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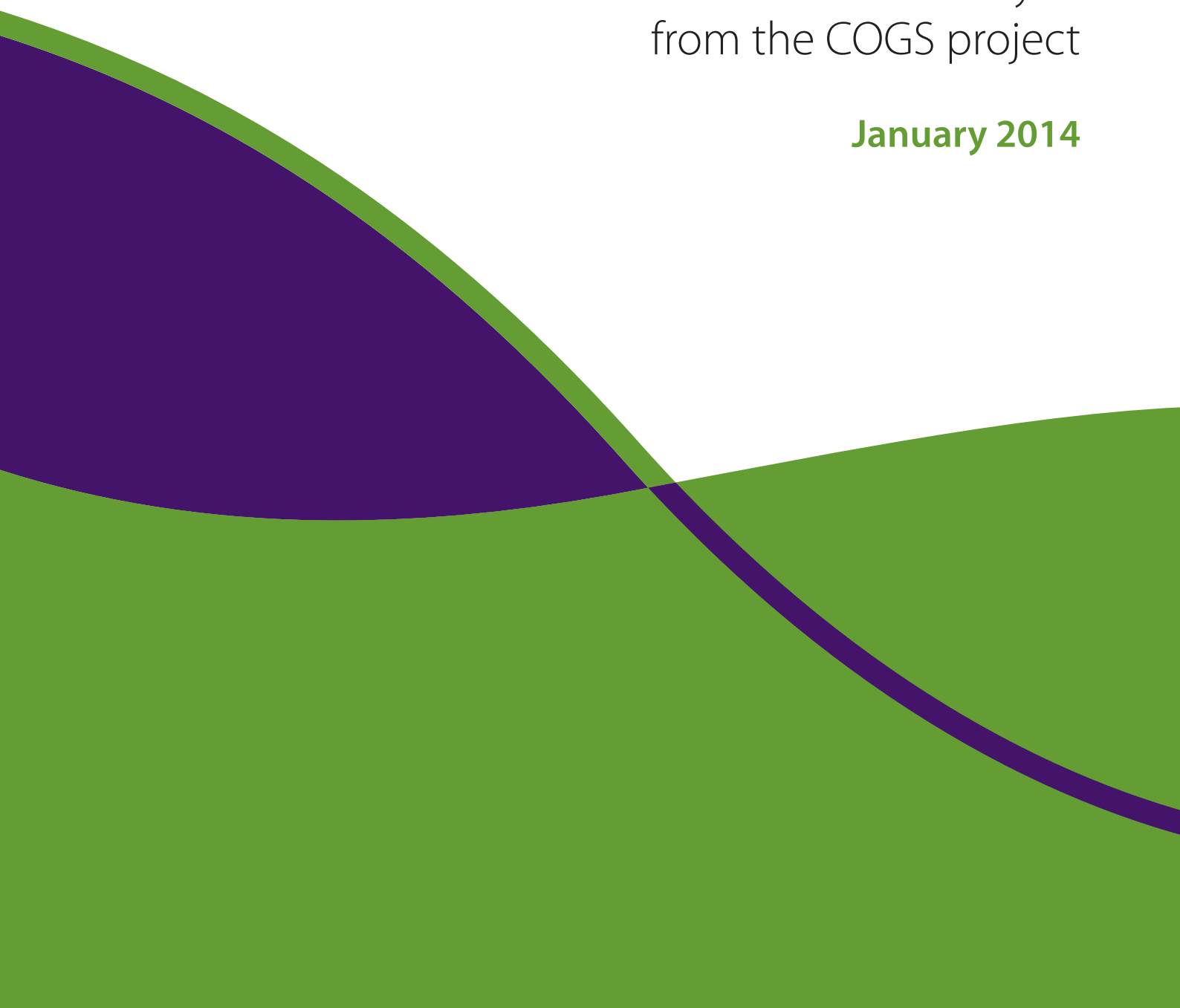
Stratified Screening for Cancer

Recommendations and analysis from the COGS project

January 2014



Authors: Tom Dent, Susmita Chowdhury, Nora Pashayan, Alison Hall, Paul Pharoah and Hilary Burton

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Published by PHG Foundation
2 Worts Causeway
Cambridge
CB1 8RN
UK

Tel: +44 (0) 1223 761900

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Correspondence to:
tom.dent@phgfoundation.org

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Contents

1 Summary

This report on the PHG Foundation's work sets out our recommendations. It describes the background to the COGS project, how we carried out our work and our findings in the four main areas of our enquiry.

The Collaborative Oncological Gene-environment Study (COGS) (www.cogseu.org) was an investigation to improve understanding of the causes and prevention of cancer of the breast, ovary and prostate. Funded by the European Commission, it ran for four years from 2009. It concerned the use of genomic and other information to estimate individuals' risk of developing cancer, with a view to offering different screening and other preventive interventions according to the results.

The PHG Foundation was responsible for Work Package 7 of COGS, supported by Professor Paul Pharoah of the University of Cambridge. The Foundation's steering group for the project is listed in Appendix 1. The aim of Work Package 7 was to investigate the efficacy and cost-effectiveness of using genomic and other information in stratified cancer prevention strategies, and the organisational, ethical, legal and social implications that would then arise. This report on the PHG Foundation's work sets out our recommendations. It describes the background to the COGS project, how we carried out our work and our findings in the four main areas of our enquiry.

Screening programmes have made an important contribution to improvements in public health, but their value often depends on careful targeting. Stratification holds the prospect of achieving high rates of diagnosis and effective early treatment, while sparing lower risk, disease-free people from the risks and inconvenience of screening. It may also reduce overall costs. Using genomic information to improve this targeting is therefore attractive in principle and increasingly feasible.

We modelled the efficiency of a personalised approach to screening for prostate and breast cancer based on age and polygenic risk-profile, and compared it with the efficiency of screening based on age alone. We showed that personalised screening based on age and polygenic risk would reduce the number of people who need screening while detecting the majority of the cancers identified through a programme based on age alone.

We organised three workshops for international experts in fields of relevance to the project, and worked iteratively throughout the project to prepare analyses and reviews that developed the ideas and themes that emerged at the workshops. We considered the organisational context within which implementation of stratified prevention would occur, how the offer of screening would be made, how individuals' risk would be estimated, the age at which risk estimation should occur and the potential use of genetic data for other purposes. We also considered how management might differ depending on individuals' risk, how their results would be communicated and their follow-up arranged, and the different issues raised by modification of an existing screening programme, such as that for breast cancer, and the establishment of a new one, for example for prostate cancer. None of these issues constitutes an insuperable barrier to successful implementation, but all need careful handling to ensure outcomes are optimised and harms minimised.

Using two alternative approaches to consent, collection, storage and communication, we reviewed ethical, legal and social implications of stratified screening in terms of respect for autonomy, non-maleficence, beneficence and justice. Important issues include consent, privacy, the age at which sampling and genetic analysis occur, genetic solidarity and managing those in whom screening is no longer advised because of low estimated risk. If the use of genomic information to stratify population screening entails the retention of samples and data for diverse uses over many years, it will give rise to further ethical, legal and social concerns including data security, managing logistical issues around capacity to consent, re-contact, withdrawal and linkage of samples. Conversely, the use of a once-only targeted test with immediate disposal of the sample and data raises fewer ethical and regulatory problems.

Many of the competences required for stratified prevention programmes should already be present in the current health professional workforce. Gaps arise in those specific elements relevant to stratified prevention and the inclusion of genetic testing in initial risk assessment. Such gaps will need to be filled by the development of specific educational resources and their integration into existing educational programmes.

Although we do not think the evidence is yet adequate to support risk-stratified screening, we believe that point will probably be reached before long. Preparing for the change would be wise. In the meantime, further research is needed into impact, utility, cost-effectiveness, acceptability and ethical, legal and social implications. A critical factor may be whether targeting resources according to risk is seen as compatible with the interests of the entire screening population.

Although we do not think the evidence is yet adequate to support risk-stratified screening, we believe that point will probably be reached before long. Preparing for the change would be wise.

2 Recommendations

Key recommendation: that decision-makers prepare for the introduction of risk-stratified screening for breast and prostate cancer.

1. Effectiveness of risk-stratified screening

1.1 We recommend that stratified screening should not be implemented until further empirical evidence is available about whether a risk-based screening approach improves the benefit-harm balance of screening for prostate and breast cancer

1.2 If further research indicates that risk-stratified screening improves the benefit-harm balance of screening, then we recommend decision modelling to identify the optimum screening strategy for breast and prostate cancer

1.3 Before implementing the optimum risk-based screening strategy, we recommend investigation of the feasibility of implementation.

2. Delivery

We recommend that:

2.1 The implementation of stratified screening is tailored to the organisation of health services in the country in question

2.2 Policy-makers develop detailed plans for the delivery of stratified screening, giving attention to the issues in Appendix 2

2.3 Policy-makers develop sound quality assurance systems to maximise benefits and minimise harms

2.4 Policymakers develop and articulate clear policies on risk stratification, particularly where the purpose is targeting of limited resources

2.5 Research into the impact of technological change on the delivery of stratified cancer screening is instigated.

3. Ethical, legal and social issues

3.1 In the short term, we recommend that any risk-stratified programme that is introduced has a specific clearly defined purpose, and that the storage and linkage of samples and data are minimised.

We recommend that:

3.2 More comprehensive programmes genotyping multiple conditions involving lifetime storage of samples or data should not currently be introduced

3.3 Personalised screening is restricted to adult populations. We do not support the systematic genotyping of newborns or young children as a preliminary to risk assessment

3.4 The consent process should address the benefits, harms and uncertainties of genotyping and risk assessment, the precise nature of which will be dependent on context. Where possible, we recommend the use of an encompassing consent which takes account of reasonable and foreseeable future developments

3.5 Providers of risk stratification incorporating a genotypic element should be transparent about the evidence base and quality assurance processes that are used, to ensure that, regardless of provider, the risk assessments that are generated are safe, robust and evidence-based

3.6 Decision-making should be fully inclusive, ensuring meaningful engagement of all stakeholders in the policy-making process

3.7 Research to clarify the wider ethical, legal and social impact of stratifying on the basis of genotypic and phenotypic risk, as compared with determinants such as age, sex and ethnic group is undertaken. In particular, we recommend research to clarify the potential for generating inequalities relating to distributive justice

3.8 Comprehensive conceptual and empirical research into the impact of ethnic and cultural factors on understanding, acceptability and uptake of personalised screening is undertaken.

4. Professional education and training and public understanding

We recommend that:

4.1 Health care professionals are prepared for the use of genomics in common disease prevention including risk-stratified screening, building on existing knowledge and skills. We recommend formal educational needs assessment as a prerequisite for implementation.

5. Public understanding and acceptability

5.1 We recommend research on public understanding of risk stratified screening and its acceptability to the public before risk stratified screening is implemented.

