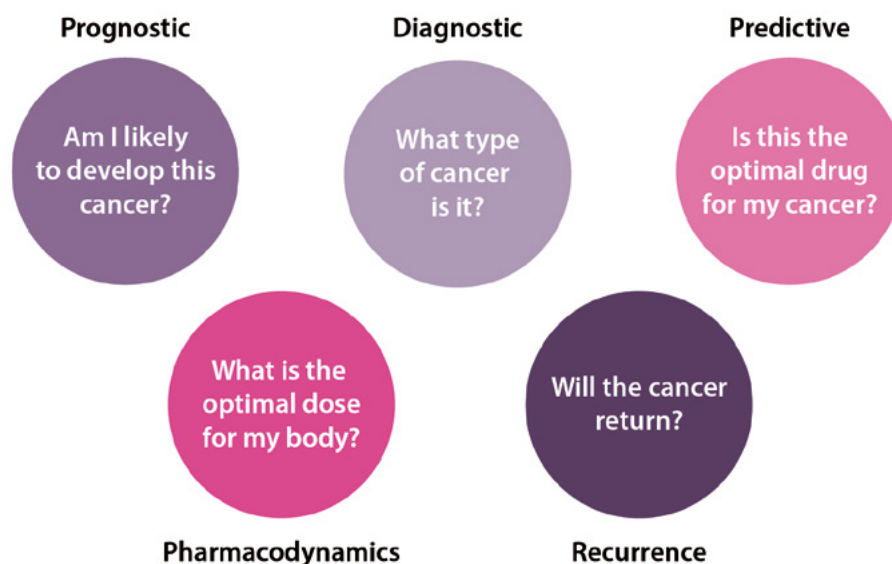
Key points

- Biomarkers have a number of different applications in healthcare
- There are challenges to overcome in applying knowledge about biomarkers
- Emerging biomarker knowledge can be used to improve current prevention pathways

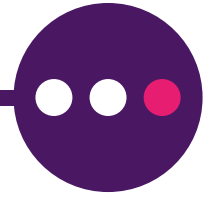
Biomarkers in breast cancer

Biomarkers can be used to answer a number of questions in clinical practice (Figure 5). Biomarkers are currently used in breast cancer for disease prediction and to guide therapeutic decision-making. More recent developments in biomarkers for breast cancer include gene expression profiling tests to predict the 10-year risk of metastasis and likelihood of benefit from adjuvant chemotherapy, such as MammaPrint and Oncotype DX.

Figure 5: Questions that can be answered by cancer biomarkers



Source: adapted from slides provided by E.Lips



Early detection of cancer: blood based tests

Tumour DNA (ctDNA) that has been shed into the bloodstream and collected as a blood-based 'liquid biopsy' is an exciting area of research that may enable earlier detection of cancer and generate insights into the genetic characteristics of the tumour. In confirmed cases of cancer, ctDNA offers the potential to detect responses to treatment, to identify emergent mutations that confer resistance to chemotherapeutic agents and to monitor progression of the disease.

In the future, liquid biopsies may allow detection of circulating tumour cells (CTCs), circulating tumour RNA (ctRNA) and exosomes, and could be applied to other bodily fluids such as urine, saliva and cerebrospinal fluid.²⁹ The majority of research relating to ctDNA-based and blood-based tests for cancer detection thus far has been conducted in the context of metastatic disease.

The challenge now is to attempt to detect disease at earlier stages and from lower grade tumours. Studies such as CancerSEEK are attempting to develop a multi-analyte blood test for circulating proteins and mutations in cell-free DNA. Blood-based tests involving analysis of mRNA profiles of tumour-educated platelets (TEPS) are also being developed for the early detection of cancer.

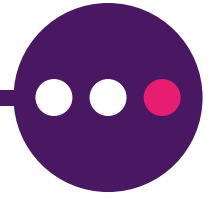
Risk stratification biomarkers

Risk stratification using genetic biomarkers to predict risk of developing breast cancer³⁰ or for prognosis is an area of active research in numerous international projects, including B-CAST. There is an unmet need for risk stratification, particularly among women with ductal carcinoma *in situ* (DCIS) to predict likelihood of tumour progression and clinical management. Twenty five percent of all breast tumours detected by mammographic screening are DCIS.

The PRECISION (PREvent ductal Carcinoma *In Situ* Invasive Overtreatment Now) study aims to understand the biology of initiation and progression of DCIS in order to allow discrimination between low- and high-risk lesions. This has the potential to inform clinical decision-making and enable avoidance of unnecessary surgical interventions in those women at lowest risk of DCIS progression.

The PRECISION project also seeks to create a paradigm shift in the language around diagnoses of breast cancer precursors and to improve patient acceptability of active surveillance, such as through referring to tumours as 'lesions'.

This study is generating insights into the genomic basis, mammographic characteristics and tumour microenvironment of DCIS, which will be complemented by *in vitro* and *in vivo* assays and used in the development of a risk prediction tool. In collaboration with the LORIS (Surgery versus Active Monitoring for LOw RiSk Ductal Carcinoma *in Situ*), LORD (LOw Risk DCIS) and COMET (Comparison of Operative to Monitoring and Endocrine Therapy) clinical trials, 10-year outcome data will be collected from women with DCIS to determine the safety of active surveillance.



Prevention by personalised interventions

Personalised interventions have significant potential to improve prevention. Tamoxifen has known benefits for reducing the incidence of invasive oestrogen receptor (ER)-positive breast cancer,³¹ although the side-effect profile can reduce compliance with therapy. Current biomarkers, such as oestrogen exposure, are not optimal for selecting those patients at highest risk of ER-positive breast cancer who will benefit most from using ER modulators, or who will experience the highest level of side-effects.

Other biomarkers such as breast density, genomic-based biomarkers and the presence of breast cancer precursor lesions may aid selection of the subgroup of patients most likely to benefit from chemoprevention in the future, such as a polygenic risk score using 88 SNPs which is predictive of ER-positive breast cancer risk.³² The development of targeted, preventive interventions for inherited cancers is being supported by the HeritX organisation, which aims to characterise normal breast tissue, DCIS and invasive breast cancer lesions in *BRCA1* mutation carriers and to identify recurrent early oncoantigens and immunosuppressive conditions in *BRCA1*-associated breast cancer development.

Summary

- Biomarkers have a number of different applications in healthcare

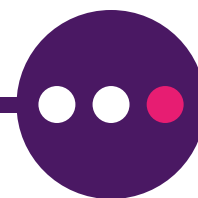
Biomarkers can be used to answer a host of questions relating to prediction, diagnosis, therapeutic choice, prognosis, pharmacodynamics and likelihood of cancer recurrence. In early detection, novel markers such as ctDNA are areas of intensive research as are methods to distinguish benign and malignant lesions.

- There are challenges to overcome in applying knowledge about biomarkers

Development of biomarkers for healthcare settings can be technically demanding. It is important that the desired sensitivity and specificity of a screening test is defined prior to or during its development, in order to ascertain the likelihood of its clinical utility and the rate of false positive results requiring further investigations to definitively refute a diagnosis of breast cancer.

- Using emerging biomarker knowledge to improve current prevention pathways

Emerging biomarker knowledge could be used along with current knowledge to improve pathways. For example, it is feasible that the future use of biomarkers in personalised prevention could extend to *BRCA* mutation testing for all women and annual blood tests for early detection, which could inform personalised, risk-adapted screening approaches and targeted preventive interventions for those in the highest risk groups.



3.3 Biosensors for cancer diagnosis and patient stratification: electrochemical protein and DNA sensors

Dr. Pedro Estrela (Senior Lecturer, from the Centre for Biosensors, Bioelectronics and Biodevices at the University of Bath) presented on how developments in biosensors might contribute to personalised breast cancer prevention.

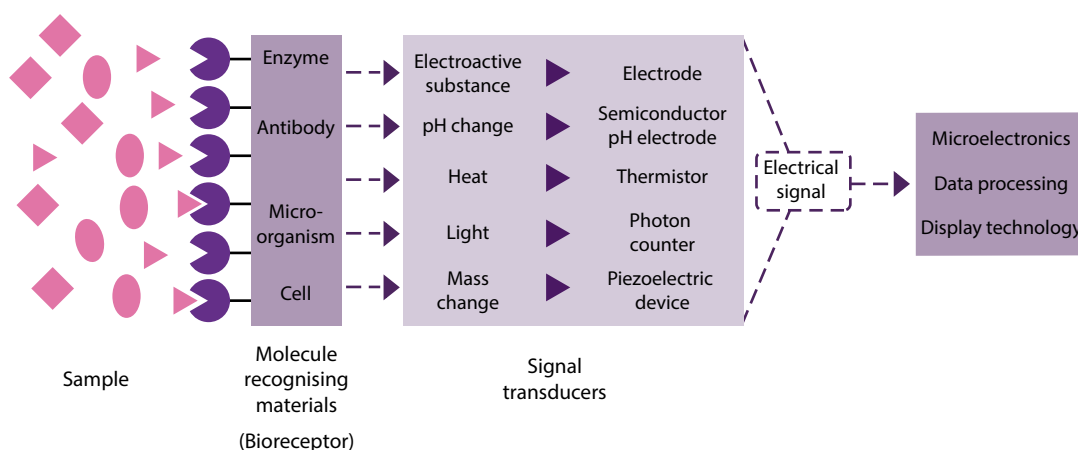
Key points

- Biosensors have the ability to detect a wide range of molecules
- Appropriate sampling is paramount, and consideration must be given to the presence and relevance of biomarkers in different bodily fluids
- Understanding biology is important in developing biosensor applications

Introduction to biosensors

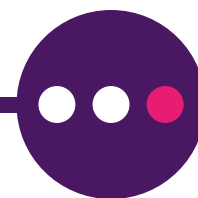
The definition of a biosensor is “a device incorporating a biochemical sensing element either intimately connected to or integrated within a transducer”. The integral components of a biosensor include biomolecular recognition elements, signal transducers and microelectronics and display technologies (Figure 6).

