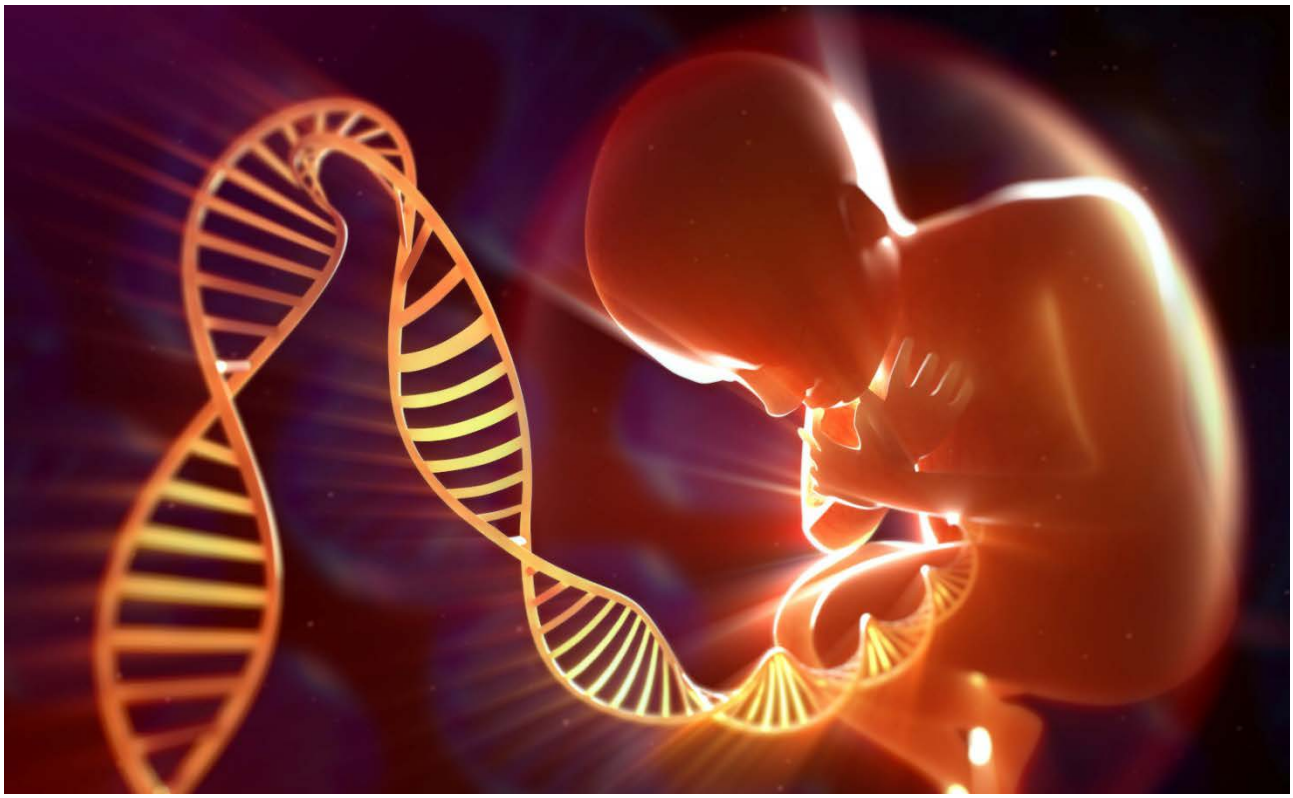
UK National Screening Committee

Generation genome and the opportunities for screening programmes



About the UK National Screening Committee

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

The UK NSC secretariat is hosted by Public Health England (PHE).

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Executive summary

The annual report of the chief medical officer 2016 subtitled ‘generation genome’ noted the potential for improving care to patients and considered how we currently utilise genomics in our health and care system. The CMO challenged the UK National Screening Committee to look at the opportunities offered by genomics for present and potential screening practices. This report provides a summary of these opportunities.

The report briefly defines genome sequencing and how, by improving our understanding of genetic activity, we can determine how best to use genetics in screening.

As evidence accumulates on the use of genomics in population screening, the UK NSC will incorporate this new knowledge into the process of considering proposals for new population screening programmes or to modify existing ones. The UK NSC reviews evidence against specified criteria and engages with stakeholders and experts in order to undertake comprehensive reviews of evidence and asociated proposals for programme modifications.

This report explores how genomic technologies can help us to improve screening programmes, and opportunities for individuals, for:

- whole population screening
- cascade screening

It considers:

- opportunities for developing differential screening strategies
- the potential for additional tests to increase the range of conditions screened for
- the potential to improve the acceptability of tests
- confirmatory uses, where a person who might have a higher-chance standard test result could receive a confirmatory result with a genetic assessment
- how genetic knowledge might support personalised treatment opportunities to ensure that the most effective treatments are used
- the role of genetics in improving our understanding of the causes of disease

The report raises the societal, ethical, and logistical factors that will need consideration when genomic technologies are introduced, such as:

- timing, and whether or when whole genome sequencing is offered

- what information needs to be developed to best inform people of the outcomes and implications of using genomics in screening
- what infrastructure is required to support the programme, including IT systems, storage facilities, workforce capacity, and education and training needs

The report then reflects the specific opportunities afforded by genomics which were identified by each of the 11 population screening programmes, for example:

- the antenatal and newborn screening programmes are exploring opportunities for contingent non-invasive pre-natal testing (NIPT) which may reduce the harms associated with invasive tests and improve test acceptability
- understanding how genomic test results can help decide how best to manage the patient, including whether to have additional genetic assessments when the biochemical test indicates the need for referral
- how we might use genetic testing as a first line test to identify conditions which do not have a suitable biochemical marker, and
- how risk stratification opportunities using genomics can deliver a more efficient service and reduce harm by tailoring management to cancer type

The report concludes that the advances in genomic technologies present exciting and potentially effective developments for screening programmes. We expect to use the current and developing research and technology to determine how, going forward, we can best use genetics in screening.