3 Introduction

The Collaborative Oncological Gene-environment Study (www.cogseu.org) was an investigation funded by the European Commission to improve understanding of the causes and prevention of cancer of the breast, ovary and prostate.

The project ran for four years from 2009, and had five goals:

1. To determine the important common genetic variants that underlie breast, ovarian and prostate cancer risk, and to estimate their effects on risk, individually and in combination
2. To assess interaction between genetic loci and known or suspected environmental/lifestyle risk factors, *i.e.* to examine whether environmental/lifestyle risk factors modify genetic susceptibility to breast, ovarian and prostate cancer
3. To assess whether the association between genetic factors, environmental/lifestyle risk factors and cancer risk is stronger for certain tumour subtypes, and affects clinical outcome
4. To develop comprehensive risk models including genetic and environmental/lifestyle factors for these cancers, to allow the prediction of breast, ovarian and prostate cancer among individuals in the population at large
5. To investigate the efficacy and cost-effectiveness of using these risk models in prevention strategies, and the associated organisational, ethical, legal and social implications.

The PHG Foundation was responsible for the fifth goal. This is a report on the Foundation's contribution to the COGS project. It sets out the background to the COGS project and how we carried out our work. It then describes our findings in the four main areas of enquiry. Our recommendations are set out in section 2 above. Publications from the COGS project WP7 are highlighted in the text.

4 Background

Risk stratification holds the prospect of achieving high rates of diagnosis and effective early treatment, while sparing lower risk, disease-free people from the risks and inconvenience of screening, and of reducing overall costs.

Screening programmes have made an important contribution to improvements in public health, but the value of many depends on careful consideration of the balance of benefit and risk in different populations. The risk of disease is not uniform throughout the population. Some people are at increased risk because of factors such as their age, gender, ethnicity, family history and lifestyle, and it is these who are most likely to benefit from screening.

Those responsible for designing and operating screening programmes should ensure that people at highest risk are offered screening, while minimising the inevitable harms that screening imposes on all those who accept it. These vary from the inconvenience and unpleasantness of the test and the anxiety it causes, especially if it is positive, to harm from the investigation and treatment of false positive results or of disease which would never have troubled the individual. The goal is to ensure that those with most to gain are invited, while those whose risk is too low to justify the harms and costs are spared them[1].

Occasionally, the risk of disease is so closely associated with a clear phenotypic or personal characteristic that screening can be targeted on that basis; for example, Ashkenazi Jewish ancestry and screening for Tay-Sachs disease carrier status[2]. However, this is unusual; the risk of developing most common chronic diseases is multifactorial and normally distributed, with a small number of people at high and low risk and most of the population in the middle range.

Despite the multifactorial nature of risk, lack of knowledge about how to estimate an individual's risk accurately tends to lead to necessarily simple policies about whom to invite for screening which take account of only one risk factor and offer only one mode of screening. For example, women are invited to the NHS mammographic breast screening programme on the basis of age alone, which is only one, albeit important, indicator of their individual risk[3]. The NHS Health Check programme screens nearly all adults between the ages of 40 and 74 years for heart disease, stroke, diabetes, kidney disease and certain types of dementia (www.healthcheck.nhs.uk).

The risk of developing most common chronic diseases is multifactorial and normally distributed, with a small number of people at high and low risk and most of the population in the middle range.

PHG COGS paper

Population-based screening in the era of genomics

Personalized Medicine 4.10

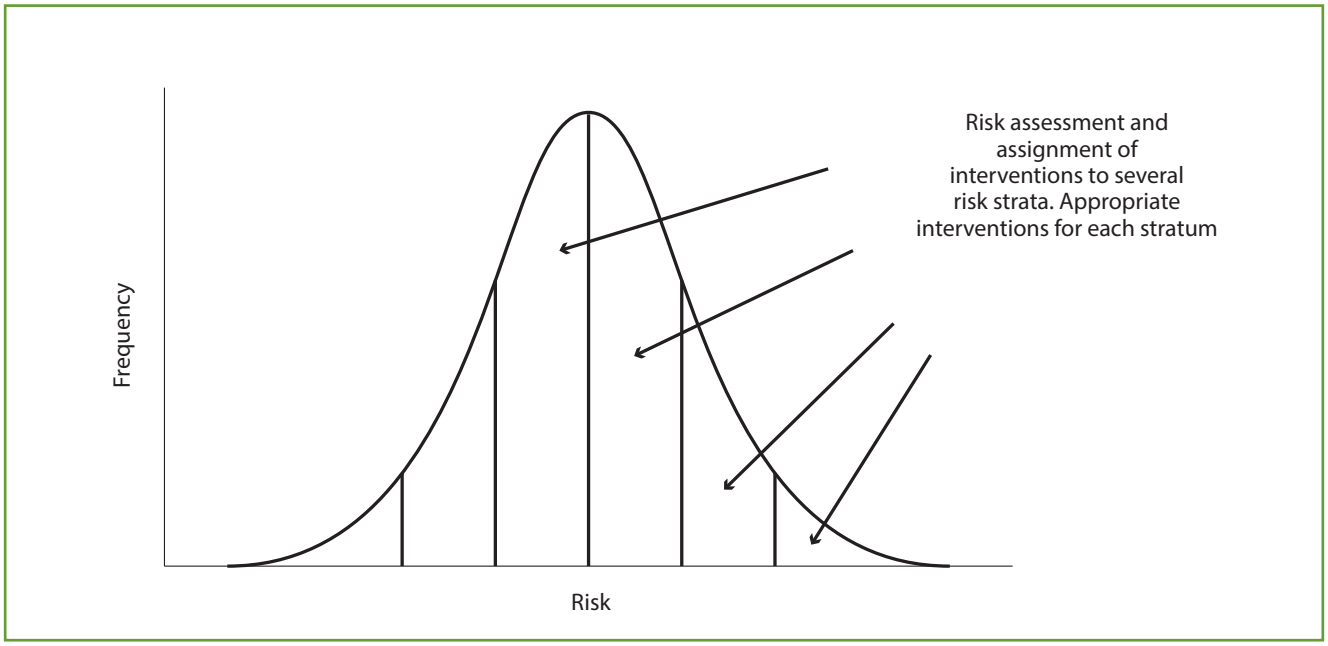
This reliance on age alone to target screening does not permit the identification of groups who might benefit from more or less intense screening and the tailoring of interventions to risk levels. However, in the case of breast cancer, our growing understanding of aetiology may allow us to improve on this. Genome-wide association studies have brought new information about the genetic variants that modify risk[4]. Each allele usually increases risk by less than 30%, too small an effect to be useful individually, but if enough such alleles are found, their cumulative effect may be enough to support stratification.

For example, Pharoah *et al.* showed in 2008 that the seven alleles related to breast cancer risk then known, which each conferred risks between seven and twenty-six per cent higher than average, were enough to produce wide separation of absolute risk[5]. The authors used as a threshold for screening the 2.3% ten-year risk of a breast cancer diagnosis of a 50 year old British woman; this is the age at which population mammographic screening begins in the United Kingdom. Using these seven alleles, one in five women could be shown never to attain this risk and could thus avoid screening, while the five per cent at greatest risk attained it at the age of 41 years and might therefore be offered screening earlier.

Since Pharoah *et al's* paper, the COGS investigators have identified more than fifty further alleles associated with breast cancer risk, increasing the power of this approach to risk estimation. Furthermore, we have known for some time that breast cancer risk is increased by modifiable lifestyle factors such as obesity, higher alcohol intake and smoking, as well as by the use of oral contraceptive pills and hormone replacement therapy. Reproductive factors – such as early menarche, late menopause and increased age at first childbirth – are also known, but are more difficult to modify; breast-feeding has a protective effect, as does the number of pregnancies experienced. Taken together, these factors indicate the growing potential of risk stratification based on genetic and environmental information.

This understanding of genetic and environmental risk can be used as a basis for stratified prevention. This means estimating the risk of individuals developing specific cancers, grouping or stratifying them according to their risk, and targeting screening or other preventive interventions according to that risk threshold (Figure 1). Stratification holds the prospect of achieving high rates of diagnosis and effective early treatment, while sparing lower risk, disease-free people from the risks and inconvenience of screening. It may also reduce overall costs.

Figure 1: Stratified prevention – the categorisation of the population into risk groups, each of whom would be offered a different intervention



From: Burton H, Sagoo GS, Pharoah P, Zimmern RL. Time to revisit Geoffrey Rose: strategies for prevention in the genomic era? IJPH 2012; 9: e8665-1.

The addition of risk information from common susceptibility variants can improve the discrimination of established risk models such as those of Gail and Tyrer-Cruzick[6,7], that is, they may improve the model's ability to rank correctly the degree of risk of an individual in relation to the whole population. While promising, this is not enough to make implementation appropriate. To be suitable for use, a risk-stratification model must also have adequate calibration (accurately estimating each individual's risk); it must also have clinical utility, which includes producing risk distributions for categories of people that are separated widely enough to justify different management of each category so as to improve outcomes overall. We do not yet know whether these criteria are satisfied, and for which cancers.

The COGS project was concerned with three cancers – breast, prostate and ovary. The first two are of particular public health importance, being in industrialised countries the most commonly diagnosed cancers in women and men respectively. Both are also of interest from the perspective of screening.

- Breast cancer provides the best basis for consideration of the potential of stratified screening: more is known of its genetic and environmental aetiology, there are established screening programmes against which stratified approaches can be compared and the effects of preventive interventions have been better investigated. Many industrialised countries have introduced mammographic screening for breast cancer[8], though the value of this approach is still contested[9].

PHG COGS paper

Time to revisit Geoffrey Rose: strategies for prevention in the genomic era?

Italian Journal of Public Health [4.8]

- Prostate cancer also raises important questions about the potential value of a screening approach. The organised use of prostate-specific antigen as a screening test for prostate cancer is not in place, though many men are screening opportunistically, especially in the United States[10]. The publication of two randomised trials has not ended the controversy about the value of prostate-specific antigen in screening[11,12], a controversy made particularly important by the high incidence of impotence and incontinence after the treatment of prostate cancer. One proposed response to the doubts about whether to screen all men for prostate cancer with prostate-specific antigen alone is to assess each man's risk of cancer using that assay as part of an estimation that also includes genetic and lifestyle risk markers. Only men with high estimated risk would be offered more invasive investigation, for example with prostate biopsy[13].

There are three separate elements to the change in prevention of breast and prostate cancer that we foresee:

- *Risk stratification:* at present, only broad factors such as age and gender are used to select people for the offer of a single package of screening. In future, many factors will be combined to create an individual risk estimate
- *Incorporation of genomic information:* we expect the stratification of risk to include genomic and phenotypic information; this will probably be the first time genomic information has been used widely in health care
- *Different management on the basis of the risk assessment result:* the series of further tests and treatments will vary depending on the results of risk estimation. This is in contrast to the current undifferentiated approach.