Figure 6: Elements of biosensors



Source: adapted from slides provided by P. Estrela

Each of these elements impacts on the type and functioning of the biosensor. For example, the size of the molecule to be detected plays a key role in determining the type of sensor to be used. The development of nanotechnologies has enabled substantial progress in the evolution of biosensors towards detection of single molecules.



The availability of a range of biochemical receptors will be important for developing a new generation of biosensors. Suitable molecular probes for detecting protein biomarkers include antibodies, antibody fragments and peptides, and synthetic molecules such as affirmers (peptide aptamers), DNA aptamers and molecular imprinted polymers.

Potential applications of biosensors

DNA aptamers may be of use in monitoring circulating concentrations of therapeutic compounds to ensure that they are maintained within therapeutic ranges.³³ They have also been developed for detecting prostate specific antigen (PSA) at clinically relevant concentrations.^{34, 35} More information regarding the stage and prognosis of cancer can be generated through measuring microRNAs (miRNAs) as 'fingerprints' of cancer. Of relevance to prostate cancer, miRNA-145 can be detected using a peptide nucleic acid (PNA)-based sensor at femtomolar concentrations.³⁶ PNA is an analogue DNA of neutral charge that, in combination with gold nanoparticles, generates changes in capacitance upon binding miRNAs. Peptide aptamers are small artificial proteins with peptide inserts that bind to their targets with high specificity and affinity, and have been applied to the detection of biomarkers relevant to cancer such as cyclin dependent kinase (CDK)-2 and Her4.³⁷

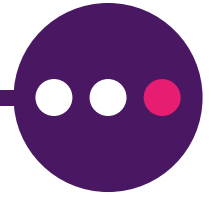
All of these technologies are easy to multiplex, by which multiple biosensing elements can be mounted onto one chip as part of a multichannel sensor. Potentially, multichannel sensors with multiple transistors could be used to measure individual biomarkers and to generate insights into correlations between multiple biomarkers in certain disease states. Current capabilities allow detection of up to eight biomarkers simultaneously, which could potentially be used in the context of cancer should biomarkers and patterns of biomarkers with sufficient specificity for different tumour types be identified.

Lab-on-a-chip

Going forward, it will be important to be able to start developing complex matrices that enable the burden of sample preparation and purification to be reduced, as this constitutes most of the workload involved in processing a sample. 'Lab-on-a-chip' approaches have been developed which have integrated and miniaturised complex systems performing sample manipulation and analysis. Subsystems include microfluidic control units, sample processing units, and components performing biochemical reactions, detection, quantification, and system integration. These also have the potential to be combined with antennae, mobile phones and cloud storage, and to provide continuous monitoring.

Continuous monitoring

Continuous monitoring can be provided through wearable devices, for which glucose monitoring is the most common application. It may also be useful for surveillance and monitoring in the context of cancer. A range of electrochemical sensing approaches can be used for the detection of biomarkers or panels of biomarkers in complex samples, such as proteins, miRNAs, ctDNA and CTCs. Such sensors are low-cost, amenable to being multiplexed and miniaturised, and can be integrated with easy-to-use point of care readers for diagnosis, prognosis, surveillance, and monitoring of treatment. The use of synthetic receptors can enhance the specificity of the sensors, enabling better diagnosis and stratification, and the delivery of personalised approaches.



Summary

- Biosensors have the ability to detect a wide range of molecules

Developments in biosensors are enabling a larger array of molecules to be detected. However, whilst it is possible to develop biosensors capable of detecting single molecules, questions remain regarding the utility of such technologies in clinical practice. Capturing a single molecule in a biological sample is probabilistically low and offers no insight into the concentration of the molecule at the whole body level. It is most likely that panels of biomarkers will be most informative for the purposes of prediction, diagnosis and/or prognosis.

- Appropriate sampling is paramount, and consideration must be given to the presence and relevance of biomarkers in different bodily fluids

In the future, sensors will be low cost and easy to use at the point of care. However, whilst biosensors themselves can be adapted to suit different biological samples, some sampling sites are unsuitable for accessing particular molecules, such as detecting circulating proteins through skin.

- Understanding biology is important in developing biosensor applications

There will be some hurdles to overcome in the future development of biosensors, in order for applications to be realised. Circulating concentrations of biomarkers such as ctDNA may be too low to permit detection and measurement. Furthermore, our understanding of the correlation of biomarkers (including ctDNA, protein and RNA) with different types and stages of cancer remains incomplete, and necessitates further investigation.

3.4 The role of wearables and apps in prevention

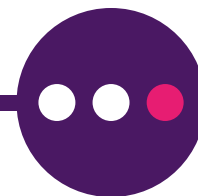
Louise Brennan (a chartered physiotherapist at Beacon Hospital, Dublin and PhD researcher in cancer rehabilitation and connected health at University College, Dublin) presented an overview of the current capabilities of apps and wearables.

Key points

- Wearables and apps come in a variety of forms
- Wearable sensors and apps can help with managing modifiable risk factors and facilitate research
- Quality, safety and effectiveness are barriers to widespread adoption in healthcare
- A robust regulatory framework can ensure effective uptake

Introduction to apps and wearables

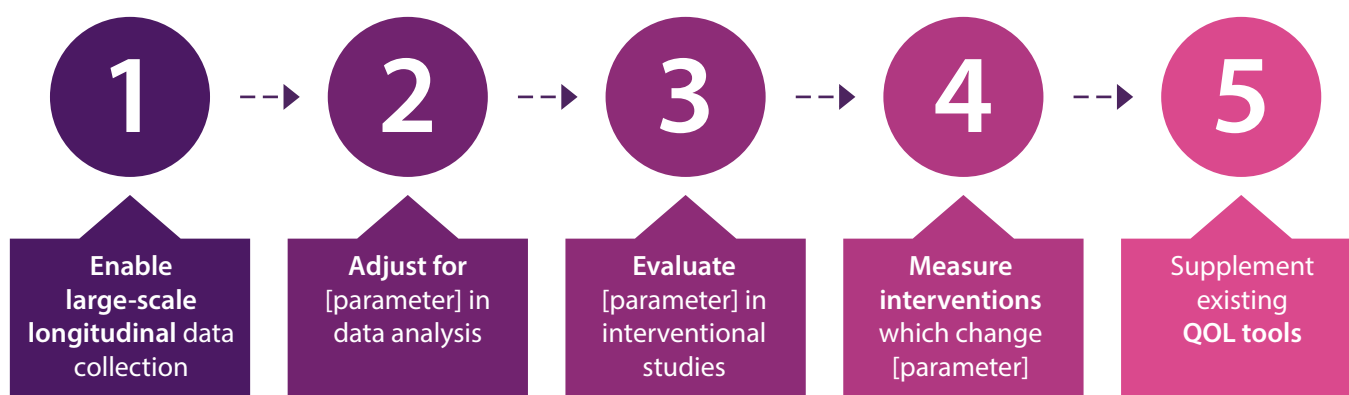
Apps are software designed for mobile devices, and wearables are sensors worn on the body that collect longitudinal data. Both fall under the umbrella of 'mHealth' technologies, and although often used in conjunction, they can also be used as standalone technologies. They can be used for a variety of purposes: to objectively measure different parameters; for 'real world' and momentary data collection; to identify at-risk individuals; to deliver personalised feedback and education; and to provide motivation for behaviour change and the adoption of healthy behaviours.



Current capabilities

Apps and wearables can be used in a variety of ways for the management of modifiable risk factors and in research and development (Figure 7). A fictional case study was used to highlight the potential for relatively simple apps and wearables system to facilitate behaviour change and improve health systems. It also demonstrated that, despite the hype around advanced and complex new mHealth technologies, simple technologies such as video chat and lifestyle monitoring apps can be extremely effective tools if used and embedded into the health system correctly.

Figure 7. Apps and wearables for management of modifiable risk factors



Source: adapted from slides provided by L.Brennan

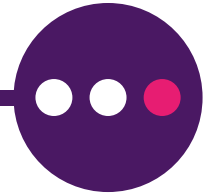
Barriers to the use of apps and wearables

Quality and validity concerns

A recent review conducted on the use of mobile applications for breast cancer identified 61 apps on the iTunes Apps store and the Google Play store (which together represent 98.9% of the smartphone app market share).³⁸ This is a dramatic increase since 2013, when a similar review by Bender *et al.*³⁹ found three such apps. A lack of appropriate oversight means that many of these apps are shrouded in quality and validity concerns.