Introduction

This report provides a summary of the opportunities afforded by genomics technology for present and potential screening practices.

This will feed into the work of the UK National Screening Committee (UK NSC) and inform discussions on those technologies which are likely to require consideration in the immediate term as a major modification to the current screening programme, and those which we can look forward to as a more medium term prospect.

In genomics we talk of germ line or somatic mutations. This paper is specifically concerned with germ line mutations.

Germ line mutations are inherited whereas **somatic** mutations are not inherited and are not passed on. They may have a lifestyle or environmental cause.

Genomics[1]

The study of all the DNA in the genome together with the technologies that allow it to be sequenced, analysed and interpreted is collectively called genomics, or genomic medicine if applied to patients.

DNA is the main constituent of chromosomes and the carrier of genetic information

[1] from https://www.genomicsengland.co.uk/understanding-genomics/cancer-genomics/

A genome is an organism's whole set of DNA. A gene is a piece of DNA with a code for a specific instruction – like whether your eyes are blue or brown. A person has around 20,000 genes which make up about 5% of DNA. The rest of the DNA has a vital role in controlling and regulating the way your body works. That's why the whole genome is sequenced.

About 99.8% of our DNA is the same as other human beings. The 0.2% that is different – about 3 to 4 million letters – is what makes each of us unique.

Genes give the code for a specific instruction. This instruction may or may not be 'followed', this means that it does not always lead to a specific condition or state. We are exploring how and when a specific genetic code has an impact on a person, and we know that this might be affected by the external influences a person is exposed to.

The degree to which a gene might lead to a specific disease is called its penetrance. A gene's penetrance may be modified by other genes or lifestyle issues. In the study of genetics and penetrance of a gene we refer to phenotypes, genotypes and epigenetics.

Phenotype refers to the characteristics of the organism. It is determined by the interaction of the genes of the organism and its environmental (or lifestyle) factors.

Genotype refers to the genetic make-up which contributes to the phenotype of the organism.

Epigenetics is concerned with the study of inherited characteristics which are not genetic changes.

It is important for us to understand the impact of factors which influence genetic activity in order that we can determine how best to use genetics in screening. For example, understanding the penetrance of a gene can help us identify people at very low or very high risk of disease so we can offer appropriate advice and treatment.

Gene penetrance is the potential risk that the gene might lead to a specific condition.

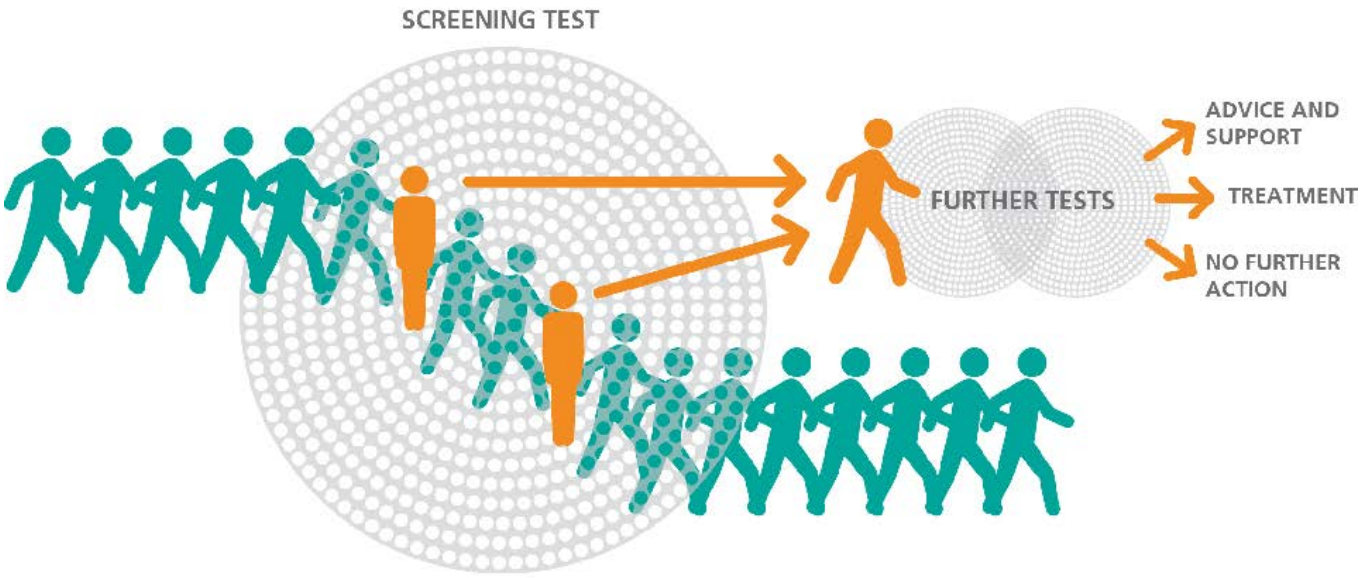
Genomic technologies in screening

Genomic technologies in screening might be used by different people in different ways, for example:

- whole population screening
- cascade screening
- individual access

Whole population screening

Whole population screening is where screening is offered to everyone in a large population group, for example, all eligible women between 25 and 64 years old are offered cervical screening to assess and manage risk factors for cervical cancer.

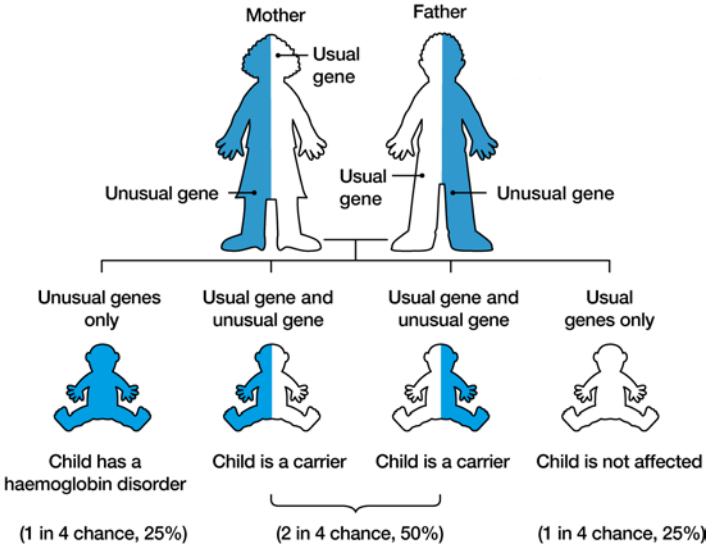


Population screening can be thought of like putting people into a sieve. The sieve represents the screening test and most people pass through it. This means they have a low chance of having the condition screened for.The people left in the sieve have a higher chance of having the condition. A further investigation is then offered to them.