It is *risk stratification* which brings the most novelty to what is proposed. Without that fundamental change of approach, none of the further issues would need consideration. Even if stratification was based only on phenotypic information, many of them would still arise.

The implications of *incorporating genetic information* will depend on how testing is provided and the resulting information used. A point-of-care test with immediate disposal of the genetic sample would raise fewer ethical issues than the separate acquisition, processing and possible storage of the sample or data. Incorporating genetic information makes only a modest difference to the delivery of a stratified approach.

It is risk stratification which brings the most novelty to what is proposed. Without that fundamental change of approach, none of the further issues would need consideration.

Most issues of operational delivery considered under this theme arise because of *different management on the basis of the risk assessment result*, the third of these elements.

5 Aims and objectives

Our aim was to investigate the efficacy and cost-effectiveness of using risk prediction models in stratified prevention of specified cancers, and to consider the organisational, ethical, legal and social implications.

Our objectives were to:

- Use the results of primary research into gene-disease association, gene-environment interaction and individual risk prediction models to evaluate the potential for stratification of the population according to individual risk of breast, ovarian and prostate cancer
- Evaluate the potential of stratified prevention to reduce the incidence of and the mortality from these cancers by risk stratification and targeting of population-based screening and prevention programmes, including cost-effectiveness analysis
- Identify the key organisational, ethical, legal and social issues that would arise from such targeted screening and other prevention programmes and make appropriate policy recommendations.

6 Method

There were two strands in this work programme of the COGS project: modelling the effectiveness and cost-effectiveness of stratified screening for breast and prostate cancer, and a series of three workshops to explore emerging issues.

The three workshops were attended by international experts in fields of relevance to the project . The project team worked iteratively to prepare analyses and reviews that developed the ideas and themes that emerged at the workshops.

Modelling

We modelled the efficiency of a personalised approach to screening for prostate and breast cancer based on age and polygenic risk-profile. Using the 31 prostate cancer and 18 breast cancer susceptibility loci with common risk alleles then published, we estimated the proportion of the population with a polygenic risk of diagnosis greater than a given absolute risk threshold, and the proportion of cases that will occur within this high-risk subgroup. For breast cancer, the risk threshold was 2.5% over ten years, the average risk of women invited to the NHS breast screening programme. For prostate cancer, it was 2% over ten years, the risk of an average British man aged 55 years.

We then compared two approaches with screening for prostate cancer in men aged 45 to 79 years: screening based on age alone in which all men are invited for screening from age 55 to 79 years, and personalised screening of men aged 45 to 79 years in which eligibility for screening is determined at a 2% absolute risk that is age- and polygenic risk-dependent. We compared the number of individuals eligible for screening under the two approaches and the number of cases occurring in the eligible population that are therefore potentially screen-detectable.

Similarly, we compared breast cancer screening based on age alone in women aged 47 to 79 years with screening women aged 35 to 79 years with a 2.5% ten-year risk based on age and polygenic profile.

Workshops and analysis of issues

The workshops involved presentations, group work and plenary discussions, designed to elicit the views of participants and promote clarification of and consensus about the issues under review. The workshop participants had expertise in genetics, epidemiology, social science, health economics, primary care and screening, they are listed in Appendix 3. We held the workshops at Madingley Hall, near Cambridge, United Kingdom.

We used the first workshop, in July 2010, to identify as many as possible of the issues which would arise from stratified screening for breast and prostate cancers. Participants grouped, refined and prioritised these, selecting areas for further work before the next workshop.

At the second workshop, in July 2011, we reported on our progress and considered how the stratified screening might be delivered, identifying three distinct approaches and discussing how they might be implemented in countries with different health care systems. We also considered ethical, legal and social implications of stratified screening in greater depth and presented cost-effectiveness analyses on stratified and non-stratified approaches to cancer screening.

The second workshop generated a set of further questions and issues which we developed in collaboration with some of the workshop participants. These included the practicalities of implementing stratified screening, the wider implications of the approach and the new competencies that health professionals would need if stratified disease prevention were introduced. We also refined and developed our models of the effectiveness and cost-effectiveness of screening.

Our results were presented at the third workshop in October 2012, along with draft recommendations. These were considered and refined by the participants, and finalised by us after the workshop. The recommendations appear in section 2 above.

7 The results of modelling

Our modelling shows that personalised screening based on age and polygenic risk would reduce the number of people eligible for screening while detecting the majority of the cancers identified through a programme based on age alone.

Prostate cancer

Under the age-based approach, 63% of men aged 45 to 79 years would be aged at least 55 years and therefore eligible for screening. Ninety-six per cent of cases of prostate cancer would occur in this subset of the population, so these cases are potentially screen-detectable. By contrast, under the personalised approach, 53% of men would be eligible for screening and 93% of cases would be screen-detectable. Thus, the personalised approach spares 10% of men from screening, at a cost of detecting 3% fewer cases. For the population of men aged 45 to 79 years in England, there would be an additional three screen-detectable cases per 100,000 population in men younger than 55 years of age with polygenic risk at least 2%, and 12 cases per 100,000 population would be missed in men older than 55 years whose polygenic risk was less than 2%.

We based our modelling on the 31 prostate cancer susceptibility variants then known. Since then, a further 23 have been identified[14]. We estimated that, if all possible susceptibility variants for prostate cancer were known and used in estimating men's risk, 35% of men aged 45 to 79 years would be at 2% 10-year risk with 90% of cases being potentially screen-detectable. This is a much larger reduction in the number being screened compared with the use of the 31 alleles, with only a small reduction in cancer detection; this shows the value of identifying further susceptibility variants: compared with screening from the age of 55 years, 28% fewer men would be offered screening at a cost of 6% fewer cases being potentially screen-detectable.

PHG COGS paper

Polygenic susceptibility to prostate and breast cancer: implications for personalised screening

British Journal of Cancer [4.9]

Breast cancer

Under the age-based approach, 65% of women aged 35 to 79 years would be aged at least 47 years and therefore eligible for screening. Eighty-five per cent of cases would occur in this subset of the population, so these cases are potentially screen-detectable. By contrast, under the personalised strategy, 50% of women would be eligible for screening, with 73% of cases being potentially screen-detectable. Thus, the personalised approach spares 15% of women from screening at a cost of 12% fewer screen-detectable cases. There would be nine screen-detectable cases per 100,000 population under personalised screening in women not eligible under age-based screening and 38 potentially screen-detectable cases per 100,000 population under age-based screening in women not eligible for screening based on polygenic risk.

If all possible susceptibility variants for breast cancer were known, 28% of women 35 to 79 years would be at 2.5% risk eligible for screening and 76% of the cases would occur in this group. Compared with screening from age 47, 37% fewer women would be offered screening at a cost of detecting 9% fewer cases.

Implications

Our modelling shows that personalised screening based on age and polygenic risk would reduce the number of people eligible for screening while detecting the majority of the cancers identified through a programme based on age alone. Alternatively, screening the same number of individuals in a personalised screening programme could potentially detect a greater number of cases than a screening programme based on age alone.

Our modelling only extends to estimating how many people would be offered screening and the number of cases that would arise in that group. The public health impact of a screening programme depends also on the sensitivity of the test and the effectiveness of treatment. These are broadly understood for breast cancer, though improvements in the effectiveness of treatment have raised doubts on the value of the programme[15]. In subjects of a given age at high genetic risk, the test sensitivity is likely to be the same or better than in those of the same age at low genetic risk, but both the prostate-specific antigen test[16] and mammography are less sensitive in younger subjects. It is not known how test sensitivity will differ between younger and older subjects at the same absolute risk; the duration of the pre-clinical, screen-detectable phase may also vary by underlying genetic risk.

We need empirical data in order to estimate the population impact of stratified screening. We also need further modelling to estimate the cost-effectiveness of stratified screening. The use of genetic tests will entail higher costs, but these may be offset by savings on repeat screening and diagnostic work-up of false positives. Our work on modelling the cost-effectiveness of stratified screening will be submitted for publication shortly.

Recommendation 1.1: Screening approach

We recommend that stratified screening should not be implemented until further empirical evidence is available about whether a risk-based screening approach improves the benefit-harm balance of screening for prostate and breast cancer.

Risk-tailored screening that targets individuals with an absolute risk above the risk threshold could potentially improve the efficiency of screening programmes. However, there is yet no strong evidence that overdiagnosis and overtreatment would be reduced by this approach, nor that the mortality benefits of screening are limited to high-risk individuals. So we recommend studying whether and how the following vary by absolute risk levels:

- The natural history of prostate and breast cancer
- The probability of overdiagnosis and overtreatment following cancer screening
- Mortality reduction following cancer screening.

These analyses will identify whether polygenic risk profiling can be used to differentiate potentially life-threatening disease from overdiagnosed cancers, will indicate whether the inter-screening interval should be varied for different absolute risk levels, and will indicate the potential, if any, of polygenic risk profiling in improving sensitivity or specificity of the screening test.

Recommendation 1.2: Optimum screening strategy

If further research indicates that risk-stratified screening improves the benefit-harm balance of screening, then we recommend decision modelling to identify the optimum screening strategy for breast and prostate cancer.

This will involve cost-utility analysis taking a societal perspective to incorporate a wide range of benefits and harms such as benefits of reassurance if low risk and harms of inconvenience or anxiety. Moreover, decision modelling will be needed to define the optimum risk score composition (polygenic profile, age and other relevant conventional risk factors such family history and breast density), the inter-screening interval, the screening modality (*e.g.* mammogram vs. MRI), the optimum age range for screening and the care pathway. In addition, further research will be needed to study the acceptability of the chosen screening strategy to the public and health professionals.

Recommendation 1.3: Pilot programme

Before implementing the optimum risk-based screening strategy, we recommend investigation of the feasibility of implementation.

Evidence will be generated by undertaking an implementation or feasibility study. This will provide information on the feasibility, practicalities of implementation and ability to deliver the specific outcomes in actual practice. This will be an iterative process.

8 Delivering risk-stratified screening

Whether the potential advantages in offering screening programmes according to the estimated risk of the participant are achieveable in practice will depend, in part, on how the new approach is implemented.

There are several potential advantages to offering different screening programmes according to the estimated risk of the participant:

- It might reduce the number of people needing to be screened to achieve the same preventive impact
- It might increase the preventive impact from the screening the same number of people
- It might permit different screening approaches to be used in people with different risks, matching benefits and risks more precisely.

Whether these advantages are achievable in practice depends on the extent to which the addition of extra information on risk permits screening to be targeted at those more likely to have the disease. But it also depends on how the new approach is implemented. We considered these in the following categories: fundamental policy issues, operational issues and other delivery issues.

Fundamental policy issues

The implementation of stratified screening for breast or prostate cancer would take place against a wider policy background, with the feasibility of different approaches varying according to the extent to which screening is organised centrally or locally, by government or another public authority or based on professional practice guidelines or provider policy. There is substantial variation even within Europe in how countries fund healthcare and arrange primary healthcare and population screening[17]. Primary care professionals may be well placed to provide initial risk assessment. Countries with organised screening that is delivered using population databases will be able to collect samples to determine relevant genetic and other biomarkers, estimate risk, issue tailored invitations, and arrange further investigation and treatment in the light of the result; those that rely on opportunistic approaches may find it more difficult to do this systematically.