Lack of safety and effectiveness guidance

Good apps with reliable information exist amidst a host of poor quality ones, with no reliable way for the public to distinguish between the two and no indication of the qualifications of the developers. The public tend to look to star ratings for guidance, but this does not always reflect the quality of the app (for example, some highly-rated apps promote treatments which have little or no scientific basis). Due to the lack of guidance and regulatory oversight, apps that have not been recommended by a healthcare professional are an inadvisable way for individuals to search for health advice.



Falling user engagement

There are also barriers to the sustained use of wearables, with studies finding that 50% of people no longer use their wearable device and one third cease use within the first six months of purchase.⁴⁰ This can occur due to a number of factors, including usability of the device, practicality (e.g. battery life), compatibility with other apps and wearables, a lack of user-centric design, and privacy and security concerns (e.g. privacy of personal data and device vulnerability to hacking).⁴¹

Looking to the future

The proliferation and ease of use of smartphones make mHealth a convenient and appealing option for individuals interested in their health. Better engagement with the users could lead to improved health outcomes. For this, devices need to be functional, reliable, usable, convenient and, crucially, enjoyable and meaningful for the user. Individuals are more likely to engage with an app if it has personal significance for them. Apps provide a means of delivering interventions and prevention programmes in a variety of different ways so as to be accessible to the whole population.

Apps and wearables need to improve in order to be able to deliver greater health benefits through:

- Improved engagement with users
- Smarter, smaller, seamless sensors
- Advanced data analytics
- Development of a more robust regulatory framework
- Interconnected networks of sensors and systems

Summary

- Wearables and apps come in a variety of forms

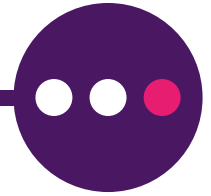
mHealth can range from simple technologies such as video chats to more complex analytical or decision support systems.

- Wearable sensors and apps can help with managing modifiable risk factors and facilitate research

Benefits include providing objective measurements of biological parameters, delivering personalised feedback and enabling large-scale, longitudinal data collection.

- Quality, safety and effectiveness are barriers to widespread adoption in healthcare

Although studies are underway examining the effectiveness of apps and wearables for healthcare, the evidence base is still lacking, especially from long-term randomised clinical trials. However, this evidence may be hard to collect in an evolving technological landscape.



- A robust regulatory framework can ensure effective uptake

In the future, a robust regulatory framework for apps should be in place. Rigorous regulation and international communication is needed, so that the intense work of ensuring that every aspect of an app is safe for the public is not duplicated. This is to protect patients, but must not hamper innovation.

3.5 How digital disintermediation (apps) and cloud computing change the precision prevention landscape

Professor Jonas Almeida (Chief Technology Officer from Stony Brook University, USA) provided an overview of how advances in digital technologies and precision analytics is changing and enabling precision prevention.

The previous talks have illustrated how technologies such as wearable sensors, apps and consumer-facing information systems are changing the healthcare landscape profoundly, not just for cancer,⁴² but also in the way they configure the digital neighbourhood of individuals. This is creating opportunities to form a learning health system and is enabling the move away from traditional models of evidence-based medicine based on randomised control trials.

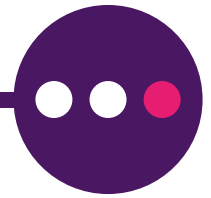
Key points

- The digital environment for individuals is changing
- Broader trends towards patient centred information systems are likely to overcome current technological or regulatory barriers
- Critical interpretation of outputs will always be needed

Impact of digital technologies on prevention

The stratification of risk by wearable devices and consumer-facing genomics services changes fundamentally how disease is studied and what signals best serve the goal of preventing it.^{43,44} Precision prevention is being enabled in ways that had been predicted by Predictive, Preventive, Personalised and Participatory (P4) medicine but also in ways that derive from artificial intelligence (AI), wearable sensors and more broadly, consumer facing digital technologies.

Looking further ahead towards a 20 year horizon, it is tempting to predict that the digital neighbourhood of each individual will include a continuum of apps and sensors that can be used in ways that fill the continuum between health (e.g. fitness) and disease. Apps (particularly WebApps) bring real-time ubiquity to the reporting and contextualisation of sensor data. This is likely to disintermediate the traditional hospital-bound 'Patient Portal'. In a nutshell, patients will follow their apps into preventive behaviours as well as treatment courses.



New tools for data analysis

Advances in the past two generations of methodologies have led to the preeminent role of modern data science in precision prevention. Most data analytical methods are not breast cancer specific and many are not even specific to biomedicine, while at the same time playing the key function of risk stratification with increasing granularity. These new tools are giving us the ability to carry out integrative analysis, develop artificial intelligence and computational disintermediation.

Given the complex nature of many common diseases, the argument for very large scale longitudinal studies such as AllOfUs⁴⁵ is likely to become the norm in the next two decades. At that scale, information systems that aggregate the reference big data for fine grained stratification of risk will require the use of Cloud Computing. The set of technical specifications and policy frameworks needed to manage the new data assets and related analytical pipelines is taking form as Data Commons, of which TCGA-derived Cancer Genomics Commons (CGC) provides a template.⁴⁶ One has to expect that these large scale community-driven resources will become the critical reference for breast cancer prevention in 20 years, when the longitudinal records of these large scale cohorts allow for the resolution of cumulative risk factors that could not have been detected any other way.

Data versus information

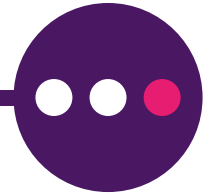
A tension in biomedical research is ensuring the correct balance between mechanisms for data protection and data sharing to accelerate research that can lead to health benefits. Increasing amounts of data lead to greater opportunities to make scientific discoveries but this has to be balanced against the risks of bringing together diverse data sets, which could lead, for example, to issues for de-identification. This can also work against citizen partnering and participation.

Studies have shown that approximately 50% of people are prepared to share all their data and 25% are unwilling to share any of their data. Even if only 1% of a population share all of their data, this could enable creation of enough of a data landscape to facilitate analytics. Consequently, data is not needed from everyone, but just enough is required to populate a domain of possibilities. Ecosystems to support this in open source environments are being developed. The fact that the code is open source allows verification which can lead to increased participation by increasing trust.

Data and information can and should be managed differently. For example, the genetic code is data and once interpreted provides information. The separation of these two components can enable the development of resources that can be interrogated by multiple users.

Predicting versus modelling

Machine learning techniques permit analysis of large volumes of data to produce meaningful answers, enabling variable selection for models, sensitivity analysis to evaluate them and identification of variables that are not being measured. This is enabling a move towards multiple different ways of achieving the same answer and loss of a specialised definition of what constitutes a biosensor. Application of machine learning to such resources can potentially provide better prediction that is hypothesis free. However, we still need to carefully interpret the outputs and ensure they are valid.



Understanding preferences

Breast cancer has well-defined genomic and environmental risk factors. However, as with most other tumour types, the molecular modulation of tumourigenesis is complex, and so is the response to targeted therapies. This will only increase the difficulty of engaging the patient in decision making that avoids false positives^{47,48}. However, creating a learning health system that is able to carry out micro-trials much in the same way as software systems, could help develop mechanisms that take into consideration patient/user preferences.

Summary

- The digital environment for individuals is changing

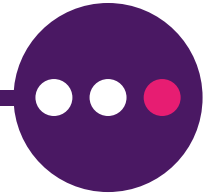
Precision prevention is being enabled in ways that had been predicted by P4 medicine but also in ways that derive from advances in artificial intelligence, wearable sensors and, more broadly, consumer-facing digital technologies that are leading to the availability of increasing amounts of data.

- Broader trends towards patient centred information systems are likely to overcome current technological or regulatory barriers

The way we approach big data analysis is fundamentally changing i.e. how, where and by whom. With an increased move towards participatory, partnered collaboration between citizens and researchers, data ecosystems are emerging to support this in open source environments.

- Critical interpretation of outputs will always be needed

Although we are developing technical capabilities to amass and analyse vast amounts of data, key to gaining information and knowledge from data is the critical interpretation of outputs to ensure they are valid and useful.



4 Identifying opportunities for personalisation

4.1 Discussant reflections

We asked discussants with backgrounds in different areas of healthcare to provide some feedback and thoughts on how current knowledge could be used to personalise prevention over the next five years. The aim was to gather thoughts on the clinical scenarios where detailed risk assessment could add value, highlight what the needs are throughout the care pathway and to consider if these are likely to change over the next five years given evolving knowledge.

Public Health

Don Lavoie (Alcohol Programme Manager for Public Health England) provided thoughts from a general public health perspective.

Public health efforts to prevent breast cancer work at many different levels, from efforts concentrated around particular risk factors, such as alcohol, to provision of screening programmes. For example, with respect to alcohol, in the United Kingdom the stance is that there is no safe level of alcohol that confers a low risk of breast cancer. Consequently, from a broad population perspective with respect to messages about alcohol and risk, population risk stratification currently does not offer opportunities for personalisation. However, raising awareness of risk factors such as alcohol should be considered, given lack of knowledge in the general population of its association with breast cancer.