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Cascade screening

Cascade screening is a way of targeting screening for those who we think might have certain genetic mutations which may increase their risk of disease.



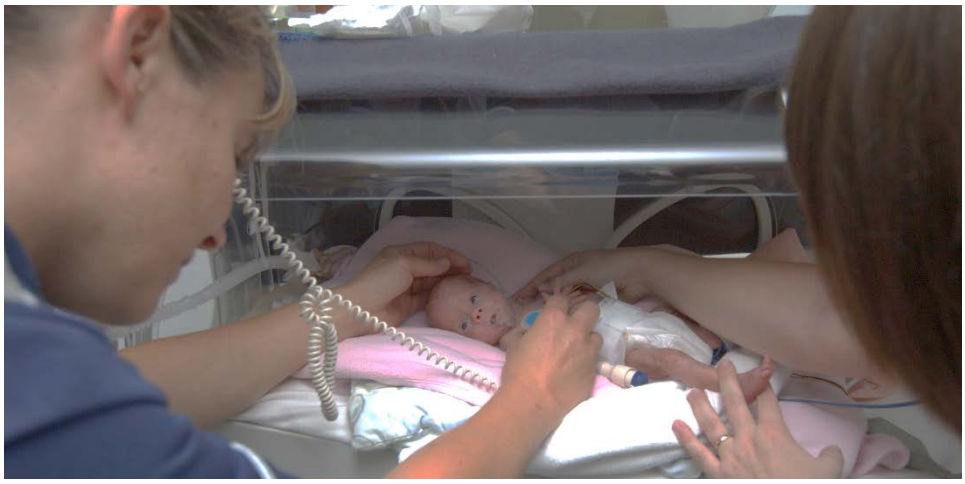
Cystic fibrosis is an example of a recessive disease. This means both the mother and father must pass on the mutated gene for their baby to be affected.

For example, we screen family members for certain gene mutations if that mutation is found in another family member. Cystic fibrosis is an inherited gene disorder, so if someone has been diagnosed with cystic fibrosis, family members will be offered screening to see if they carry the cystic fibrosis gene.

Individual opportunities

Individuals might benefit from genomic technologies to help personalise their treatment pathways or the results of screening tests.

For example, there is a genetic mutation which indicates susceptibility to a certain type of antibiotic (aminoglycosides), and therefore is at risk of aminoglycoside-induced hearing loss. Should a child require these drugs then they could be tested for this mutation in the event of this drug being considered for use[2].



In the future, babies could benefit from genomic technologies

[2] These are a group of strong bactericidal medications used in treating some serious infections such as TB. Their use is managed very carefully.

UK National Screening Committee (UK NSC)

The UK NSC remit is to specifically consider population screening programmes, rather than small sub-groups such as cascade screening of family members. However, where there are screening opportunities identified which do not fall into the category of population screening, then the UK NSC will draw attention to them through the usual routes such as the National Institute for Health and Clinical Excellence (NICE) and the relevant Royal Colleges.

The UK NSC is an independent committee that:

- advises ministers and the NHS in the 4 UK countries about all aspects of population screening
- supports implementation of screening programmes
- works with partners to ensure it keeps abreast of scientific developments in screening, including screening trials, screening policy in other countries and emerging technologies
- is accountable to the 4 chief medical officers (CMOs), who agree work plans for the UK NSC on an annual basis

The Fetal, Maternal and Child Health Group and the Adult Reference Group advise the UK NSC on issues relating to screening policy in the relevant populations.

Screening programmes are assessed against criteria to understand the balance of harms and benefits they deliver to the population, and include consideration of:

- the condition for which screening is suggested
- the test, which should be simple, safe, precise and acceptable
- whether there are effective interventions which lead to better outcomes for patients identified through screening
- whether there is evidence that screening would be effective in reducing mortality or morbidity, or where screening is aimed solely at providing information to allow the person being screened to make an ‘informed choice’ (such as Down’s syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk
- the process of implementation, which includes the managing and monitoring of screening against agreed standards

For population based screening programmes, the UK NSC reviews proposals for new screening programmes or to modify existing ones using these criteria. Such proposals

might be brought forward because there are new more reliable tests, treatments, or evidence available. Accordingly, as evidence accumulates on the potential role of genomics in population screening, UK NSC will incorporate it into this process.

Background to this report

The 2016 annual report of the chief medical officer, subtitled ‘generation genome’, focuses on the current and potential opportunities for genomic services and technologies to improve prevention, health protection and patient outcomes

In her report, Professor Dame Sally C Davies takes a ‘detailed look at genomics, exploring how we currently utilise genomics in our health and care system and how its potential may be developed’.

She says:

> Genomics is not tomorrow. It’s here today. I believe genomic services should be available to more patients, whilst being a cost-effective service in the NHS. This is exciting science with the potential for fantastic improvements in prevention, health protection and patient outcomes.

Her report particularly notes the potential for improving care to patients with cancer and contains an associated recommendation for the UK NSC asking that it undertakes:

‘A systematic evaluation of the opportunities offered by genomics for present and potential screening practices. These may be national, population-based programmes as well as cascade or individual. This should include evaluation of:

- cost-effectiveness
- feasibility
- acceptability
- impact on uptake.’

Potential in screening

Public Health England (PHE) sought expert opinion from the advisory committees for each of the 11 screening programmes on the potential use for genomic technology.

