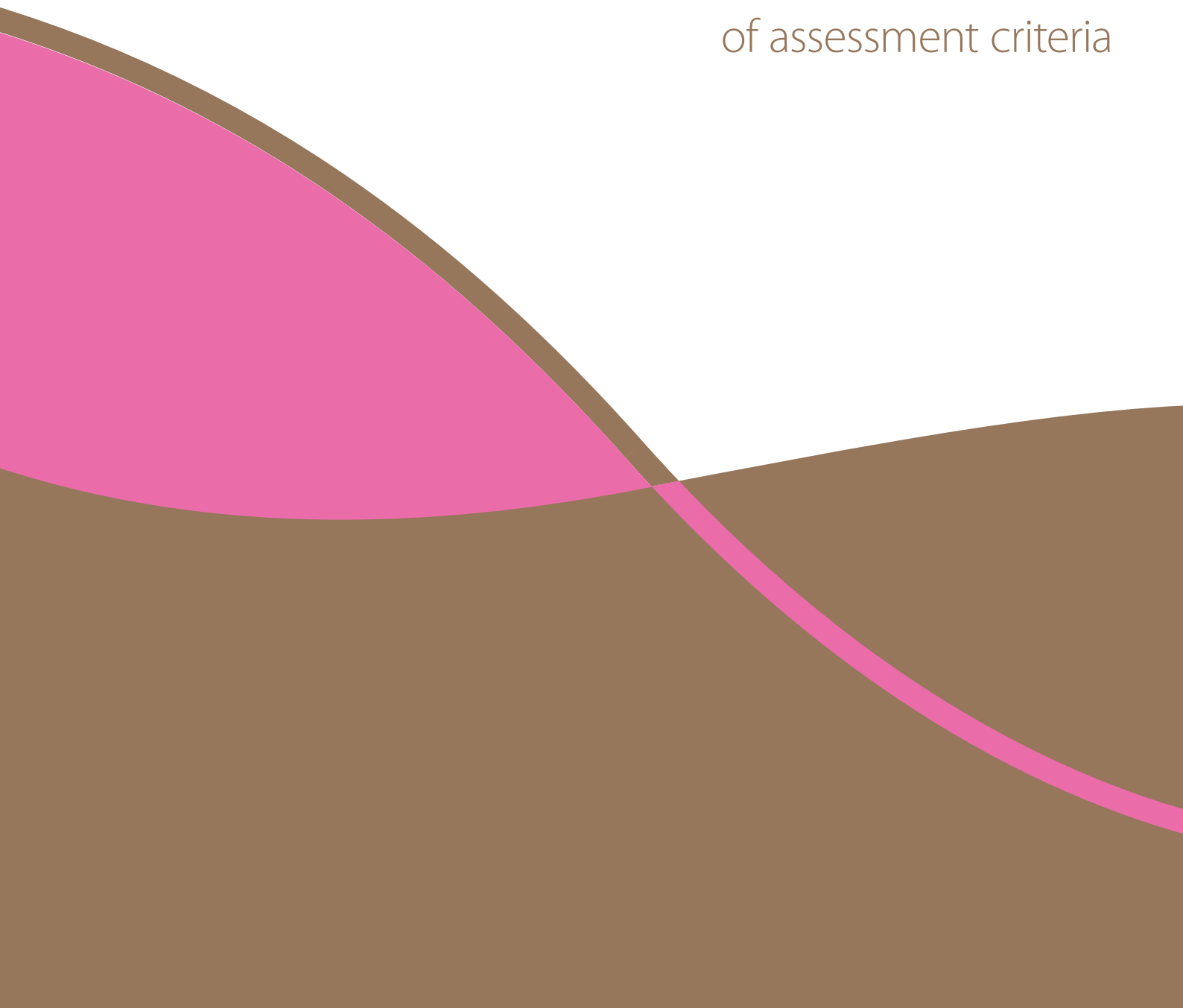
phgfoundation
making science work for health

Genetic screening programmes

An international review of assessment criteria



Authors: Louise Cameron*, Hilary Burton

Acknowledgements

We would like to thank Farah Seedat and Sian Taylor-Phillips for their help in producing this report, particularly for sharing information on searches and methodology.