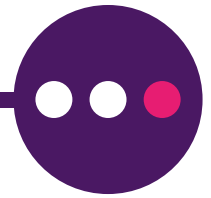
Don Lavoie speculated whether there are missed opportunities for prevention, especially for increasing awareness in younger women who are not the focus of current breast cancer screening programmes. He questioned whether women's reproductive health services at different life stages (e.g. HPV vaccination or contraceptive advice) provide an opportunity for healthcare providers to increase awareness about breast cancer risk. This raises important questions as to what extent health services want to engage in active prevention of breast cancer at the level of the general population. This is highlighted by the debates around proactive identification of women with a family history of cancer, which is currently not a part of prevention efforts in many European countries.

In conclusion, it is clear that the science with respect to risk stratification is encouraging and what needs to be considered is how this is placed with respect to broader public health initiatives. There may be opportunities to discuss risk with individuals when they come into contact with health services, but this requires communicating the information in a way that is meaningful to individuals.

Screening

Dr Mireille Broeders (Associate Professor at Radboud University Medical Center in the Netherlands) provided thoughts from the perspective of screening.

In the context of breast cancer screening by modalities such as mammography or MRI, the potential to tailor screening regimes according to risk is believed to lead to a more beneficial programme. It is clear that current knowledge can be used to stratify populations either using individual factors such as mammographic density or multiple factors through risk prediction models.



Two key bottlenecks to implementation are:

- Firstly, a clear consensus on when risk tools can be considered to be ready for clinical implementation. This is important given the variety of currently available approaches to risk stratification
- Secondly, there is still incomplete understanding as to what subsequent pathways of care will encompass for populations at different levels of risk. Establishing subsequent pathways requires collaboration between those involved in developing risk tools and healthcare providers to map out these pathways and assess if they have clinical utility

In practical terms, it is clear that tailoring screening to risk will require a programme that involves multiple players, including risk communicators and potentially other imaging specialists. Current regimes consist solely of an appointment with a radiographer for a mammogram. Consequently, moving away from current provision will require a major shift in the way that breast cancer screening programmes are delivered with implications for resources in terms of personnel and investment.

Ultimately, screening programmes are providing a service for women and their participation is required to run a successful programme. Consequently, the shape of screening programmes will also need to take into consideration individual willingness and need for such a programme.

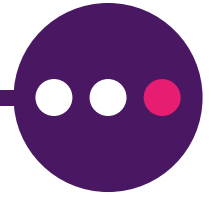
Focus groups carried out in the Netherlands, Sweden and UK indicate risk communication is key. In addition to risk information, women are interested in understanding factors that contribute to their personal risk estimate. However, this is not an easy task.

The focus groups also indicate that there are uncertainties amongst the general population about the likely impact of behaviour change aimed at lifestyle risk factors. In addition, risk reducing medications do not have a favourable perception.

Primary care

Dr. Juliet Usher-Smith (GP and Cancer Research UK Prevention Fellow from the University of Cambridge) provided a primary care perspective.

Primary care is usually the first point of contact for individuals concerned about their health. With respect to breast cancer, clinical decisions at this level are mostly concerned with ensuring the right individuals are referred on for secondary care led preventative interventions (e.g. enhanced screening, chemoprevention, genetic testing etc.). In the majority of cases, these are individuals who self-present and are deemed to cross a set threshold and considered at moderate/high risk. Assessing this risk level is usually based solely on assessment of family history.



Two important questions are raised by evolving capabilities in risk stratification. Firstly, can the risk models help better identify individuals who are likely to benefit from these preventative interventions and/or enable more accurate identification of individuals for onward referral? Secondly, should we be moving towards a more proactive system at the primary care level to identify individuals who are likely to benefit from preventative interventions? Both require consideration of the data available within primary care.

Given that current knowledge indicates that information on mammographic density and SNP profile can alter risk categorisation, consideration needs to be given to how this impacts on current practice in determining risk and onward referral. This raises the issue of how accurate risk determination needs to be at the primary care level and whether less information can be used to inform onward referral.

Current methods of assessing risk are based on family history, although tools to collect this information are not optimal. However, this is an evolving field and in 20 years' time it is likely that tools to collect this information as well as SNP profiling will be more easily obtainable. Even if data is obtainable, identifying what data are sufficient for different groups of individuals, when it is obtained and how often it needs to be updated need to be considered. This requires consideration of how breast cancer risk models would work in primary care and accumulation of evidence in support of their benefit.

With respect to preventative interventions, general practitioners are also well-placed to provide health promotion advice. This may not require risk stratification but will require improving health professional education with regards to the links between lifestyle factors and cancer. It also requires supportive services that enable individuals to act on health promotion advice. Attempts are being made to do this through the development of a risk tool for five different cancers being trialled through the NHS Health Check programme.⁴⁹

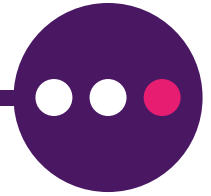
In addition to health promotion, general practitioners are also well-placed to offer drug therapies. Research has reported a number of barriers, particularly to initiating such therapies within primary care. However, a shared process between different levels of care may enable general practitioners to feel better supported with such therapies, once a particular regimen has been agreed upon.

Similarly to other discussants, Dr. Usher-Smith stressed the importance of risk communication and the challenges associated with this.

Secondary and tertiary care

Dr. Suzette Delaloge (a medical oncologist from the Institute Gustave Roussy in France) provided a perspective from secondary/tertiary care.

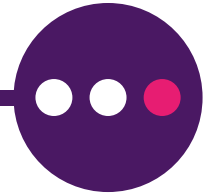
Dr. Delaloge made a distinction between personalised prevention and precision prevention. Personalised prevention works at the general population level to better deliver preventative interventions, mainly in the form of screening.



Precision prevention sits within the domain of secondary and tertiary care and aims to cater for the needs of high risk individuals. In this setting, risk stratification is a mechanism for identifying areas where there is a medical need and developing novel targeted therapies. It could lead to primary prevention in the form of drug therapies or enhanced screening. Current drug regimens have a negative perception, need to be taken over long periods of time, and have too many side effects which impacts on their uptake.

Dr. Delalogue stated that, although successful interventions were available in the form of prophylactic surgery and chemopreventative agents, more options are needed, especially in the form of short-term therapies that target the disease early in a subclinical phase. Such therapies may not be breast cancer specific, but target particular mutations early in disease development. They will be aided by the development in the field of oncology of novel methods to identify biomarkers for preclinical disease.

Thus, in the 20 year future it may be possible to screen women using ctDNA and treat them once existence of subclinical disease is identified. This will require the design of appropriate trials involving smaller numbers of participants to test interventions in early trials followed by larger trials to test and launch them. It is important to involve patients in this process to ensure that available interventions are understandable and acceptable. Consideration also needs to be given to the economic viability of such models of care, which involve shorter treatment spans such as the Hepatitis or HPV vaccine model, which may not appeal to current developers of therapies.



5 Break-out session – prevention pathways

5.1 Background

Recent research has increased knowledge of the genes underlying the heritability of breast cancer and has led to the development of refined tools for risk assessment. The use of these tools to enable personalisation of prevention pathways is a matter of much debate and discussion. There is little consensus about how current and forthcoming knowledge could be used in breast cancer prevention pathways.

During this session the delegates were assigned to three facilitated small groups to discuss how personalised prevention pathways could be developed over the five year timescale. Although the intention during this session was to identify how prevention pathways might change over the next five years, discussions were more fluid and also considered the longer, 20 year horizon. Consequently, the summary of the discussions presented below incorporates both these timescales.

Discussions were framed around key features and stages of the pathways with participants providing expert knowledge from scientific projects such as B-CAST and bringing perspectives from public health, screening, primary, secondary and tertiary care. Participants were provided with a schematic of the current pathway, which they could annotate to indicate potential strategies for prevention (Figure 8). Below is a summary of the various themes that emerged from the group discussions.

The questions posed to participants were as follows:

- What groups should be identified for preventive interventions?
- How should target groups be identified?
- How would risk assessment fit within the prevention pathway?
- What changes are needed to the current pathway to achieve this?
- What needs to happen to achieve these changes?