These uses may include:

- replacement first screening tests – where the usual screening process is replaced by a new test
- potential additional tests – where genomics might give us information additional to that which can be provided by the current test
- confirmatory purposes – where a person might have a higher risk standard test result confirmed by a genetic assessment

Genomic technologies can help us to improve screening programmes by enabling us to develop:

- **differential screening strategies** – genome sequencing can help us to identify germ line mutations and genetic variants that predispose someone to a specific disease. When we can identify people at higher risk of developing a condition then we can develop differential screening strategies for them. That is: screening options that fit a person's risk picture best. As our knowledge grows, differential screening strategies could replace or add to current population screening programmes
- **new tests** to improve the range of conditions and the acceptability of testing, for example, where tests might be less invasive or be more accurate in identifying risk
- **personalised treatment opportunities** – as our understanding of the complex relationship between our genes, how they are expressed within our bodies and how they influence the effectiveness of treatments, increases then we will be able to personalise treatments to ensure that the most effective treatments are used
- **a greater understanding of the causes of disease**. Once a condition has been identified then there is a role for genome sequencing in helping to understand the aetiology, or causes, of the condition. It is also starting to help understand which genetic variants will cause symptoms and which may not cause the person any symptoms at all

General considerations

There are many societal, ethical, and logistical factors that will need consideration when genomic technologies are introduced. Advisory committees for population screening

programmes, PHE, and the UK NSC are already exploring these, and they can include considerations of timing, information and consent issues, infrastructure including data collection and storage, and training needs. These are summarised below.

Timing

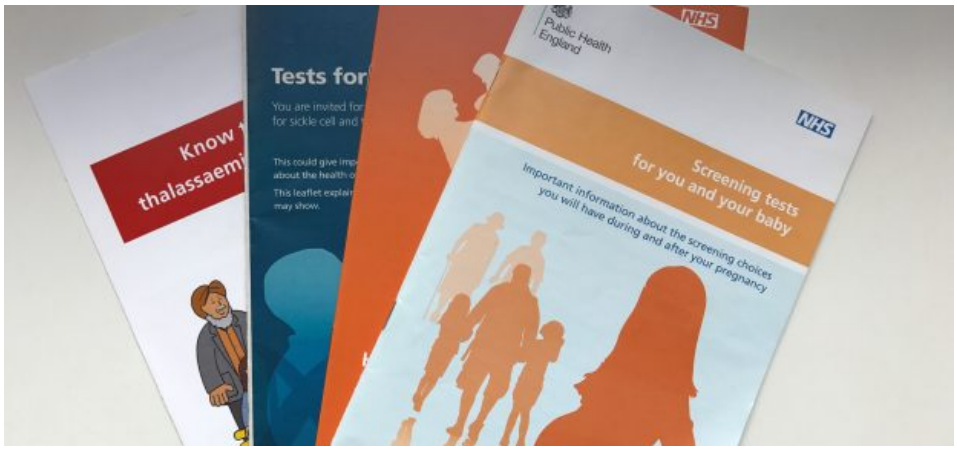
Consideration should be given to whether whole genome sequencing is offered:

- **on diagnosis** of a condition to inform personalised treatment
- **on request**, for example for those with family history or a tissue diagnosis that may be associated with a specific condition
- **by age**, for example, in association with, or before, the primary screen to personalise the individual screening strategy within the population
- **as part of a bank of diseases or risks** that are evaluated as part of a health screen and could be used to advise individuals about personal risk

Information to individuals

The development of information regarding genome testing will need to deliver:

- messages about genome testing and the additional information that may be discovered about an individual's health and risk of other diseases
- information for relatives if a significant mutation was identified
- more general education about the interpretation of risk, and ensure that each individual is able to interpret personal risk of breast cancer alongside risk of other health issues
- clear messages to ensure that individuals understand the full impact of the extent of any screen being proposed to ensure informed consent[3]



PHE already produces the information to support screening invitations made by the NHS

[3] Guidance on the importance of personal informed choice can be found at https://www.gov.uk/government/publications/uk-national-screening-committee-information-development-guidance.

Infrastructure

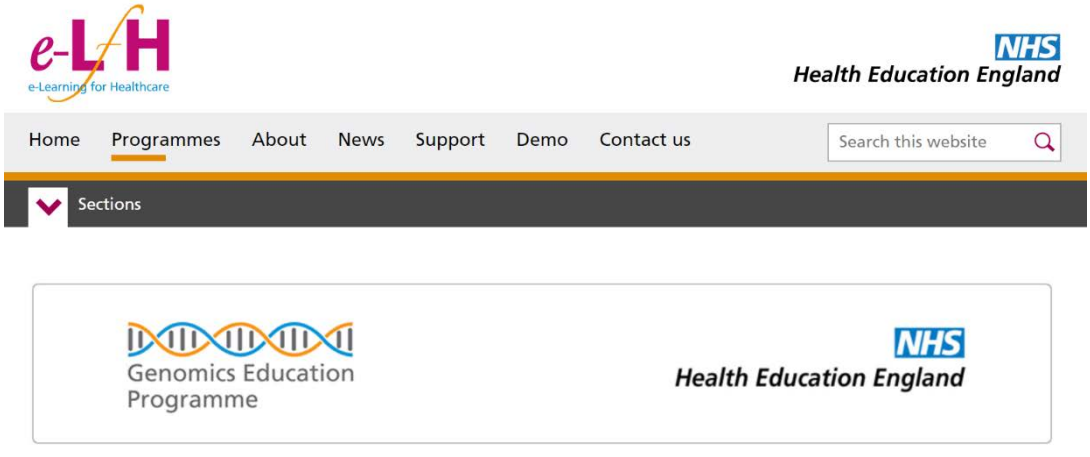
Any screening programme development needs to consider the infrastructure required to support the programme. Genomic technologies have the potential to individualise services which add an additional complexity into the system. The infrastructure needs to include:

- **an IT system** that is designed to manage different screening strategies within the population, including variation in age of onset, screening interval and screening test. The system should be adaptable such that the screening strategy can be effectively changed for an individual or population with relative ease
- **a workforce** that is able to deliver the screening test to the population and safely adapt changes in screening activity
- **integration of information** (for example about radiology, genomics and histopathology) to support decision-making. For example, if a particular genome profile is associated with a mammographic feature in the development of a cancer, then that feature would be weighted more heavily in the individual concerned
- **storage facilities** for diagnoses and higher risks that might influence reproductive choice, where we need to be able to store and retrieve data until such time as a person might need the results

Education and training

The UK NSC is engaging with training and education opportunities in this complex and fast-developing topic by encouraging staff to access opportunities to further develop their knowledge.