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

Tel: +44 (0) 1223 761 900

January 2015

Correspondence to:
louise.cameron@phgfoundation.org

How to reference this paper:
Genetic screening programmes: an international review of assessment criteria
PHG Foundation (2014)

Contents

1. Executive summary 4

2. Introduction 15

3. Methods 17

4. Results 19

5. Criteria 21

6. ELS issues in genetic screening policy 27

7. International organisations responsible for screening and genetic screening 40

8. Discussion 43

9. Conclusions and recommendations 47

References 57

Appendix 1: Search terms 60

Appendix 2: Data extraction form 61

Appendix 3: NSC criteria for appraising the viability, effectiveness and appropriateness of a screening program 62

1 Executive summary

Background

The UK National Sceening Commitee (NSC) was founded in 1996 to appraise proposals for new screening programmes, periodically reassess new evidence for screening programmes and implement and monitor the impact of approved programmes. As part of the NSC's terms of reference, a review of the criteria used to assess screening programmes is carried out triennially. In order to assist with this review and in light of recent evolving genetic technologies, the PHG Foundation undertook a literature review of criteria for and ethical, legal and social issues (ELS) issues pertaining to the appraisal of current and future genetic screening programmes.

Objectives

The key objectives of the review were:

- To identify and compare the criteria used by other countries or proposed in the literature to appraise genetic screening programmes and compare this specifically to the current NSC criteria
- To summarise the key ELS issues identified in the UK and other countries which may inform appraisal of genetic screening programmes
- To summarise the regulatory structures responsible for decision making in UK and other countries, with particular reference to genetics
- To make recommendations for the UK NSC Review Committee

Methods

We searched four databases: Medline; Embase; Applied Social Science Index and Abstracts (ASSIA); Social Science Citation Index (SSCI), for articles on genetic screening programme appraisal using a modified search strategy based on the methodology set out by Farah Seedat (FS) and Sian Taylor-Phillips (ST-P) in their review (see Appendix 1 for search terms). Titles and abstracts were reviewed to identify papers which were focused on genetic screening programmes. The data was then extracted using a customised extraction form (Appendix 2) and synthesised under two main headings of criteria and ELS issues.

Findings

The electronic searches identified a total of 3852 papers. Along with papers identified through hand-searching, a total of 35 papers and sources were found to be relevant to genetic screening programme criteria, appraisal or policies. Of these, eight sources explicitly mentioned screening criteria and a further 27 included discussion of ELS issues. Information on criteria was mapped onto the original Wilson & Jungner and NSC criteria for comparison. Key ELS issues were also considered in terms of their relationship with the current NSC criteria.

A total of 84 discrete criteria were identified from the included sources, to compare with the 22 NSC criteria (Table showing comparison of criteria available on request). Comparison showed that five of the 22 NSC criteria were unique to the NSC; nine of the 84 criteria from the included sources suggested modifications to or were not explicitly mentioned in the NSC criteria, and a further three criteria were identified which were not included in the NSC list. In the literature there was one account of development of a support guide to enable an interdisciplinary and iterative approach to decision making for genetic screening programmes.

A total of 27 articles describing the ethical, legal and social issues arising in genetic screening programmes were included in our review. These fall broadly into areas concerned with purpose and scope of screening; test performance; informed consent; social and psychological impact of testing, such as effect on family members; particularities related to the taking, storage and handling of genetic samples and data; societal equity.

The structure and function of the decision making bodies varied amongst different countries. There was no current evidence of any genetic screening authorities acting independently from generic screening or healthcare bodies in other countries, but some countries such as the Netherlands do have input from a specialist sub-committee on this topic.

Discussion

Many authors have considered the congruity between current screening criteria such as those of the NSC and the new possibilities and demands of genetic screening. They have been concerned about issues such as whether cascade genetic testing of family members, preconception carrier testing and testing of ethnic minority groups at higher risk of disease should rightly fall within the scope of screening programmes.

Regarding criteria, authors have discussed, or suggested, amendments to many of the current screening criteria, including the very preliminary judgment about the importance of a particular health problem and whether or not rare inherited conditions should be bundled together for decision making where technologies can be multiplexed. A further set of concerns hinge around unachievable standards for evidence for inherited conditions, where rarity and heterogeneity make epidemiological, natural history or outcome studies extremely problematic. They also note that it may be difficult to apply current criteria where the purpose of screening relates to information giving, increasing speed of diagnosis, or reproductive choice rather than a reduction in mortality or morbidity in the population. Finally they question the practicality of criteria related to availability of treatment services for rare disease, noting that these may need to be aspirational and driven by the screening programme, rather than already in place before the programme is implemented.