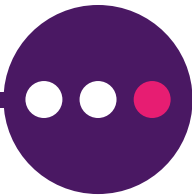
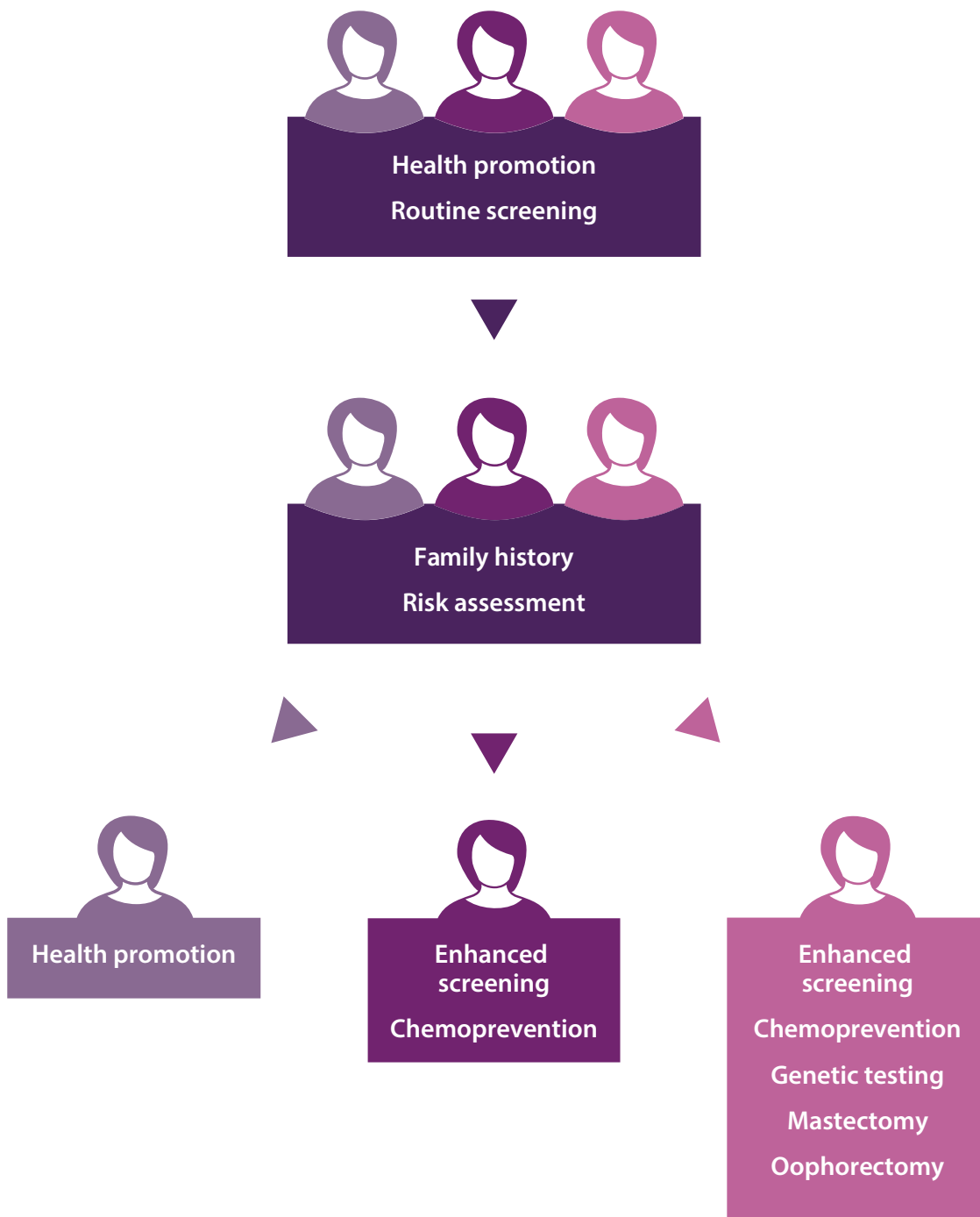
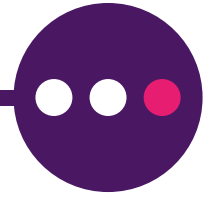


Figure 8: Schematic of current prevention pathway





5.2 What groups should be identified for preventive interventions?

Participants felt that breast cancer prevention should consist of population-wide and risk-based preventive interventions. Population-wide structural, health promotional and education messages that raise awareness are expected to have a large impact across all risk categories. Hence they were considered as equally important as identifying particular sub-groups for preventative interventions.

In addition, such population-wide measures will also play a role in supporting personalised prevention by assisting in the assessment and identification of particular sub-groups at increased risk.

For risk-based interventions, delegates suggested it would be useful to be able to identify:

- Women at increased risk of developing fatal breast cancer – this is not possible currently but may become feasible over a 20 year horizon with risk tools aimed at specific sub-types of disease
- Women at low risk who could be excluded from active preventive pathways
- Women with a high risk of disease due to family history at the age of 20 or 30 years. This is because these women tend to develop disease at a younger age and treatment options may have an impact on their reproductive decision making. In addition, identification of at risk women at an earlier age has the advantage of earlier instigation of preventative interventions

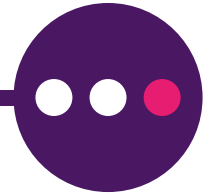
Discussions around these sub-groups raised questions as to a) whether risk assessment can allow better identification of women eligible for available interventions and b) does risk assessment enable benefit in terms of prevention pathways?

There was a tension between the ability to better refine risk categorisation and the implications of this for subsequent management leading to uncertainty about who would benefit from preventative interventions.

5.3 How should groups be identified?

Tools for different at-risk populations

It is theoretically possible to identify groups of women at differing levels of risk using various strategies alone or in combination, including genetic testing, measurement of mammographic density, family history assessment or comprehensive risk assessment based on genetic and clinical risk factors. Over the next five to twenty years women at varying levels of risk could be identified using a broad range of markers, although it was acknowledged that this information needs to be carefully interpreted as particular risk factors or biomarkers may be more informative in different scenarios and different life stages. Therefore, different strategies are likely to be needed depending on the purpose of the risk assessment, taking into consideration the life stage of the individual.



Proactive or reactive identification

It is possible to identify a larger proportion of women eligible for management by family health clinics. This would be through a more proactive approach to collection of family history data or through the offer of genetic testing for genes linked to moderate-high risk of breast cancer at a general population level during early adulthood.

It was postulated that these strategies could potentially be offered at the primary care level in order to better identify women who could then access more comprehensive risk assessment and counselling at risk assessment centres. However, a proactive approach would mean that individuals might not have the opportunity to express a view as to whether they wish to be informed about future risk of breast cancer. There is also a possibility of ensuing harm from the potential worry as a result of this.

For more general risk assessment there was no agreement as to whether this should be part of a proactive programme, provided on an opportunistic basis (and if so to whom), or whether it was something that would simply be made available to those who expressed an interest.

Time point (age) for identification

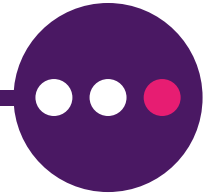
The participants could not suggest a single, optimal time point where more systematic risk assessment would allow better identification of those at increased risk. This was due to the evolving nature of risk factors through the life-course. For example, although mammographic density is a recognised risk factor, it may not be useful in assessing risk in those below the age of 40 and there is no evidence-based programme of care for this subgroup. Identifying those with a high risk due to genetic factors is also problematic because it needs to be interpreted in light of family history. Taking a sufficiently detailed family history is not simple and this information changes over time; conversely, although genetic information is stable, there are currently ethical concerns about widespread genetic testing (informed consent, privacy and confidentiality, genetic responsibility and genetic discrimination etc.).

5.4 How would risk assessment be incorporated into the prevention pathway?

Risk assessment tools bring together multiple sets of information and can help to inform decision making. The types of models and the risk factors included impact on clinical use. Risk assessment was discussed by participants as providing two slightly different purposes; to inform individual and clinical decision making at different stages of the pathway.

Risk assessment to inform individual decision making

Detailed risk assessment could be useful to assist an individual in making future decisions to prevent breast cancer. For example, a novel role for risk assessment could be in enabling a woman to make better informed decisions about subsequent involvement with health services, such as participating in early detection programmes or uptake of genetic services. However, this is reliant on ensuring that the information and knowledge gained from a risk assessment is conveyed in an appropriate, accessible, timely and useful fashion to both health professionals and individuals.



Risk stratification to inform intervention choices

Improved risk categorisation could enable risk stratification and inform preventive interventions, including lifestyle advice, preventive therapies or early detection to be targeted optimally. This is already used to some extent in secondary and tertiary care settings.

Participants discussed how risk tools could be applied to existing screening cohorts to create more effective screening programmes. This could be, for example, to better identify women who would need additional examinations following a negative screening mammogram or those who may benefit from less frequent mammograms.

The future application of risk assessment at the general population level leading to a risk-based prevention and early detection programme were also discussed. This information could inform an individual's decision about screening attendance or the health system's offer of screening frequency or mode of screening (e.g. women with dense breasts may need alternative or additional screening tests). It could also be a potential mechanism to enable women to understand and address risk factors or take up other prevention pathways, such as chemoprevention (though in the discussions it was recognised this was unpopular among women), or enhanced surveillance.

It was suggested that it would be important to consider how risk assessment by sub-type could inform early detection programmes. For example, in those with a high risk of triple negative breast cancer, earlier screening with MRI might be a better detection modality.

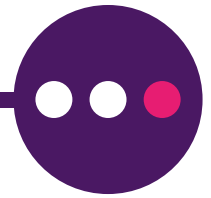
5.5 What changes are needed to the current pathway to achieve this?

It was recognised that although the current pathway offered some elements of preventive activities through educational material, the focus is primarily on early detection via provision of a test – mammography starting at around 47 years. Currently, there is little interaction with a healthcare professional to discuss risk and possible mechanisms to reduce risk.