PHG COGS paper

Stratified Cancer Screening: The Practicalities of Implementation. Public Health Genomics

Public Health Genomics [4.6]

The selection of interventions should be based on good evidence of effectiveness, including the balance of benefit and harm for the different risk groups and relevant costs, but little such evidence yet exists.

Operational issues

We envisage that a stratified screening programme using genetic and other biomarkers, for example for breast or prostate cancer would comprise:

- Offer of stratified screening
- Risk estimation
- Delivery of screening intervention
- Communication of results.

Further management would depend on the results of screening, rather than the previously estimated risk, though genetic information may come to influence treatment too.

The *offer of stratified screening* initiates the process, introducing a person to the likely benefits and possible harms, and providing information about what subsequent preventive interventions may entail. We considered carefully the age at which this should take place. People must be offered screening at an age that precedes usual development of the disease and gives an opportunity for preventive action. The age at which stratified screening is offered will also depend on the nature of the risk profiling, as some genetic risk factors may be associated with disease onset at an early age. It may be best to offer prevention advice from childhood for some conditions, for example familial hypercholesterolaemia in cardiovascular disease.

People need to be able to make an informed decision about whether to accept an offer of risk assessment as part of a screening intervention. Those planning screening programmes will have to determine the amount and type of information people need and how it should be presented, which will vary for different recipients according to background understanding, interest or concerns about genetics and ethnicity for example. We see a need for resources to support this process for stratified screening, with parallel development of education for health professionals providing this element of the programme (see Section 10).

The formal conclusion of this stage would be to seek consent for participation in the risk-stratified programme. This may be limited to the specific purpose and test proposed when the sample is taken, or may permit other tests with other aims in future. Another alternative is dynamic consent, in which participants can be approached for extensions to the original consent as the need arises; this combines flexibility with the preservation of autonomy and has merit. Appropriate arrangements must be in place for recording the offer and acceptance of consent. In addition, any policy will need to take into account those who decline risk stratification but still wish to be screened.

The three main components of *risk estimation* are genetic testing, assessment of non-genetic risk factors and the integration of genetic and non-genetic information into a risk score/risk category. Details of these will be worked out at local level, but the risk assessment process requires access to genetic data. The DNA sample could be obtained and the sequence analysed and stored before the individual has reached the age at which risk assessment would occur, allowing the necessary testing of variants for the specific risk assessment to be

undertaken *in silico* by interrogation of sequence data. The scope and precise detail of the variants to be tested must be agreed, although these may change over time as further evidence accrues.

An immediate question for any breast screening programme that uses genetic risk stratification is whether to test for high-risk alleles such as deleterious mutations in *BRCA1* or *BRCA2*. The public may realistically expect screening to cover all genetic variants related to their risk of a particular cancer. However, as with variants for common disease, the inclusion of high-risk variants would need to be based on evidence of utility in this context and not just their performance in other clinical settings, for example where there is a strong family history of cancer. Their inclusion would also raise issues about the need for counselling about the potential familial implications of testing.

In providing *risk estimation* that includes genetic data, there are important concerns about the handling of genetic material and data. These include the basis upon which the samples were originally collected, the form and scope of consent, the security of storage of both samples and data and safeguards from abuse, and the arrangements for access for clinical or non-clinical uses such as medical research or forensic analysis. These uses may relate to the family as well as the individual.

Assessment of non-genetic components of risk is likely to require a questionnaire oriented towards the cancer concerned. For example, in breast cancer this may include reproductive history, past medical history, family history, environmental exposures, and lifestyle information such as alcohol intake. In contrast to the genetic data, this information will change through life – for example, a mother or sister may be diagnosed with cancer, pregnancies may occur or alcohol intake may change. Policy-makers will need to decide the age at which this information will be obtained and to decide when and how it is kept up-to-date.

The final stage of assessment will take place through entry of data into a computer programme that will generate a risk score. This will require assurance of the validity of all the data, the underlying algorithms and the evidence on which they are based, and specification of the data sources and methods for capture. The method of risk estimation will need updating as knowledge of genetic and environmental risk factors increases.

The general principle of *delivery of screening interventions* in stratified prevention is that interventions are more intensive for those at higher risk and less intensive for those at lower risk. The selection of interventions should be based on good evidence of effectiveness, including the balance of benefit and harm for the different risk groups and relevant costs, but little such evidence yet exists.

There are several ways in which the intensity of screening could be modified to reflect individual risk. For example, in breast cancer screening, alternatives include:

- The offer of an earlier start or later finish to mammographic screening for those at higher risk
- The offer of a later start, earlier finish or even no screening for those at lower risk
- A combination of these approaches with gradation of these offers from high to low
- Different modalities of screening such as magnetic resonance imaging[18] for high-risk groups
- Chemoprophylaxis.

For all groups, including those at low risk, general advice about modifiable lifestyle factors such as alcohol intake would be given.

Throughout the process, the *communication of results* will depend on the professionals involved having adequate understanding to use the system confidently and communicate risk assessments to individuals. In some countries, primary care staff will already be used to explaining the nature and results of risk scores to patients, because of their use in cardiovascular diseases. The inclusion of genetic information in the risk assessment process may not make much practical difference to the educational requirements for professionals and the explanation needed by patients.

These issues will become even less onerous if point-of-care testing is introduced. This would likely involve immediate disposal of the genetic sample, raising fewer ethical issues than separating the acquisition, processing and possible storage of the sample. Incorporating genetic information in this way would secure the benefits of stratification while only constituting modest difference to the delivery of a stratified approach.

Other delivery issues

A stratified screening programme is more complex to set up and administer than the current programmes based on age alone. It proceeds through several stages over a longer period of time, involves more testing modalities and requires more interactions between the service and the recipient. All elements must be subject to the same standards of quality control that exist within current screening programmes. Issues around DNA testing add a further layer of complexity. Substantial organisational effort will be required to adapt services already in place or to develop new ones, and a range of evaluative research will be needed to ensure that the level of extra value merits the additional complexity and cost.

The offer of stratified screening, which needs to convey the message that the value of screening depends on whether participants are low or high risk, has the potential to confuse recipients. Such confusion may result in reduced uptake of screening. Nevertheless, the debate about the value of mammographic screening for breast cancer may increase the appeal of stratified screening by ensuring screening exposure is related to individuals' risk of disease[19].

Where there is an established screening programme, such as for breast cancer, there may be political or public resistance to a reduction of the screening offered to low-risk groups

Where there is already an established screening programme, such as that for breast cancer, there may be political or public resistance to a reduction of the screening offered to low-risk groups because recipients have been encouraged for many years to see screening as universally beneficial[20] and may regard this reduction as a denial of access or a form of health-care service rationing. This may be exacerbated as, inevitably with stratified screening, a small group of women assessed as low risk and receiving less intensive or no screening will subsequently develop cancer. This group may feel let down by the screening programme and would need to be very carefully managed. In particular, the possibility of such an outcome must be raised as part of the initial discussion of the risks and benefits of screening.

Similar problems are less likely with prostate cancer screening, where there is no existing screening programme (such as in the United Kingdom) and where the complications such as incontinence and impotence following treatment are more widely recognised. The introduction of stratified screening for prostate cancer might, therefore, be easier where an existing programme is not in place than where a programme has to be modified, such as the current breast cancer screening programmes in the UK.

Recommendation 2.1: Approach to implementation

We recommend that the implementation of stratified screening is tailored to the organisation of health services in the country in question.

The availability, structure and funding of health services, and of screening specifically, vary substantially between countries. In principle, primary care provides a good setting for parts of the delivery of stratified screening, such as sample acquisition and information provision, but its suitability for this purpose and the most useful role for it to play need assessment.

Recommendation 2.2: Design of delivery programme

We recommend that policy-makers develop detailed plans for the delivery of stratified screening, giving attention to the following issues:

- Whether to include testing for highly penetrant alleles, such as *BRCA1* and *BRCA2*
- Whether to organise screening on a national or local basis, and how to involve primary care
- Whether to offer opportunistic screening, a centralised invitation system or both
- Whether to specify a clinical pathway for implementation at local level, or arrange a screening programme delivered across a larger area by one provider
- How to handle the implications for existing screening programmes
- Taking, retention and storage of samples and information
- Governance, service structure, data management, quality assurance and other important aspects of the provision of screening
- The services available to those who screen positive.

Recommendation 2.3 Quality assurance

We recommend that policy-makers develop sound quality assurance systems to maximise benefits and minimise harms.

The greater complexity of stratified screening will make quality assurance more challenging.

Recommendation 2.4: Communication

We recommend that policymakers develop and articulate clear policies on risk stratification, particularly where the purpose is targeting of limited resources.

The introduction of an effective and robust risk-stratified screening programme will require development of clear communication methods. For example, invitation letters should include information about risk categories, the benefits and harms, and what to expect at different stages of the process. If there is a significant delay between sample collection and analysis, more generic materials may be needed, as it will be difficult for screening providers and participants to accurately assess the benefits and harms involved.

Policy-makers should develop appropriate public, patient and professional resources explaining benefits and harms of the approach they have selected. These will include the information that people need to make a properly informed decision about whether to accept an offer of risk assessment.

Policy-makers should decide:

- The processes to be involved in offering and consenting to risk stratification
- The subsequent choices that may be available to patients
- How those choices will be supported.

The rationale that underpins stratified screening is that knowledge of an individual's genotype allows screening interventions to be targeted at those at higher risk, so that the benefits are proportionate to the risks and costs inherent in the screening process. It follows that those at lower risk may not be offered screening, on the basis that for these individuals, the likely risks and costs do not justify the potential benefits. However, we recognise that the introduction of personalised screening programmes might necessitate additional explanation and support being given to those at lower risk, particularly where screening has previously been offered on the basis of age alone.

Policy-makers should develop appropriate alternative prevention messages for individuals at low risk.

Recommendation 2.5: Research into the impact of technological change

We recommend research into the impact of technological change on the delivery of stratified cancer screening.

New technology will alter the way that stratified screening is delivered, for example by allowing near-patient testing, enabling more rapid analysis, providing more information about the implications of results or reducing costs. Examples include desk-top analysers capable of use in primary care settings, on-line data repositories and smartphone apps. The likely impacts of such advances may not be immediately discernible, so research is likely to be of use.