There is a specific drive to develop training opportunities and discussions with genetics and ethics specialists to support UK NSC Stakeholder engagement activity, the Adult Reference Group and the Fetal and Maternal Child Health Group.



PHE already works closely with Health Education Education, who provide genomics education through their e-Learning for Health portal (https://www.e-lfh.org.uk)

Children

PHE screening and the UK NSC are represented on the national Genomics Analysis in Children task and finish group.

The particular focus of PHE screening is to provide guidance and advice on genomics about:

- diagnostics for acutely ill children, or chronically ill children where there has been limited success in diagnosing an ongoing condition
- research to explore how whole genome sequencing (WGS) might be used in screening of newborns: in addition to current programmes or to replace them, and either to screen for the same conditions or to extend the current scope

We are providing advice and guidance with regards to screening principles and how these might translate to WGS, with their concomitant ethical considerations. We feed into the 2 sub-groups: ethics and societal impacts, and developing the research questions.

Specific opportunities

The specific opportunities afforded by genomics which were identified by each of the screening programmes are described below.

There are 11 population screening programmes. Antenatal and newborn screening comprises the:

- NHS Fetal Anomaly Screening Programme (FASP)
- NHS Infectious Diseases in Pregnancy (IDPS) Screening Programme
- NHS Sickle Cell and Thalassemia (SCT) Screening Programme
- NHS Newborn Hearing Screening Programme (NHSP)
- NHS Newborn and Infant Physical Examination (NIPE) Programme
- NHS Newborn Blood Spot (NBS) Screening Programme

Young person and adult screening comprises the:

- NHS Breast Screening Programme (BSP)
- NHS Bowel Cancer Screening Programme (BCSP)
- NHS Cervical Screening Programme (CSP)
- NHS Diabetic Eye Screening (DES) Programme
- NHS Abdominal Aortic Aneurysm (AAA) Screening Programme

Fetal anomaly screening programme

PHE is exploring opportunities for contingent non-invasive pre-natal testing (NIPT) for Down's syndrome (trisomy 21), Edwards' syndrome (trisomy 18) and Patau's syndrome (trisomy 13), with cell free DNA (cfDNA) testing.

Contingent: NIPT is where a second non-invasive test is offered following a higher chance result from the first test.

Non-invasive pre-natal testing (NIPT) is at the vanguard for population screening. The current FASP screening pathway can lead to further tests or treatments and interventions that some people find unacceptable, for example invasive antenatal tests. A genetic assessment may reduce the harms associated with invasive tests and improve acceptability.

Currently, pregnant women who are identified as higher chance for having a child with Down's syndrome can have further more reliable tests, however, because these are

invasive they carry a risk of miscarriage. NIPT is less invasive and has a high level of accuracy.

NIPT, as a second line test for Down's syndrome, will take blood from the mother for analysis, rather than involve collection of a sample of tissue or amniotic fluid from inside the uterus. NIPT also provides a more reliable result than other prenatal tests which draw inferences from ultrasound scans and the hormone levels of the mother.

Blood being taken from a pregnant woman for NIPT

Pilot studies are currently underway to consider effectiveness, impact on uptake, and acceptability of NIPT. It is likely that NIPT will become the follow up test for people who are identified at their first screen as having a higher chance for having a child with Down's syndrome. In the future, we can anticipate that NIPT may replace some of the more invasive elements of the current fetal anomaly screening programme.

The evaluation of the introduction of NIPT in a contingent model will inform the consideration of NIPT as a first, or primary, screen. The FASP advisory committee is expecting to consider the role of NIPT as a primary screen in the near future, assuming it meets the required UK NSC criteria. Of course this is a huge ethical issue so any expansion will be carefully considered by the UK NSC and the advisory committee according to agreed procedures.

NIPT is developing at a rapid pace and newer technologies will likely bring improved performance and reduced cost. There is additional potential to expand the number of conditions that NIPT can test for.

Sickle cell and thalassemia screening

NIPT for haemoglobinopathies[4] is very likely to become available and will be considered as a replacement for invasive testing for conditions such as sickle cell and thalassemia (SCT).

Current research is underway to use blood samples taken from the mother (as for the NIPT technique for fetal anomaly screening) where cell-free DNA is collected. The aim is to test this using Next Generation Sequencing (NGS). A diagnostic test (rather than a test which gives a risk result) will mean that no further invasive testing is required.

The improvements in technologies are likely to bring rapid progress in the development of these tests, and it is anticipated that in the first instance the non-invasive prenatal diagnosis tool will be used in high risk pregnancies.

Newborn blood spot screening

The newborn blood spot is a process of testing for rare but serious conditions. A blood spot sample is sent for analysis and the result is based on biochemical measurement of pathogenic compounds in the dried blood spot sample and when these are found in greater concentration than the agreed cut-off, a clinical referral is made to the specialist physician.

Genomics has huge potential for newborn blood spot screening

[4] Haemoglobinopathy is the term for genetically determined blood disorders or diseases that affect red blood cells

There is a clear potential for genomics in the testing for many of the conditions currently included in the blood spot test. These might benefit not only the baby but other family members via better cascade screening opportunities.