Participants postulated that the availability of detailed risk assessment for breast cancer could alter current pathways in many different ways, from incremental additions to restructuring and creation of a diverse risk-based prevention and early detection programme.

The groups discussed incorporating breast cancer risk assessment within other chronic disease prevention programmes (for example as part of the UK Health Check programme), which could then form part of a holistic approach through which individuals maintain their health.

Participants were unsure whether improvements were needed to current early detection programmes to incorporate a risk-based approach. This uncertainty arose because risk-based interventions were not available across the whole spectrum of risk categories and, where they did exist, there was insufficient evidence of benefit, with the exception of risk-reducing surgery for *BRCA1/2* mutation carriers. It is thus unclear if a risk-adapted mode of early detection is more efficacious than the current paradigm based solely on age in the general population and thus whether there should be a change in the way women are approached for early detection. Randomized clinical trials such as MyPeBS and WISDOM may provide some evidence but these programmes are currently still in the early stages.



From a practical point of view, providing diverse pathways of care on the basis of a range of risks would require a greater level of resources and investment, particularly for personnel, including health professionals to carry out risk assessment and provide subsequent counselling around the information provided. Radiographers able to undertake and understand the significance of different types of screening would also be required.

5.6 What needs to happen to achieve these changes?

Participants discussed the requirements for a move towards more personalised, risk-based prevention of breast cancer. Some of the areas identified through the discussion are presented below.

Need for evidence

Participants agreed that current scientific knowledge and technologies enable improved risk assessment and stratification based on multiple risk factors, but that evidence for clinical utility of risk-based prevention for breast cancer is still lacking. Achieving this requires consensus on what preventive interventions would be offered to individuals at differing levels of risk, based on evidence of benefit for these differing pathways. It will also require collaborative working with policy makers, health professionals, citizens and researchers to develop pathways of care that are mutually acceptable.

Although on-going studies will answer some clinical questions, considerations for the future include study designs and the level of evidence needed to implement change and to ensure that validated tools for risk assessment become available for more widespread use.

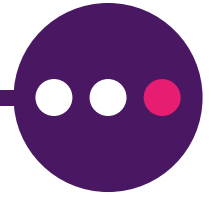
Improving the linkage between clinical systems and the research arena to improve the use of existing resources would be a possible mechanism to improve the evidence base and allow for a learning healthcare system. For example, in the UK, better collection and integration of data on family history, identified genetic variants and outcomes of screening in those at moderate risk could lead to a quality assured programme for these individuals. It was also suggested that information should be gathered from ad hoc use of existing tools to gain a better understanding of utility.

Developing infrastructure

Participants felt that supporting the use of risk tools and developing the evidence base is reliant on harnessing IT/digital support to streamline pathways and enable the flow of patient data across the system.

Although risk assessment centres are currently available, these are primarily for the management of individuals with a family history who may be at high risk. The participants discussed the potential for equivalent centres for individuals from the general population interested in understanding their risk, addressing risk factors and maintaining their health. Such dedicated centres for risk and prevention would require suitably trained healthcare professionals, including experts in health promotion, risk communication, risk assessment and radiography.

Incorporation of novel biomarkers (e.g. mammographic density/SNPs) will also require mechanisms and infrastructure to collect, store and analyse relevant data.



Bottlenecks

As risk assessment tools are considered medical devices there is a need to adapt regulatory frameworks to make the processes to achieve accreditation understandable, easier and more streamlined. This will be important to ensure appropriate implementation.

The challenge of the lack of preventative therapies for risk-adapted prevention could be addressed by encouraging industry investment.

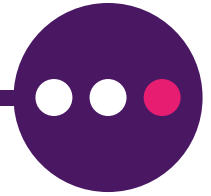
Finally, participants acknowledged that a variety of risk assessment tools are available and more sophisticated fully integrated models are on the horizon. Along with the academic sector, the commercial sector is becoming a significant source of such tools and of genetic testing. It is important that policy makers, health professionals and individuals should have an evidence base available for informed decision making as well as considering the role of these tool within prevention pathways.

5.7 Summary

Generally, the ability to categorise risk has advanced more quickly than the availability of evidence of utility for preventive pathways for different levels of risk information. Evidence about the effectiveness of preventive interventions for individuals at different levels of risk is limited, particularly for individuals with no prior risk. Therefore, there is a tension between the ability to better refine risk categorisation and the implications of this for subsequent management, leading to uncertainty about who would benefit from preventative interventions.

Proactive versus reactive utilisation of risk information was a point of debate given the lack of consensus on which groups would benefit the most from existing preventative interventions beyond those already being identified (i.e. those eligible for screening or at-risk due to family history). Currently, there is no clear evidence that risk assessment could allow better identification of women who should be offered early detection programmes and, if it could, at what age this should be offered.

There was much discussion around how risk tools that bring together multiple sets of information could help move towards a prevention programme. Risk assessment using such tools could be incorporated at different stages of the pathway. It was acknowledged that different types of risk assessment provide differing information and need careful interpretation. In addition, informing individual and clinical decision making is reliant on understanding and appropriate communication of complex risk information to both patients and clinicians.



6 Breakout session – implications for health systems

6.1 Background

Personalised prevention envisages a future where individuals will access information on their risk of disease or possible early disease in order to take action to improve their health. The discussions of the previous breakout session as well as the series of talks covering technology areas, illustrated the evolving and dynamic nature of science and associated technological developments. This has resulted in the ability to accrue data and information using a variety of biomedical and/or digital technologies from diverse sources. Discourse during the course of the workshop has also touched upon issues that are raised by these emerging technologies and their adoption into health systems.

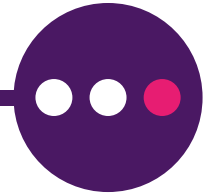
Many of these have been explored in the context of an on-going PHG Foundation project, [My Healthy Future](#), which explores the potential for personalised healthcare in 20 years' time through the lens of four life stages.

Some of the broad issues identified are outlined below:

- Ensuring technologies take into consideration the aims and values of individuals and populations
- Considering consequences for individuals (e.g. emotional impact) and society (potential diminution of public health emphasis)
- Risk of increasing health inequalities
- Risk of loss of person centred care
- Changes in professional practice
- The potential for overdiagnosis
- Practical and ethical issues related to data sharing
- Responsible use of citizen generated data
- Regulation of algorithms

The focus of this session was to identify and discuss issues and opportunities particularly relevant to personalised prevention of breast cancer. Due to time constraints, participants chose one of three groups (person centred care, overdiagnosis, health inequalities), to carry forward more in-depth discussion. Participants were given the opportunity to identify other issues that they felt were important and discuss alternate topics from the above list if time permitted.

It was clear from the discussions around these issues that technological advances could be considered as providing opportunities in each of these areas or act as barriers in the context of breast cancer prevention. Below, we summarise some of the opportunities and the issues that need to be considered and managed appropriately in order to facilitate the adoption of personalised care pathways.



6.2 The opportunities presented by personalised care pathways

Empowering individual choice

Participants felt that in the future we may expect a shift toward empowering patients through giving them greater control over their own data. Individuals would then be able to access healthcare in different ways at different points in their lives. It was seen to be an advantage that individuals would be proactive in contacting health services rather than waiting for the health system to identify them and offer care. In addition, by enabling individual choice, health systems would be better placed to provide person centred care (PCC).

Whilst limited choice was recognised as a necessary by-product of precision medicine, it was nonetheless thought that patients would still have control over their care. They could refuse treatment, even though it is better targeted, and should they choose to proceed they would be doing so with consideration for their own circumstances, preferred treatment pathways and personal outcomes.

Providing new avenues to engage with specific populations

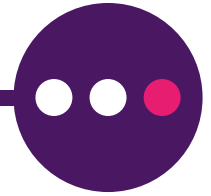
Although technologies could lead to increases in health inequalities they may also contribute to reducing these by providing means of engaging with a more diverse range of communities. For example, participants identified under-diagnosis of breast cancer in women who do not participate in screening programmes as an issue. Where breast cancer is diagnosed clinically in these women, tumours are often more advanced and more aggressive, and the women are less likely to comply with their treatment. Further efforts are required to better engage with these women and to encourage their attendance. Citizen generated data could provide a novel source of information to enable approaches to support patient engagement or develop culturally suitable access.

Increasing benefit by reducing overtreatment

Overall participants felt that although overdiagnosis was a concern, more concerning with respect to breast cancer was if this led to overtreatment. This was because many of the treatments for breast cancer were considered to be harmful (e.g. exposure to radiation via mammography or chemoprophylactic agents with potential short and long-term side effects). It was felt that the availability of technologies that could enable better discrimination (i.e. identifying those tumours that are likely to be harmful from those that are not) and increased specificity provided an opportunity to reduce overtreatment.

Linking person centred care and personalised healthcare

Person-centred care moves away from a paternalistic way of thinking about the patient's role, towards considering patients as co-producers of health, autonomous partners in treating, managing and preventing disease. Achieving this is reliant on ensuring that individuals are able to access and understand health related knowledge. As such, mechanisms that strive to enable PCC may also help to address health inequalities and help achieve genuine personalised healthcare.