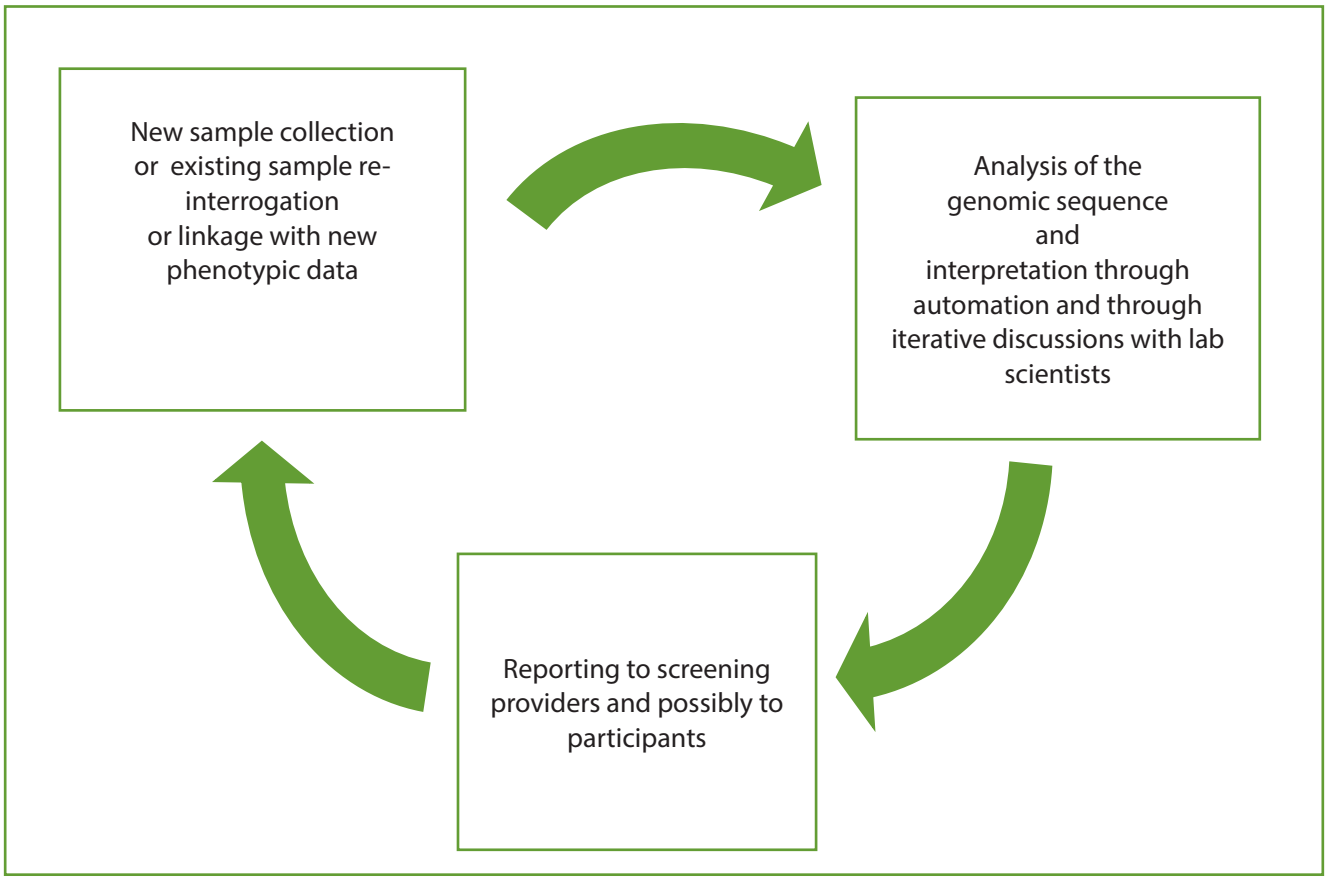
9 Ethical, legal and social issues

If the use of genomic information to stratify population screening entails the retention of samples and data for diverse uses over many years, it will give rise to many ethical, legal and social concerns. Conversely, the use of a once-only targeted test with immediate disposal of the data appears to raise fewer ethical and regulatory challenges.

What form might risk-stratified screening for common cancers take?

The ethical, legal and social issues (ELS) issues arising from the introduction of stratified screening depend on the form of risk-stratified screening adopted and the manner of its implementation. Common to all forms is an iterative process of DNA sample and data collection, interpretation and reporting illustrated in Figure 2.

Figure 2. The iterative process of sample and data collection and analysis



From [Hall A, Chowdhury S , Hallowell N, Pashayan N , Dent T , Pharoah P , Burton H. Implementing personalised screening for common cancers: a review of potential ethical, legal and social issues. Journal of Public Health 2013. doi: 10.1093/pubmed/fdt078.]

The type of samples collected and the way they are stored and interpreted (including whether personal identifiers are removed) will influence the ethical, legal and social issues that arise. We sketch two alternative data collection and storage scenarios in Table 1, suggesting some relevant ethical, legal and social issues. In reality, these issues would be more complex and dependent upon context.

Illustrative characteristics	Model A Targeted Single use/disposal	Model B Generic Multiple use/retention
Number of conditions	Single	Multiple
Number of SNP's	10's	100's
Type of sample	Buccal/blood	Blood
Storage conditions	Fresh	Frozen
Storage duration	Days	Many years
Nature of data	Sensitive personal data	Sensitive personal data
Extent of anonymisation	Data likely to be personal identifiable data stored and accessed for immediate use	Data likely to be stored as linked anonymised data
Decision support tool for sample and data donors	Unlikely	Possible
Nature of the consent	Likely to be broad consent (perhaps implied from context of care)	Likely to be explicit/specific consent
Need to accomodate changes in capacity to consent (such as child maturing to an adult, or loss of capacity through illness or disability)	Unlikely	Likely
Possibility of withdrawal	Unlikely	Opportunities and mechanisms for withdrawal should be formalised
Breadth of clinical question	Narrow	Broad
Disclosure of incidental information	Clinical question is circumscribed/ targeted so less probability of incidental information being generated	Consent should be sought for feedback of incidental information, and mechanism/process should be clear
Reinterrogation/future use for proband	-	Yes
Future use for family members	-	Yes if consented
Third party use for research (including epidemiological research)	Possible use of anonymised samples and data only	Yes if consented
Access by insurers/employers	Unlikely. Insurers/employers may use surrogates (eg invitation to screening instead)	Yes if consented
Re-contact (e.g. for additional testing or to update risk assessments)	-	Yes if consented

From [Hall A, Chowdhury S , Hallowell N, Pashayan N , Dent T , Pharoah P , Burton H. Implementing personalised screening for common cancers: a review of potential ethical, legal and social issues. Journal of Public Health 2013. doi: 10.1093/pubmed/fdt078.]

PHG COGS paper:

Implementing personalised screening for common cancers: a review of potential ethical, legal and social issues

Journal of Public Health [4.1]

In Model A, genotyping is performed as an adjunct to a targeted screening programme for a single disease. Samples are collected and promptly analysed, solely to use risk stratification to allocate to risk groups. They are then routinely destroyed, retaining only the resulting risk score. In Model B, genotyping is established as a continuing public health and health care resource to be used when necessary during an individual's lifetime, with comprehensive coverage across multiple diseases. Since genotypic and phenotypic data are retained for several purposes, more robust and comprehensive systems need to be adopted to safeguard data security, and also to provide an infrastructure for dealing with issues such as the need for re-contact, incidental or unsolicited findings or changes in capacity to consent.

What ELS issues arise?

Significant ethical, legal and social issues are potentially raised by adopting risk-stratification through Models A and B. Relevant ethical issues include the duration of storage of samples and/or identifiable personal data, safeguards taken to secure privacy and confidentiality, linkage with other phenotypic data, including lifestyle data, and interrogation and possible re-interrogation over a person's lifetime. Re-interrogation might be needed to address changing circumstances such as the discovery of new genetic variants, and alterations in lifestyle risk-factors, and may require re-contacting the participant. This possibility should have been raised explicitly at the time samples were taken. Other significant factors include the time elapsing between each genotyping phase and the role of automation and use of algorithms to refine test sensitivity and specificity and to safeguard quality assurance. We consider the extent to which the principles of respect for autonomy, beneficence, non-maleficence and justice are satisfied.

Respect for autonomy

The ethical justification for seeking consent is that an individual should understand what is proposed and its consequences[21].Securing consent indicates respect for individual autonomy. For consent to be legally valid, participants must understand, retain, use or weigh up the information needed to make a decision or communicate their wishes[22,23,24]. The consent process for risk-stratified screening will therefore need to reflect all aspects of testing and be flexible enough to accommodate variation in usage.

Thus, the consent process for Models A and B will differ regarding the information needed before sample collection, the availability of decision-support tools, and whether consent covers current and/or future use. The ethical issues that arise when consenting to targeted genotyping and risk assessment for a single common cancer as in Model A are relatively modest; in Model B, consent should also address the ownership of samples, data, and results.

The consent process will also need to address potential incidental or unsolicited findings, and describe how and when these might be fed back to participants, given the emerging consensus within genomic research and biobanking that incidental findings revealing "an established and substantial risk of a serious health condition" should be offered to participants, if clinically actionable[25].Other issues are:

- How risk prediction information is fed back to prospective screening participants, their health providers and potentially affected family members
- Secondary use of genetic variant risk information, which could result in discrimination or stigmatisation by third parties, with insurers refusing coverage or charging higher premiums to those at higher risk.

Optimising beneficence and minimising non-maleficence

One way of minimising the burdens of risk-stratified screening might be to incorporate genotyping within existing population-wide public health screening programmes, such as the newborn screening programme. Resulting risk-assessments could inform decisions about adult-onset conditions, including common cancers, through population-wide prevention programmes. Genotyping children and young people raises many ethical concerns, particularly that genotyping might compromise their future autonomous choices[26], concerns addressed by postponing risk assessment and/or targeting young adults at highest risk. In the short term, the introduction of genotyping of common genetic variants into existing neonatal screening programmes seems unlikely and might overburden providers and overwhelm existing capacity[27,28].

Another potential harm is that participants may have their confidentiality or privacy breached. Confidentiality may be threatened in both Models A and B if identifiable genetic variant information is disclosed without consent, for example, through linkage with potentially identifying phenotype or lifestyle information.

The harms and benefits of gaining predictive genetic knowledge about common genetic variants and its impact upon behaviour are uncertain; empirical evidence is limited. Systematic reviews of randomised controlled trials have explored how genetic knowledge affects smoking cessation and exercise[29] and perceived control[30]. It is unclear how knowledge about genetic susceptibility to multiple diseases might influence behaviour in the longer term[31].

The harms and benefits of gaining predictive genetic knowledge about common genetic variants and its impact upon behaviour are uncertain; empirical evidence is limited.

The principle of justice: ensuring practice that is fair, equitable and appropriate

The use of genotyping to inform access to risk-stratified screening could exacerbate concerns about distributive justice if some individuals or groups unfairly benefited and others were disadvantaged, for example through their socio-economic status, educational background or ethnicity. These concerns might be mitigated by transparency about the genetic variants forming the evidence base for risk-stratification, given that existing modelling relies almost exclusively on studies of white populations of European ancestry.