Cystic fibrosis

Cystic fibrosis (CF) is a genetic condition. You are born with CF and cannot catch it later in life, but one in 25 of us carries the faulty gene that causes it, usually without knowing. For someone to be born with CF, both parents must carry the faulty gene. If both parents have the gene, there is a 25% chance the child will have CF. If both parents carry the gene there is also a 50% chance of the child being a gene carrier but not having CF and a 25% chance they will not have the CF gene.

An example of current genetic sequencing in the case of CF is where an initial biochemical test results above the agreed cut off can prompt testing for some specified genetic mutations. By combining the biochemical test and the genetic test results a decision is made about whether to refer the patient for confirmation and possible treatment or simply advise the parents that the child may be an unaffected carrier.

Next Generation Sequencing for Cystic Fibrosis (NGS CF) diagnostics is currently being piloted, to test a significantly increased range of pathogenic combinations of the mutations and is due to report towards the end of the year. The outcomes of the pilot will be presented at the UK NSC for consideration as to potential use. It is hoped that NGS CF may reduce residual uncertainty in the programme and reduce the need for re-testing.

Medium chain acyl CoA dehydrogenase deficiency (MCADD)

Genomics can be used in diagnostic and confirmatory testing following clinical referral to help guide clinical treatment. An example where this is regularly used following screening would be in the metabolic disorder medium chain acyl CoA dehydrogenase deficiency (MCADD). When the biochemical test indicates the need for referral, then we can test for genetic mutation G985A. Depending on the result the clinical team can decide how best to manage the patient, including whether to have additional genetic assessments.

Severe combined immune deficiency (SCID)

Genetic testing can also be used as a first line test to identify conditions which do not have a suitable biochemical marker, for example: in newborn screening for Severe Combined Immune Deficiency (SCID). White blood cells help protect the body against infection. When certain white cells form they leave behind small pieces of DNA. If the

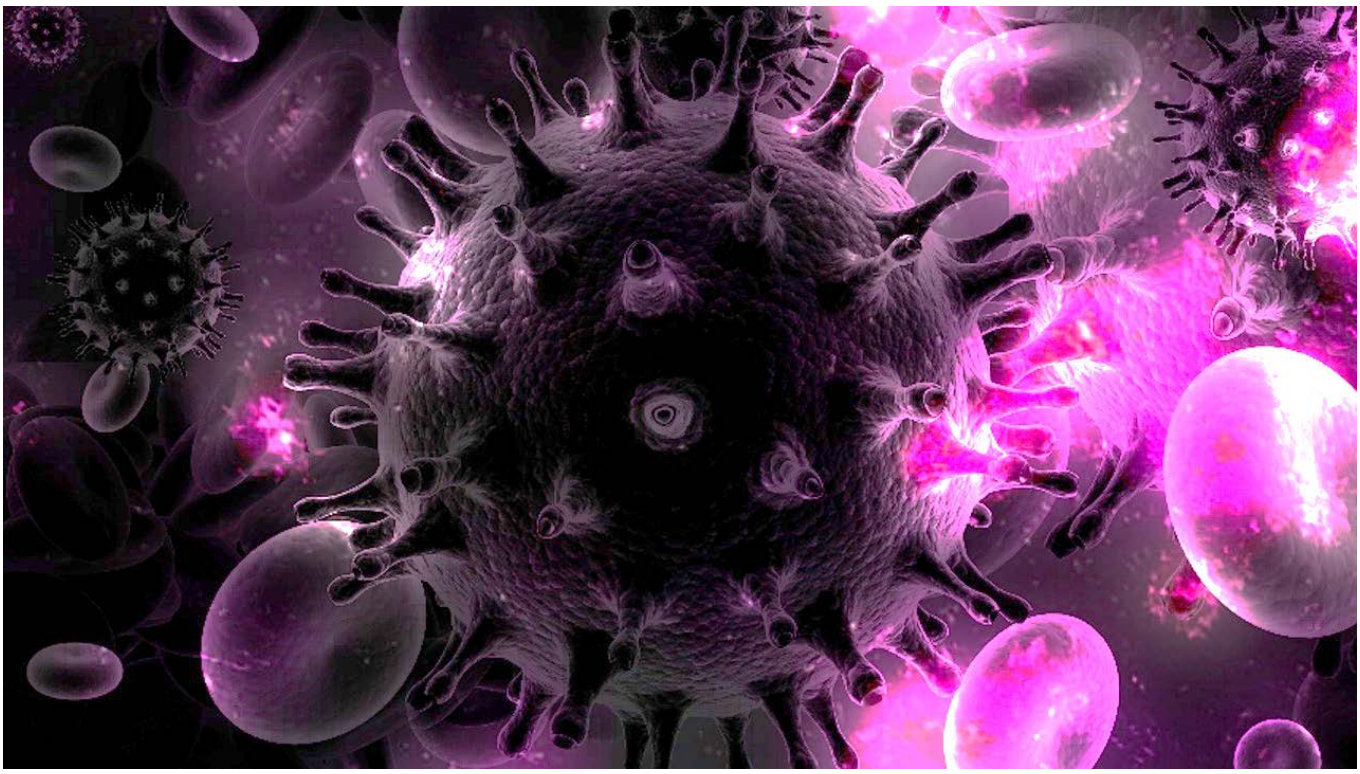
test for SCID cannot find these bits of DNA it means there are fewer white blood cells which could be an indication of SCID.

This has been introduced in many states within the USA and is under evaluation in several countries in Europe with an evaluation in the UK in an advanced stage of planning. DNA based testing for specific disorders without a suitable biochemical marker such as SCID is likely to be adopted over the coming years.

Perhaps somewhat more speculatively, next generation sequencing and other genomic approaches have been proposed as first line tests for inherited metabolic conditions and disorders such as spinal muscular atrophy. Recent work in the UK indicates that it is technically feasible to perform such analyses using dried blood spot samples, even if not currently practicable. Developments in the technology will bring further benefits for understanding other inherited metabolic disorders and the phenotype-genotype correlation offered by genomic testing.

Infectious diseases in pregnancy screening

There is currently no obvious potential genomic developments which are relevant to the IDPS programme. The advisory committee is continuing to remain alert to new developments.