6.3 Key factors that raise issues for individuals, health systems and society

Complex nature of breast cancer risk information

The move towards personalisation, as envisioned in the previous session, in many instances required greater engagement from individuals both in understanding risk and making decisions based on this information. Participants understood the fact that understanding and interpreting risk information is not an easy task and can serve as a barrier to equitable adoption.

Furthermore, it was recognised that the ability of individuals to engage with a preventative agenda may not be possible through all levels of society for a number of reasons. It requires individuals to have the capabilities and resources to be able to engage with preventative health behaviours when in fact limited access to technology, poor health literacy, and disinterest in one's own health can act as barriers to understanding and engagement.

Technology solutions not matching needs

Participants were unclear as to whether technology is likely to exacerbate existing health inequalities with respect to breast cancer prevention. However, they noted that it is important that consideration is given to whether this is likely to be the case. It was felt that supporting socially responsible user-centric technology development that addresses healthcare needs could mitigate against the potential rise in inequalities resulting from increased use of certain technologies.

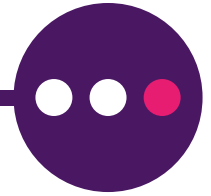
Conversely, there was concern that the availability, especially from the commercial sector, of devices that were aimed at populations who could afford them rather than at addressing healthcare needs or developing technological solutions for populations that would benefit the most, could lead to increases in health inequality.

Influx of data

Significant concerns were raised relating to the implications of new technologies for health systems and healthcare professionals, particularly with regard to the volume of health data generated, scope for overuse (particularly with continuous monitoring), the need for 'normal' reference ranges, risks of misinterpretation, and increased demands on clinical services. This also raised questions regarding clinical responsibility to review these new forms of patient data and decide whether they are clinically relevant and actionable.

Technical nature of precision medicine and its potential to limit patient choice

Participants felt it was important to maintain and enhance PCC and that this could be achieved by empowering patients. However, there were concerns that the increasingly technical and precise nature of medicine may also act as a barrier. Precision medicine is leading to more specialised care with clear and defined treatment pathways, which may impact upon patient choice. Helping patients maintain an aspect of choice, even where there is a clear therapeutic option is a dilemma.



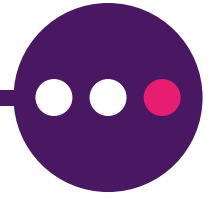
Technologies and the changing role of the clinician

There was some debate surrounding finding the balance between patient autonomy and professional guidance. The point was made that individuals go to a healthcare professional to get an expert opinion from someone with an understanding of the options and evidence base. Whilst a paternalistic approach is to be avoided, so is providing all the options without any guidance. Patients' levels of ability to make a decision themselves will depend on their activation level and so clinicians will need to tailor their interactions accordingly. This will require a shift in some healthcare professional's perceptions as to where control lies.

The increased use of direct to consumer technologies for accessing healthcare may require in some instances that the clinician's role evolves to that of translator or communicator, where patients need help interpreting information acquired from sources outside of the traditional health system.

6.4 Summary

It was clear from the conversations around the discussion topics that a move towards personalised prevention pathways provides opportunities to improve and enhance healthcare provision. However, adequate consideration needs to be given to a wide range of often interrelated issues that, if not addressed could impact negatively on technology implementation. Appropriate management of these issues is important in ensuring the benefits of a move towards personalisation outweigh the potential harms. It is clear that many of these issues are not just pertinent to the 20 year horizon but also apply to the implementation of current technologies.



7 Key findings

The objectives of the workshop were to attempt to:

- Develop a vision for a more personalised prevention pathway for breast cancer for the near term (five years) and the future (20 years)
- Identify health system and other societal requirements for moving towards a more personalised approach to breast cancer prevention now and in the future

In this report, we have provided an account of the workshop proceedings and below we summarise the key findings with respect to prevention pathways.

7.1 Vision for personalised prevention

Participants agreed that current and future breast cancer prevention should include population-wide and risk-based preventative interventions.

Structural, health promotional and education messages aimed at the whole population are vital because of their expected large impact across all categories of risk and in supporting personalised or individual-risk specific endeavours.

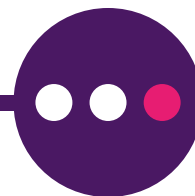
Identifying specific risk groups is a core element of personalised prevention. Workshop participants suggested that the following would be important:

- Women at increased risk of developing breast cancer likely to be fatal
- Women with a high risk of disease due genetic predisposition (as may be determined by family history and/or genetic testing)
- Women at low risk who are unlikely to benefit from mammographic screening

Breast cancer science is advancing rapidly. Increasingly sophisticated risk models and associated risk tools are being developed to improve risk assessment and population stratification based on multiple risk factors.

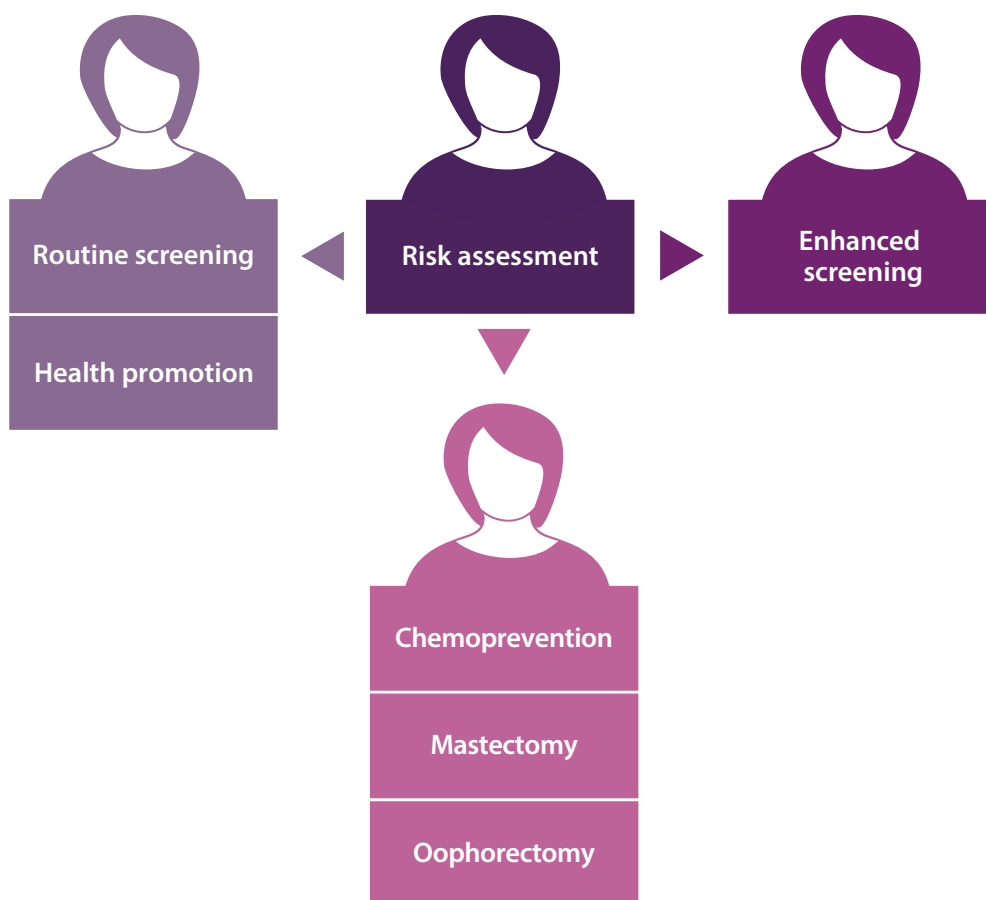
Risk assessment already informs prevention in those considered at high risk. In the near term, this may be refined by emerging knowledge, for example by incorporating mammographic density information or polygenic risk score into risk tools. The impact could also be increased by more proactive approaches to identifying those at high risk using more systematic collection and use of family history information or genetic testing.

Implementation of available risk tools and emerging technologies within prevention pathways could change current practice in different ways depending on the flexibility of the system. There may be incremental additions to existing pathways (Figure 9), with risk assessment being used as a tool to assist decision making at particular static points within the current healthcare pathway. Alternatively, a more complex, iterative and diverse risk-based prevention pathway (Figure 10) was envisioned in which the role of the new tools and technologies was more fluid, adaptable and responsive to the decision making needs of the individual and the healthcare system.



Currently no fully validated tools are available to enable risk-based prevention of breast cancer within the general population. However, this may become possible within the 20 year horizon particularly with the likely development of sub-type specific risk tools that are able to identify women at increased risk of mortality from breast cancer.