One group who may require extra resources and attention are low-risk individuals. Under a risk-stratified approach they may no longer be deemed eligible for screening or may have a less intensive regimen; some will later develop cancer. In order to avoid undermining wider trust in health services, effective communication strategies are needed to ensure that those designated as low-risk understand that the rationale in their case for not offering or reducing screening is to mitigate or avoid the risks that screening necessarily creates. In other words, less screening is about risk reduction not rationing health services.

The legal and regulatory framework

As outlined above, it is unclear what model of sample storage may be adopted by risk-stratified screening programmes. Programmes conforming to Model B will have to address the problem of storage and protection of samples and of genotypic data. Regardless of whether genotypic information is stored within a generic or dedicated databank that is central or local, publically-funded or privatised, safeguards must protect against unauthorised access and data processing and against privacy breaches. Concerns will be greater if data are readily identifiable, and linked with rich phenotypic data. More generally, there is need for harmonisation in global governance, to manage the increasing fragmentation of different elements of sample collection, analysis and interpretation.

Conclusions

If the use of genomic information to stratify population screening entails the retention of samples and data for diverse uses over many years, it will give rise to many ethical, legal and social concerns. These include data security, obtaining a meaningful consent and managing logistical issues around capacity to consent, re-contact, withdrawal and linkage of samples. Conversely, the use of a once-only targeted test with immediate disposal of the data appears to raise fewer ethical and regulatory challenges.

Our assessment is based upon an analysis of the literature rather than empirical evidence. Robust policy development will be strengthened by translational research testing the utility of adding genomic analysis to existing predictors such as family history, lifestyle factors and age, empirical evidence about how knowledge of genotype may influence risk perception and behaviour and more systematic analysis of the ethical, legal and social concerns that are generated. A critical factor might be whether targeting resources according to risk is perceived as reflecting the interests of the entire screening population.

PHG COGS paper

What ethical and legal principles should guide the genotyping of children as part of a personalised screening programme for common cancer?

Journal of Medical Ethics[4,5]

Recommendation 3.1: The storage of genotypic data

In the short term, we recommend that any risk-stratified programme that is introduced has a specific clearly defined purpose, and that the storage and linkage of samples and data are minimised.

Recommendation 3.2: The genotyping of multiple conditions

We recommend that more comprehensive programmes genotyping multiple conditions involving lifetime storage of samples or data should not currently be introduced.

A substantial number of ethical, legal and social (ELS) and organisational issues are raised by personalised screening programmes. The scale and severity of the ELS issues raised will partially depend on the delivery model that is used. Our analysis suggests that fewer ethical and regulatory concerns are likely to be raised by generating a risk assessment score that incorporates genotyping to refine screening options for adults as an adjunct to existing age-related screening programmes. Alternatively, risk-stratification might be offered as part of opportunistic stratified health care. The creation of centralised population-based databases that systematically collect and retain genotypic information for multiple diseases with linkage to phenotypic information collected over an individual's lifetime would raise substantial ethical, legal and social issues, and in the short-term, the potential harms are likely to outweigh the potential benefits. We do not support the latter approach.

Recommendation 3.3: Systematic newborn or childhood testing

We recommend that personalised screening is restricted to adult populations and do not support the systematic genotyping of newborns or young children as a preliminary to risk assessment.

Although genotyping in early life might maximise coverage and uptake, from the perspective of ethical, legal and social issues that might arise we consider it preferable to delay genotyping until individuals are mature enough (*i.e.* reach adulthood) to make a personal decision, particularly since the benefits of genotyping are at present speculative. This approach is consistent with current professional guidance on predictive genetic testing.

Recommendation 3.4: Consent

We recommend that the consent process should address the benefits, harms and uncertainties of genotyping and risk assessment, the precise nature of which will be context-dependent. Where possible, we recommend use of an encompassing consent which takes account of reasonable and foreseeable future developments.

The consent sought for genotyping should explain that the results of a buccal swab or blood test will be used to calculate a risk-assessment score, which will guide screening options. The consent should include examples of the diseases that might be detected on screening, the possibility of incidental or unsolicited information being generated and the rationale for screening and earlier detection. Depending on how, where and by whom samples, information or risk scores are retained, it should also address any implications for insurance or employment, forensic uses, potential psychological harms and the right to have samples destroyed and to opt out of continuing collection of further samples or phenotypic data. Other relevant factors include that potential participants may opt out of the process altogether if they so wish, or refuse relevant results at any stage in the process.

Recommendation 3.5: Promotion of a regulatory regime that ensures safe, robust risk assessment methods

We recommend that providers of risk stratification incorporating a genotypic element should be transparent about the evidence base and quality assurance processes that are used, to ensure that, regardless of provider, the risk assessments that are generated are safe, robust, and evidence-based.

We predict that there will be an increasingly fragmented commercial environment for providing screening, where parts of the genotyping and screening process may be funded through different methods including the state, insurer or individual. In order for policy-makers and consumers to compare what is being offered, screening providers need to be transparent about their evidence base, citing relevant scientific sources. They also need to demonstrate consistently robust quality assurance methods.

Recommendation 3.6: Policy engagement

We recommend that decision-making should be fully inclusive, ensuring meaningful engagement of all stakeholders in the policy making process.

The complexity of the risk assessment exercise reinforces the need for a diverse group of stakeholders to be involved in the policy formation, and for serious account to be taken of empirical work that measures public demand for such tests. Stakeholders and publics should be enabled to voice their concerns, and there should be transparency about how different stakeholder views are incorporated, when policy decisions are made. Particular account should be taken of public understanding in this area, and of the acceptability of risk stratification.

Recommendation 3.7: Research into the wider impact of stratification

We recommend research to clarify the wider ethical, legal and social impact of stratifying on the basis of genotypic and phenotypic risk, as compared with determinants such as age, sex and ethnic group. In particular, we recommend research to clarify the potential for generating inequalities relating to distributive justice.

It seems likely that some determinants for stratification might be regarded as being more morally justifiable than others. It follows that changing the nature of stratification could raise significant issues of distributive justice, which are likely to become apparent as pilot and early implementation studies are rolled out. One of the key research questions underpinning these studies should be to evaluate the impact of changing the basis of stratification, and in particular the potential for causing or exacerbating inequalities.

Recommendation 3.8: Research into the impact of ethnic and cultural factors

We recommend comprehensive conceptual and empirical research into the impact of ethnic and cultural factors on understanding, acceptability and uptake of personalised screening.

Much of the scientific and sociological research in this area uses populations of white European origin. Research is needed to clarify how ethnic and cultural issues may impact at every stage of the risk stratification process, on a personal and population basis.

10 Professional education and training

The introduction of stratification into prevention programmes would bring new complexities to the health system and require health professionals to adapt their practice.

Service providers would need to ensure that practitioners were competent to deliver the new services. They should set out any new competences that would be required and provide resources to meet development needs. Competences are the skills, knowledge and understanding needed to undertake a particular task to a nationally recognized level of performance. In the United Kingdom, Skills for Health is the sector skills council that assists the health sector to develop a more skilled and flexible workforce. National agreed competences are developed through formal collaborative working with relevant stakeholders, practitioners and experts. Examples of completed frameworks are provided on the organisation's website (www.skillsforhealth.org.uk).

The development of competence frameworks in the UK and elsewhere usually follows formal processes to ensure inclusion of the relevant specialists, healthcare professionals, patient groups and educators, and to ensure that the framework is in the appropriate format for translation into performance criteria and educational resources. Once completed, the frameworks are used to help in designing teams and in work-based assessment. However, their most important purpose is to guide the development of training and learning programmes, where they provide clear goals for structured learning and define learning outcomes.

In the UK, there are several competence frameworks relevant to stratified prevention (Table 2).

Table 2: British competence frameworks relevant to stratified prevention

Area of practice	Competence framework
Screening	CHS227 Conduct health screening programmes (https://tools.skillsforhealth.org.uk/competence/show/html/id/2852/)
Genetic risk	GTC6 Assessing a genetic risk (https://tools.skillsforhealth.org.uk/competence/show/html/id/2601/)
Complex risk assessment such as the UK Vascular Health Check	Vascular risk assessment: workforce competences (www.healthcheck.nhs.uk/document.php?o=164)

There are several relevant competence documents in the context of genetics[32]. These sets of competences provide a good basis but do not cover all the necessary features of stratified prevention as proposed in COGS. Those on risk assessment cover assessment and communication of disease risk and the use of risk tools in primary care. Genetics competences generally focus on rare diseases and the competences required to identify, refer appropriately, order and interpret tests, take a family history and manage issues related to prevention and reproductive choice in the individual and family members.

Competences for risk - stratified prevention programmes

There are two new elements to the preventive programmes that were proposed in the COGS programme:

- Stratified risk prevention, with tailoring of prevention according to those strata, resulting in those at higher risk having a more intensive and those at less risk having a less intensive, or no preventive intervention
- The inclusion of genetic testing as an integral part of the risk assessment tool.

The development of formal competence frameworks was beyond the remit of COGS WP7. As a step towards this, however, we examined the pathways of care under the three stages of the delivery process as set out in our service delivery models to note in general terms what it would be necessary for health professionals to know and be able to do to deliver the service. We noted that health professionals should understand the relevant policy background. They will need context-specific knowledge including understanding of the local population (for example ethnicity, deprivation and levels of education), local health services (for example the breast screening and cancer diagnostic and treatment services), and their own professional roles and responsibilities within this programme.

Key aspects for which competences will be required can be grouped according to the three stages of the care pathway:

1. Offer of risk stratified screening
2. Risk profiling, risk assessment and communication
3. The screening pathway.

New dimensions introduced by risk-stratified prevention that includes genetic testing in the risk assessment are shown below in bold.

Offer of stratified screening

- Communicate effectively with the patient about the concept of risk
- Have knowledge of the nature and determinants of the (cancer) risk including **genetic**, personal and environmental or lifestyle factors

- Understand and explain effectively the available prevention options, such as screening, and including the expected benefits and possible harms
- Understand and explain the concepts of screening, including the possibility of false positives and false negatives
- **Understand and explain the underlying rationale for a risk-stratified prevention programme, including the tailoring of prevention options according to risk stratum and cost-effectiveness**
- Explain the risk assessment tool accurately including the use of genomic, biometric and environmental/lifestyle information and its accuracy in predicting risk
- **Understand and provide information on the range and relevance of key genetic variants included in the test**
- Respond to concerns about implications of the risk assessment result for the participant and family members
- Explain how the information obtained, **including genetic information**, will be used and stored and respond to specific concerns
- Explain, as appropriate, how the information obtained, **including genetic information**, may be shared with others including researchers, and, as appropriate, commercial companies or third parties such as insurers or employers and respond to specific concerns.