HIV is one of the diseases tested for as part of infectious diseases in pregnancy screening (the others are syphilis and hepatisis B)

Newborn hearing screening

There is active research looking at genetic causes of hearing loss. About half of permanent deafness in children appears to be due to genetic causes. Not all the genes relating to deafness have been identified. The specific genes that are currently tested for depend on specific circumstances including family history and different symptoms. We know that early intervention for the child and carers allows for better educational and social development. If new cases of hearing loss that might be missed by the current programme could be detected through genetic screening then this might be a useful addition to the programme.

A hearing screening test taking place

Whole genome sequencing will be much more likely able to locate a responsible gene for a child's hearing loss, meaning that more families will get information about the cause of their child's deafness. Based on our experience of working with families of deaf children, the majority welcome the provision of further information about the causes of their child's deafness.

Individuals might benefit from genomic technologies to help personalise their screening or treatment pathways. For example, there is a genetic mutation which indicates susceptibility to a certain type of antibiotic (aminoglycosides), and therefore is at risk of aminoglycoside-induced hearing loss. Should a child require these drugs then they could be screened for this mutation in the event of this drug being considered for use.

Current evidence is not available to indicate how useful this would be on a population basis but there is evidence that a minimally invasive, cheap and effective bedside genetic test could be used to get results very quickly in the event of the drug being considered for use[5].

Improved knowledge of genetics and improvements in genetic diagnosis could enable earlier identification of other disabilities or health conditions that coexist with deafness and develop later in life (for example, some visual disorders such as Usher syndrome or kidney dysfunctions such as in Alport syndrome). This will help families and professionals plan for educational and health care needs, including audiology care.

Having a certain syndrome, for example, may mean that a hearing loss will worsen over time and therefore more frequent hearing checks may be needed. It might also mean that hearing aids will not provide a child with access to sound and that families should consider cochlear implants for their child.

Breast screening

Some programmes and conditions will benefit more obviously from using genomics at some level, for example: our understanding of the role of the BRCA1 and BRCA2 gene mutations in assessing the risk of breast cancer is increasingly informing our developing screening strategies.

The breast screening service is already considering risk stratification opportunities to inform the current programme. This has the potential to deliver a more efficient service and reduce harm by tailoring management to cancer type. We could develop pathways more closely tailored to a person's needs: the programme would still start with an offer to the whole 50 to 70 year old female population but can then vary tests, screening frequency and preventive therapies accordingly.

There is current research demonstrating that it is feasible to stratify women's risk of breast cancer, by age, breast density and single nucleotide polymorphisms, and that this is acceptable to women who attend for routine mammographic screening. This work provides an example of how risk assessment and stratification might be implemented to a population.

At present there is active work to research a better, more nuanced, set of tests for breast cancer. Any replacement for mammography would be expected to improve upon, and overcome the limitations of, the current screening practice.

[5] These are a group of strong bactericidal medications used in treating some serious infections such as TB. Their use is managed very carefully.

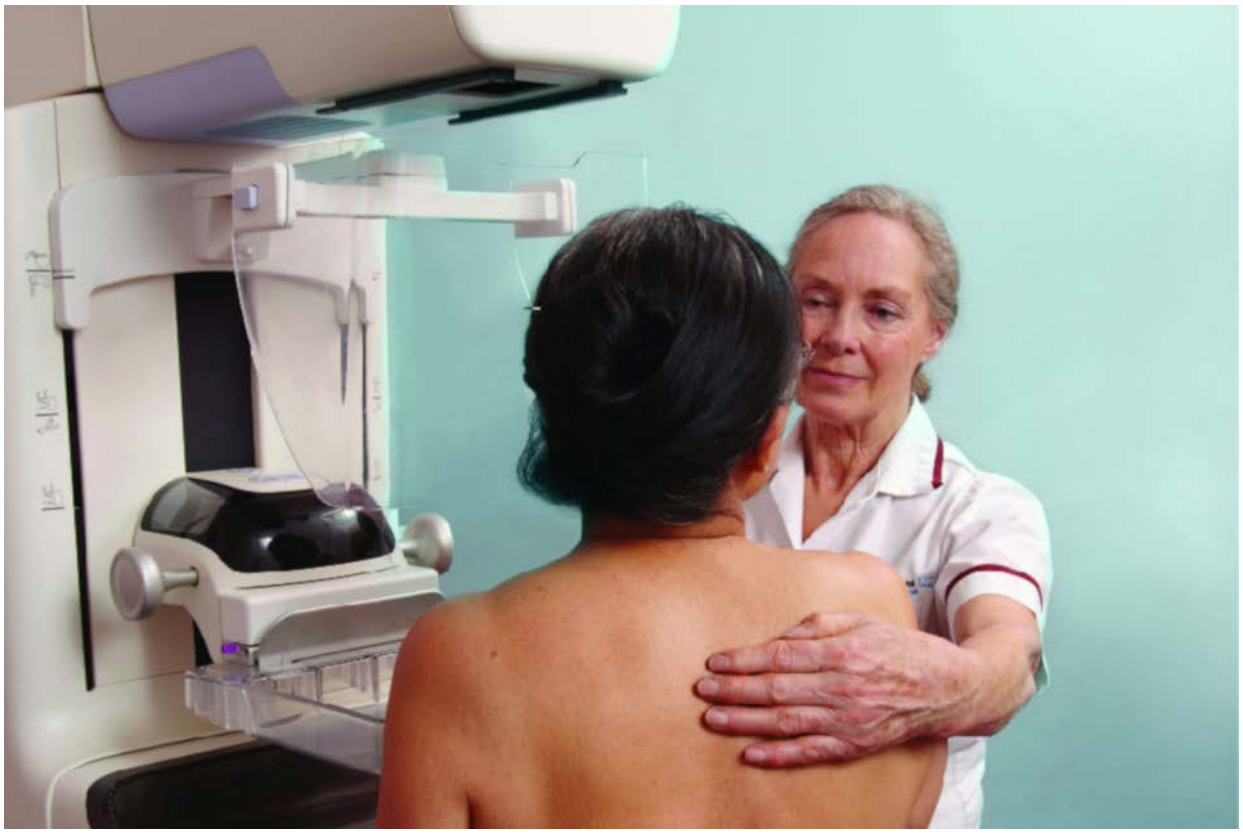
Any change to the screening test for breast cancer should improve upon the limitations of the current screening practice using mammography:

Sensitivity: a new test would be expected to change the balance in favour of screen detected breast cancer.