Figure 9. Risk assessment to inform specific interventions provided by health systems to women entering the prevention pathway



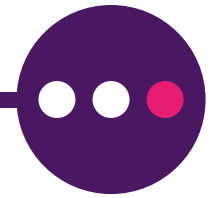
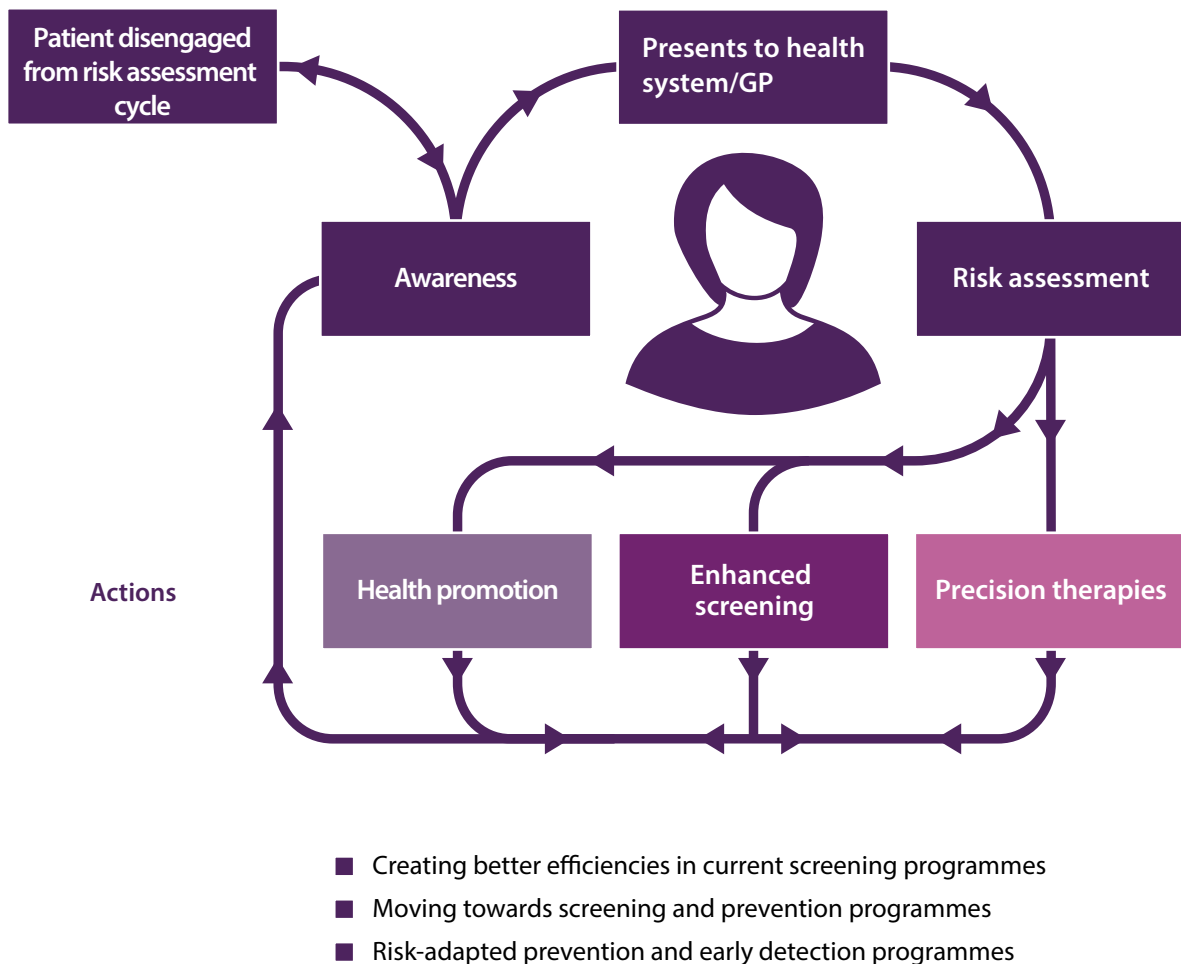


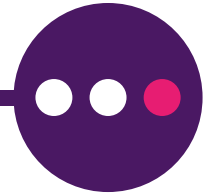
Figure 10. Risk-based prevention as a central part of individual and health system decision making



7.2 Issues in moving towards personalised prevention

Improving personalised prevention requires that the increasing refinement of risk categorisation is complemented by a set of interventions that can provide more effective management for each risk category. Currently evidence for clinical utility of risk-based prevention for breast cancer based on these different prevention pathways is still lacking. There is no consensus on which groups would benefit most from preventive interventions and as a consequence there is considerable debate about proactive versus reactive utilisation of risk information now and in the future.

Changes to screening pathways are a possibility in the medium term, as evidence accrues from studies such as MyPeBS study, the WISDOM trial and PROCAS study examining the utility of stratified prevention. This could potentially inform a move towards age and risk-based screening and prevention programmes.



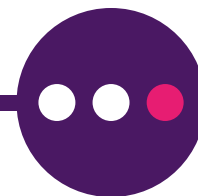
Moving towards a paradigm that offers more widespread risk-based care requires several practical changes:

- Healthcare professionals who are able to understand and communicate risk information
- Support for individuals to address their personal risk, for example through lifestyle change, participating in enhanced screening programmes or particular treatments.
- Creation of an infrastructure for the collection, collation and analysis of risk factor data

A broader range of often interrelated issues including overdiagnosis, health inequalities and maintaining person-centred care will also require consideration. There may be negative or positive impacts in each of these areas depending on how new personalised prevention programmes are developed and managed. Hence, it will be necessary to look for optimum solutions, which must also be appropriate for future diverse health systems with a wide set of providers and the inclusion of many different options for prevention pathways

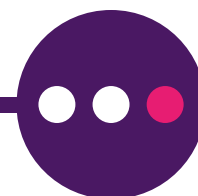
7.3 Summary

Current scientific knowledge and technologies enable improved risk assessment and population stratification based on multiple risk factors, and this landscape is likely to evolve rapidly in the future. While evidence in support of risk-based prevention is currently lacking, we expect to see a more robust evidence base emerging from ongoing trials and new studies. Through this workshop we were able to describe the developments in this field, their likely impact on prevention pathways and issues that will arise in implementation.

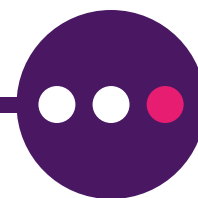


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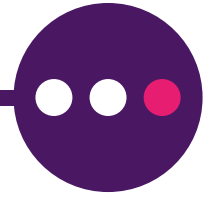
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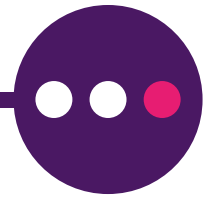


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Appendix 1 – workshop attendees

- Professor Jonas Almeida, Chief Technology Officer, Graduate Programme Director, Department of Biomedical Informatics, Stony Brook University
- Professor Antonis Antoniou, Professor of Cancer Risk Prediction, Academic Course Director MPhil Epidemiology, University of Cambridge School of Clinical Medicine
- Dr Chantal Babb de Villiers, Research Associate, University of Cambridge School of Clinical Medicine
- Louise Brennan, Chartered Physiotherapist and PhD Researcher - Cancer Rehabilitation and Connected Health
- Dr Mireille Broeders, Associate Professor, Department for Health Evidence, Radboud University Medical Center, Nijmegen, Netherlands
- Dr. Suzette Delaloge, Associate Professor of Medical Oncology and Head of Breast Cancer Department at Gustave Roussy Institute
- Maria Escala-Garcia, PhD Candidate, Netherlands Cancer Institute
- Dr Pedro Estrela, Senior Lecturer, Centre for Biosensors, Bioelectronics and Biodevices (C3Bio), University of Bath
- Professor David French, Professor of Health Psychology, University of Manchester
- Professor Montserrat Garcia-Closas, Deputy Director and Acting Chief, Integrative Tumor Epidemiology Branch, National Cancer Institute
- Professor Per Hall, Department of Epidemiology and Biostatistics, Karolinska Institutet
- Professor Anthony Howell, Chair in Breast Oncology, University of Manchester
- Jacquie Jenkins, National Programme Manager – Breast Screening, PHE Screening
- Dr Anju Kulkarni, Consultant Clinical Geneticist, Guy's and St Thomas' Hospital
- Don Lavoie, Alcohol Programme Manager, Public Health England
- Dr Esther Lips, Associate Staff Scientist, Netherlands Cancer Institute
- Dr Marta Marques, Research Associate on the Human Behaviour-Change Project, UCL
- Professor Hanne Meijers, Professor of Clinical Genetics, University of Amsterdam's Faculty of Medicine
- Professor Paul Pharoah, Professor of Cancer Epidemiology, Department of Public Health & Primary Care /Department of Oncology
- Dr Marjanka Schmidt, Group Leader Molecular Pathology, Netherlands Cancer Institute
- Professor Rita Schmutzler, Director, Center for Familial Breast and Ovarian Cancer, University Hospital Cologne
- Dr Juliet Usher-Smith, Clinical Senior Research Associate, Department of Public Health & Primary Care
- Caroline Vass, Registrar in Public Health, PHE Screening



PHG Foundation facilitators

- Dr Hilary Burton, Consultant in Public Health
- Dr Sowmiya Moorthie, Senior Policy Analyst (Epidemiology)
- Tanya Brigden, Policy Analyst (Humanities)
- Dr Louise Gaynor, Policy Analyst (Biomedical Science)

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