Risk profiling, risk assessment and communication

- Use the risk assessment tool competently. This may include taking relevant personal and family history, lifestyle information and environmental exposures, making appropriate anthropometric and biometric measurements and obtaining relevant biomarker measurements
- Calculate individual risk using the validated tool
- Interpret risk scores for the patient
- Communicate risk in a way to support patients in decision-making about screening and other preventive strategies such as lifestyle and behaviour changes.

The screening pathway

- Offer appropriate stratified screening intervention, explaining the reasons behind this choice at a policy level and at the level of the individual patient and a policy level
- Support subsequent progress through the screening pathway including dealing with any problems arising, such as positive test results, false positives or false negatives.

Health professionals should already have many of the competences required for risk-stratified prevention programmes. Gaps arise in those specific elements relevant to stratified prevention and the inclusion of genetic testing in initial risk assessment. Such gaps will need to be filled by the development of specific educational resources and their integration into existing educational programmes.

Recommendation 4.1: Professional education

We recommend that health care professionals are prepared for the use of genomics in common disease prevention including risk-stratified screening, building on existing knowledge and skills.

We recommend formal educational needs assessment as a prerequisite for implementation.

11 Public understanding and acceptability

The provision of stratified cancer screening will be novel not only for health care practitioners and policy-makers, but also for the wider public.

Rather than receiving an undifferentiated invitation to participate in screening, the latter group will be asked to provide more information on lifestyle along with a DNA sample, and then be offered a screening intervention tailored to their risk. For some people, it may be suggested that no screening is required, because the risk of disease is low.

This is a substantial change. It will affect many people and is based on technical analysis that not all will readily understand. Yet public understanding is essential to the success of stratified screening, for two reasons:

- Valid individual consent can only be secured when the individual understands what is being offered and why
- Wider acceptance depends on collective recognition that the change is in the public's interest and compatible with prevailing norms and values.

Therefore, the introduction of stratified screening depends at an individual and collective level on adequate explanation of its nature and purpose, winning public confidence and overcoming barriers to acceptability. As yet, we know little of public reaction to the prospect of stratified screening, and further investigation of this would be timely. The example of genetically modified foods shows how a technological change with apparently persuasive scientific credentials can founder when public confidence is undermined.

Recommendation 5.1: Public understanding and acceptability

We recommend research on public understanding of risk stratified screening and its acceptability before the implementation of this approach.

12 Conclusions

The COGS project led to the identification of more than eighty new susceptibility loci and new insights into the interaction between genes and environment. Although there are numerous uncertainties, they can all be addressed by further research, other forms of enquiry and carefully evaluated innovation.

The COGS project was highly successful. It led to the identification of more than eighty new susceptibility loci[33]. There were also new insights into the interaction between genes and environment[34].

Risk-stratified screening programmes for breast and prostate cancer, with eligibility for screening based on an absolute risk that is dependent on age and polygenic risk and equivalent to the risk threshold for eligibility based on age alone, are likely to detect the majority of the cancers detected by a screening programme based on age alone, but would involve screening fewer individuals.

Risk-stratified screening programmes raise new organisational, ethical, legal and social considerations. The delivery of a risk-tailored programme is more complex than that of a 'one size fits all' programme. Consequently, the decision to implement risk-stratified screening programmes has to be based on strong evidence that such programmes are worth the added complexity. So far, the evidence on the potential effectiveness and cost-effectiveness of personalised screening for breast and prostate cancers is derived from mathematical models. More evidence will be required (for example, on the ability of the common susceptibility variants to predict the aggressiveness of individual cancers) before programmes should be considered for implementation. However, it is important that policy-makers are alerted to these future options at an early stage.

Furthermore, evidence is needed that a risk-stratified screening programme will reduce harms associated with screening, mainly by reducing overdiagnosis and overtreatment, while maintaining or increasing the benefits of screening, mainly by improving quality of life and/or reducing mortality from the cancer, and that they will do so at a reasonable cost.

A number of factors are converging to make the introduction of stratified screening programmes more likely. These include increased knowledge of the relevant genetic variants, concern about the harms associated with existing screening programmes, including overtreatment, growing attention to the cost-effectiveness of health care, including screening programmes, and an enthusiasm for more personalised healthcare throughout life.

Evidence is needed that a risk-stratified screening programme will reduce harms associated with screening, mainly by reducing inaccuracy, overdiagnosis and overtreatment, while maintaining or increasing the benefits of screening.

PHG COGS paper:

Stratified Cancer Screening: The Practicalities of Implementation

Public Health Genomics[4.6]

We foresee that stratified screening programmes will be promoted as a way of simultaneously addressing these factors. However, theoretical considerations have not yet been matched by consideration of whether and how such approaches would be implemented in practice. If the theoretical advantages of stratified screening are to be converted into improved population health, then great care will be needed to ensure that the full scale of the benefits is realised and the inevitable harms to which screening gives rise are minimised.

Participant pathways for stratified screening are likely to be complex, diverse and fluid. Decision-makers need to be mindful of the rapidly changing scientific, regulatory and social environment and ensure where possible that all providers adhere to robust standards of quality assurance, whilst facilitating development of flexible systems and services over time. More work is needed to establish the wider cost-effectiveness of the likely approaches.

Stratified screening programmes will need to be flexible enough to accommodate changes in individual risk scores over time, as well as changes of mind because of people opting in and out of screening. This tailored approach could result in greater administrative costs than existing population screening programmes. Our preliminary work on health economics has demonstrated the cost effectiveness of targeted approaches, but more detailed work is needed, taking account of the variety of potential patient pathways and the wider costs involved.

More research is needed to evaluate the benefits and harms of screening in different risk groups. However, if we assume that improved health outcomes would be achieved, the translation of the science into new, stratified screening programmes is complex. Implementation needs to reflect the organisation of health care in the country in question, and how screening services are provided. There are important uncertainties about when to offer testing, how to gather and update phenotypic information, how to communicate what the stratified programme entails and how to ensure consent is adequately informed.

How stratified screening is offered will need to reflect the values of local people, the way in which health services are arranged, and specifically the structure of primary health care and of screening services. As a result, in order to be comprehensive, our recommendations are general, but in Appendix 2 are some more specific issues for consideration.

Although there are numerous uncertainties and unresolved issues arising from the introduction of stratified screening, they can all be addressed by further research, other forms of enquiry and carefully evaluated innovation. Given the speed of development of genomic knowledge, its potential importance and the growing feasibility of stratified genomic screening, the time for policy-makers to ready themselves for this change has arrived.

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Appendix 1: Steering Group membership

Hilary Burton	Principal Investigator, and Director, PHG Foundation
Paul Pharoah	Principal Investigator, and Professor of Cancer Epidemiology, University of Cambridge
Susmita Chowdhury	Project Manager, PHG Foundation
Tom Dent	Project Lead, COGS, PHG Foundation
Alison Hall	Programme Lead (Humanities), PHG Foundation
Nina Hallowell	Associate, PHG Foundation
Georgios Lyratzopoulos	Senior Research Associate, University of Cambridge
Nora Pashayan	Senior Clinical Lecturer in Applied Health Research, University College London

Appendix 2: Delivery issues in stratified screening

If they are to proceed with stratified screening, policy-makers should consider:

- Whether to implement stratified screening
- Whether to screen for single or multiple diseases
- Whether to include testing for high-risk single-gene disorders, such as BRCA1 and BRCA2
- Whether to organise screening on a national or local basis, and how to involve primary care
- Whether to offer opportunistic screening, a centralised invitation system or both
- Whether to specify a clinical pathway for implementation at local level, or arrange a screening programme delivered across a larger area by one provider
- How to handle the implications for existing screening programmes
- Taking, retention and storage of samples and information
- Governance, service structure, data management, quality assurance and other aspects of the provision of screening
- The services available to those who screen positive.

Appendix 3: Workshop participants

The PHG Foundation's work on the COGS project would not have been possible without the contributions of participants at the three workshops. We are most grateful to them all.

First workshop, 7 to 9 July 2010

Professor Yvonne Brandberg	Professor, Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden
Dr Hilary Burton	Programme Director, PHG Foundation, Cambridge
Dr Susmita Chowdhury	Project Coordinator, PHG Foundation, Cambridge
Dr Tom Dent	Programme Associate, PHG Foundation, Cambridge
Professor Stephen Duffy	Professor of Cancer Screening, Wolfson Institute of Preventive Medicine, Queen Mary University of London
Professor Rosalind Eeles	Professor of Oncogenetics, Institute of Cancer Research & Royal Marsden Hospital, Sutton, Surrey
Professor Gareth Evans	Consultant in Genetic Medicine, Regional Genetic Service, St Mary's Hospital, Manchester
Ms Ana Fernandez-Marcos	Head of Studies & Institutional Affairs, Spanish Association Against Cancer, Madrid, Spain
Dr Richard Fordham	Health Economist, Faculty of Health, University of East Anglia
Ms Alison Hall	Project Manager (Law & Policy), PHG Foundation, Cambridge
Professor Per Hall	Professor of Epidemiology, Department of Medical Epidemiology & Biostatistics, Karolinska Institute, Stockholm, Sweden
Dr Eveline Heijnsdijk	Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands
Mr Mark Henderson	Science Editor, The Times, London
Dr Lidewij Henneman	Researcher (Social Sciences), VU University Medical Center, Amsterdam, The Netherlands
Dr Christine Hill	Specialist Registrar in Public Health, Institute of Public Health, Cambridge University
Dr Stephen John	Lecturer in Philosophy, Hughes Hall Centre for Biomedical Science in Society, Hughes Hall, Cambridge University
Miss Marie Keane	Health Care Worker, Addenbrooke's Hospital, Cambridge
Professor Anneke Lucassen	Professor of Clinical Genetics, Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton
Dr Yoryos Lyratzopoulos	Senior Clinical Research Associate, Department of Public Health and Primary Care, Institute of Public Health, Cambridge University

Dr Deborah Mascalzoni	Senior Scientist, European Academy (EURAC), Bolzano, Italy
Professor Kenneth Muir	Professor of Epidemiology, Health Sciences Research Institute, Warwick Medical School, Warwick University
Dr Nora Pashayan	CRUK Training Fellow in Cancer Public Health and Epidemiology, Institute of Public Health, Cambridge University
Professor Julietta Patnick	Director, NHS Cancer Screening Programme, Sheffield
Dr Paul Pharoah	Reader in Cancer Epidemiology, Strangeways Research Laboratory, Cambridge
Dr Imran Rafi	GP, Senior Lecturer in Primary Care Education, St George's Hospital Medical School, London
Ms Jean Sinclair	Research Nurse, MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge
Dr Sven Törnberg	Director, Stockholm Screening Programmes, Karolinska University Hospital, Stockholm, Sweden
Mr Ed Yong	Head of Health Evidence & Information, Cancer Research UK