Specificity: a new test would ideally reduce the number of women recalled, and also give more useful information on prognosis and optimal management.

Acceptability: a more acceptable test may increase uptake and the effectiveness of the screening programme.

Resources: mammography involves ionizing radiation so it needs to be delivered by highly trained technicians within constraints of legislation, the equipment is expensive, and the infrastructure including call/recall, image acquisition, transfer, storage and interpretation is cumbersome.



Genomics could support mammography in breast screening

For the breast cancer screening programme, the advisory committee recommends:

- working towards ensuring that genome sequencing is available to all women diagnosed with breast cancer
- exploring attitudes to a change in screening policy with women and workforce.
- ensuring that the IT system builds in flexibility for managing several screening strategies within a population, and for changes in delivery of screening

Cervical cancer screening

We know that HPV is the cause of the vast majority of cervical cancer. However, HPV is a very common infection while cervical cancer is, thankfully, very rare.

Cervical cancer is caused by high risk human papillomavirus (HR-HPV). Thirteen oncogenic (cancerous) types are known to be associated with the disease worldwide, with around 70% attributable to oncogenic type 16. Prevention of cervical cancer in the UK is now 2 pronged, using:

- primary prevention by means of vaccinating adolescent girls aged 12/13
- secondary prevention by means of screening for precancerous lesions

Previously, this has been based on cytology, but the cervical screening programme is switching over to HR-HPV DNA testing because it is more sensitive and will enable extended screening intervals.

The risk of cervical cancer is closely aligned with persistent HR-HPV infection. It is possible that differences in the genome in a woman (and / or in the specific HPV subtype) mean that some women are at much higher risk than others of their infection going on to cause cancer. This is an area of current research. There is some evidence that indicates understanding changes to genetic activity as a marker of predicting which women with HPV infections carry greater risk of developing or having underlying precancerous lesions, but this requires further evidence from rigorous testing in controlled trials.

Hopefully the vaccination will mean that cervix cancer can be eliminated in women old enough to be vaccinated. Unvaccinated women will be in the programme for a further 60 to 70 years. Therefore in the meantime the UK NSC will remain alert to improvements in testing for women that will allow us to know whether some women are at greater risk of getting cancer from their HPV infection.

Bowel cancer screening

Genomics offers a potential approach to personalisation of screening for bowel cancer.

Screening programmes across the UK are utilising quantitative faecal immunochemical testing for haemoglobin, and this presents the possibility of stratifying risk on the basis of faecal haemoglobin concentration. This could be further refined by the addition of genetic risk in the form of family history and well characterised genetic variants.

In addition, NICE guidance indicates that every bowel cancer should be tested for microsatellite instability and if positive the germ line of the patient (and then their family) can be tested for DNA mismatch repair-gene defects that define Lynch syndrome. This will find people at very high risk of bowel cancer (and other cancers). People at very high risk require regular follow up (surveillance) by expert colonoscopy and other surveillance tests as well as holistic care from genetic counselling services. The best

Genomics could allow the personalisation of bowel cancer screening

approach for this very high-risk group is being discussed actively with NICE and NHS England.

Abdominal aortic aneurysm screening

Abdominal Aortic Aneurysm screening (AAA) is a newer screening programme. Most screen-detected AAA can be considered multi-factorial from a genomic perspective. With increasing availability of genomic data from other cardiovascular diseases, and with good evaluated research, it is possible that a genomic risk score can be derived to target AAA screening to high risk populations.

For example, there is a small cohort of men with screen-detected AAA and who have a family history of AAA, and / or are non-smokers who may benefit the most from the

investigation of gene variants causing AAA. This may develop into a case for cascade screening for families where people have certain risks as identified by a calculation of a range of genetic and lifestyle risks and to target screening and treatment to the people with the highest risk score.

It is also possible that genomic risk scores could be developed for general cardiovascular disease which can be then be used to target AAA screening for high risk populations. This would probably have to be combined with clinical risk scoring.

Managing cardiovascular risk in men with abnormal aortae is likely to bring greater healthcare benefit than the management of AAA. Good genomic risk scores for cardiovascular disease are becoming available and it may be that we should be exploring using screening outcomes to identify groups of men to target for cardiovascular genomic risk scoring.

The main use of genomics in surveillance or management of men with AAA is likely to be in the identification of those in whom future drug treatments are going to work. Hopefully pharmacogenomics will start to identify variants associated with response to common cardio-metabolic drug treatments which can then be used to tailor drug treatments.

Diabetic eye screening

There is some progress in understanding the genetics of diabetes however phenotype and genotype correlation is generally considered to be poor.

There are no current suggestions that genetic testing would affect the cost-effectiveness, feasibility, acceptability or uptake of diabetic eye screening.

Conclusion

The advances in genomic technologies present exciting, and potentially effective developments for screening programmes. We are exploring opportunities for replacement first screening tests, additional tests, and confirmatory tests.

Genomic technologies can also help us with developing differential screening strategies, with personalised treatment opportunities, and in developing our understanding of the causes of disease.

We are discussing when and how to offer genome sequencing, including the timing of the offer and what might be the most useful information for people who could benefit from genomic technologies. This will include understanding penetrance and the additional information that may be discovered about an individual's health and risk of other diseases so we can offer appropriate advice and treatment.

In order to do this we are starting to develop education and training opportunities and deciding what information structures will best support these new technologies.

The current and developing research and technology will help us to understand the impact of factors which influence genetic activity in order that, going forward, we can determine how best to use genetics in screening.

Contributors

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