Second workshop, 6 to 8 July 2011

Professor Emerita Cornelia Baines	Deputy Director, Canadian National Breast Screening Study, Dalla Lana School of Public Health, University of Toronto, Canada
Professor Yvonne Brandberg	Professor, Department of Oncology-Pathology, Department of Oncology, Karolinska University Hospital Solna, Stockholm, Sweden
Dr Hilary Burton	Programme Director, PHG Foundation, Cambridge
Dr Graham Byrnes	Head of Biostatistics, IARC, Lyon, France
Dr Susmita Chowdhury	Project Coordinator, PHG Foundation, Cambridge
Dr Tom Dent	Programme Associate, PHG Foundation, Cambridge
Professor Stephen Duffy	Professor of Cancer Screening, Wolfson Institute of Preventive Medicine, Queen Mary University of London
Professor Diana Eccles	Professor of Cancer Genetics, Southampton University, Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton
Professor Ros Eeles	Professor of Oncogenetics, Institute of Cancer Research, Sutton
Dr Richard Fordham	Director, Health Economics, Faculty of Health, University of East Anglia
Ms Alison Hall	Project Manager (Law & Policy) PHG Foundation, Cambridge
Dr Nina Hallowell	Senior Lecturer in Health Services Research, Institute of Health & Society, Newcastle University
Dr Eveline Heijnsdijk	Modeler, Department of Public Health, Erasmus MC, Rotterdam, Amsterdam
Dr Lidewij Henneman	Senior Researcher, Department of Public & Occupational Health, VU University Medical Center, Amsterdam

Dr Jalila Jbilou	Associate Professor, Moncton and Sherbrooke Universities, Moncton, Canada
Dr Peter Kraft	Associate Professor of Epidemiology, Harvard School of Public Health, Boston, USA
Dr Yoryos Lyratzopoulos	Senior Clinical Research Associate, Department of Public Health and Primary Care, Institute of Public Health, Cambridge University
Dr Deborah Mascalzoni	Senior Researcher, European Academy EURAC, Bolzano, Italy
Dr Tiago Moreira	Senior Lecturer, School of Applied Social Sciences, Durham University
Dr Colleen McBride	Chief Senior Investigator, National Human Genome Research Institute, Bethesda, Maryland, USA
Dr Ellen Nolte	Director, Health and Healthcare Policy Programme, RAND Europe, Cambridge
Dr Nora Pashayan	Consultant in Public Health Medicine, PHG Foundation, Cambridge
Professor Julietta Patnick	Director, NHS Cancer Screening Programmes, Sheffield
Dr Paul Pharoah	Reader in Cancer Epidemiology, Strangeways Research Laboratory, Cambridge
Dr Nadeem Qureshi	Clinical Reader, Division of Primary Care, Nottingham University
Dr Imran Rafi	GP, Senior Lecturer in Primary Care Education, St George's University of London
Ms Jill Rogers	Jill Rogers Associates, Cottenham, Cambridge
Dr Nereo Segnan	Director, Unit of Cancer Epidemiology and Department of Cancer Screening, CPO Piemonte and S Giovanni University Hospital, Turin, Italy
Dr Ros Skinner	Senior Fellow, PHG Foundation, Cambridge
Dr Hilary Thomas	Professor of Health Care Research, Centre for Research in Primary and Community Care, University of Hertfordshire
Dr Sven Törnberg	Director, Stockholm Screening Programmes, Karolinska University Hospital, Stockholm, Sweden
Dr Susan Wallace	Lecturer in Population and Public Health Sciences, Department of Health Sciences, University of Leicester

Third workshop, 24 to 26 October 2012

Professor Michael Burgess	Professor and Chair in Biomedical Ethics, University of British Columbia, Vancouver, Canada
Dr Hilary Burton	Director, PHG Foundation, Cambridge
Dr Graham Byrnes	Biostatistician, IARC, Lyons, France
Dr Jennie Carpenter	Consultant in Public Health Medicine, Screening and Specialised Services, Department of Health, Quarry House, Leeds
Dr Susmita Chowdhury	Project Manager, PHG Foundation, Cambridge
Dr Tom Dent	Programme Associate, PHG Foundation, Cambridge
Professor Stephen Duffy	Professor of Cancer Screening, Wolfson Institute of Preventive Medicine, Queen Mary University of London
Professor Doug Easton	Professor of Genetic Epidemiology, University of Cambridge
Professor Ros Eeles	Professor of Oncogenetics, Institute of Cancer Research, Royal Marsden Hospital, Sutton
Dr Alfonso Frigerio	Medical Doctor and Radiologist, SSCVD Senologia di Screening, AO Citta Della Salute e Della Scienza, San Giovanni Battista, Turin, Italy
Ms Alison Hall	Senior Policy Adviser, PHG Foundation, Cambridge
Professor Per Hall	Professor of Epidemiology, Department of Medical Epidemiology & Biostatistics, Karolinska Institute, Stockholm, Sweden
Dr Nina Hallowell	Programme Lead, PHG Foundation, Cambridge
Dr Judith Hayward	GP with a special interest in Genetics, Yorkshire Regional Genetics Service, Leylands Medical Centre, Heaton, Bradford
Dr Lidewij Henneman	Senior Researcher, Department of Clinical Genetics, VU University Medical Center, Amsterdam, The Netherlands
Dr Dennis Ip	Clinical Assistant Professor, School of Public Health, University of Hong Kong
Ms Chris Jacobs	Consultant Genetic Counsellor and Joint Lead for Cancer Genetics, Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London
Dr Jalila Jbilou	Associate Professor, Moncton and Sherbrooke Universities, Moncton, Canada
Dr Mark Kroese	Programme Director, PHG Foundation, Cambridge
Dr Deborah Mascalzoni	Senior Researcher, EURAC, Bolzano, Italy
Dr Colleen McBride	Senior Investigator, National Institutes of Health, Social and Behavioral Research Branch, Rockville, USA
Professor Steven Morris	Professor of Health Economics, UCL Centre of Applied Health Research, UCL Research Department of Epidemiology & Public Health, University College London
Professor Kenneth Muir	Professor of Epidemiology, Health Sciences Research Institute, Warwick Medical School, Warwick University

Dr Nora Pashayan	Senior Clinical Lecturer, Department of Applied Health Research, University College London
Dr Christine Patch	Consultant Genetic Counsellor, Guy's & St Thomas' NHS Foundation Trust, Guy's Hospital, London
Professor Paul Pharoah	Professor in Cancer Epidemiology, Departments of Oncology and Public Health & Primary Care, Strangeways Research Laboratory, Cambridge
Professor Nadeem Qureshi	Professor of Primary Care, Nottingham University
Ms Jill Rogers	Director, Jill Rogers Associates, Cambridge
Dr Susan Wallace	Lecturer in Population and Public Health Sciences, University of Leicester
Dr Fiona Walter	Clinical Lecturer in General Practice, Cambridge University
Dr Ron Zimmern	Chairman, PHG Foundation, Cambridge

Appendix 4: PHG Foundation COGS papers

1. Hall A, Chowdhury S, Hallowell N, Pashayan N, Dent T, Pharoah P, Burton H. Implementing personalised screening for common cancers: a review of potential ethical, legal and social issues. Journal of Public Health 2013. doi: 10.1093/pubmed/fdt078.

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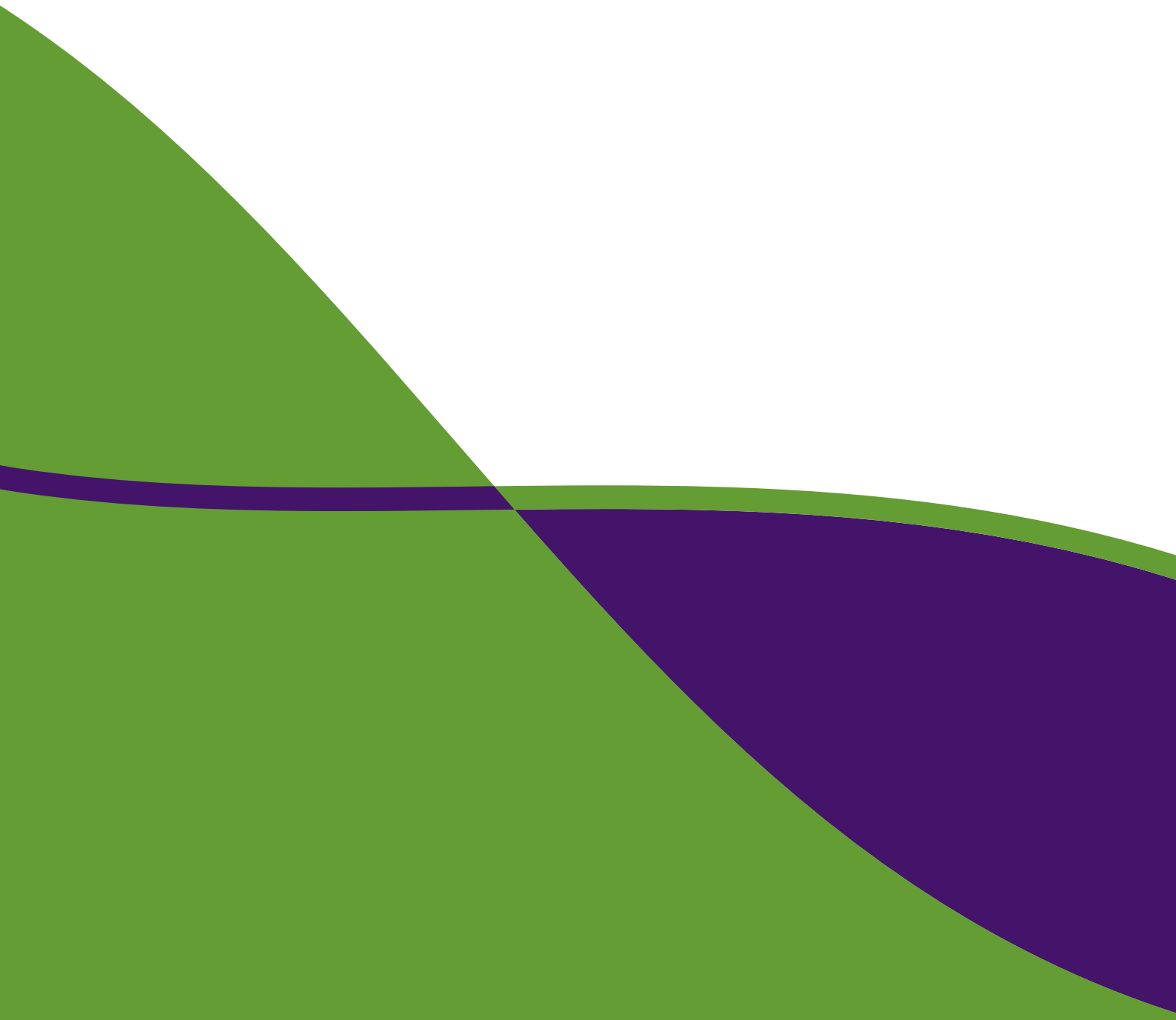
About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.



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PHG Foundation
2 Worts Causeway
Cambridge
CB1 8RN

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