Ethical, legal and social issues again cover a wide set, some general to screening and others more specific to genetic screening. However, overall we felt that genetic screening increases the scale and complexity of ELS issues. Fundamental issues arise because of new uses for screening in reproductive choice, the ability to predict risk of late onset disease at a very early age (or even before birth) and implications for family members. Consent, and the taking and storage of genetic samples and information are not unique to genetic testing, but there are often perceptions of increased significance.

Ethical, legal and social issues again cover a wide set, some general to screening and others more specific to genetic screening. However, overall we felt that genetic screening increases the scale and complexity of ELS issues.

Conclusions and recommendations

We have concluded that the existing NSC criteria are not congruous with the needs of decision makers for genetic screening programmes including those for inherited disease and those that incorporate genetic susceptibility into risk assessment. Such screening applications are likely to become an increasingly significant part of the NSC remit over the next decade, and we have therefore suggested some modifications to the existing criteria to account for this. The ethical legal and social issues that arise from genetic screening are too complex to be dealt with in the simple, 'catch-all' statements made in the current screening criteria and we therefore propose modifications to the current criterion 14 to make more explicit consideration of ELS issues. We also query whether the current NSC structures and processes are suitable for the complexity of decision making regarding genetic / genomic screening programmes, and suggest an appraisal of alternative models which might embrace this and facilitate the decision making process.

Recommendations

1. **The NSC review committee should determine the scope of genetic screening that falls under its remit, with particular reference to preconception carrier screening, cascade testing, and screening of subpopulations defined by genetic risk.**

2. **Consideration should be given to modifying current screening criteria in accordance with the recommendations in Table 4.**

3. **A supportive checklist of ethical, legal and social aspects to consider should be developed as a reference resource to support the screening criteria. An initial set is included in Table 5.**

4. **Consideration should be given to developing more robust and systematic processes to appraise new applications against amended NSC criteria, such as the iterative approach proposed by Blancquaert *et al.*[1] which allows for greater interaction between opposing concerns and priorities.**

5. **The NSC should make arrangements to ensure that it possesses or can gain access to the necessary capability and capacity to assess new genetic screening programmes. In particular it should consider how it obtains the necessary scientific, epidemiological, clinical, ethical, legal and social advice to support decision making.**

Table 4 Amended criteria

	Current NSC criterion	Proposed amendment	Comment and clarification
		There should be an agreed case definition for the condition.	New criterion.
1A	The condition should be an important health problem.	The condition should be an important health problem as judged by its frequency and severity OR The conditions should together constitute an important health problem.	
1B		For rare diseases, it may be appropiate to consider groups of conditions.	This may be particularly suitable for conditions where testing can be multiplexed.
2	The epidemiology and natural history of the condition including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.	The incidence and prevalence of the conditions should be understood.	This criterion merges several ideas. If judgments are to be made it is more transparent to separate them. With regard to natural history of rare disorders best level evidence should be used and there may need to be a commitment to build up this knowledge through international cohorts of screened and clinically presenting cases.
		There should be robust evidence about either: • The association between risk factors and disease (for inherited disease the penetrance and expressivity of gene mutations should be known) • The association between disease marker and serious/ treatable disease	
		The natural history of treated and untreated disease should be known. However, it is recognised that for rare disease best available evidence should be used and there may need to be a commitment to build up this knowledge through international cohorts of screened and clinically presenting cases.	
3	All the cost-effective primary prevention interventions should have been implemented as far as practicable.		

	Current NSC criterion	Proposed amendment	Comment and clarification
4	If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.		This may not be possible. Evidence should be used with prospective data collection.
5	There should be a simple, safe, precise and validated screening test.		
6	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.		
7	The test should be acceptable to the population.	The test and subsequent handling of resulting samples, data and results should be acceptable to the population.	
8	There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.		
9	If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.	If the test is for a set of mutations or genetic variants, the method for selection of variants and the means through which these will be kept under review should be clearly set out.	The term mutations is more appropriately used when considering changes in DNA sequence that are rare (frequency less than 1%) and strongly related to severe disease as in most single gene or 'inherited disorders'; 'variants' is the more commonly used term in the context of susceptibility to common chronic disease where differences occur with greater frequency but the association with disease is much weaker. Used with the term 'genomics' it reflects the fact that the whole genome has been scrutinized rather than particular genes.

	Current NSC criterion	Proposed amendment	Comment and clarification
10	There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Whilst accepting that the primary benefit should be to the child screened, evaluation of effectiveness of management options should be broadened to include avoiding the diagnostic odyssey and providing information to enhance reproductive choices for family members.	
11	There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	There should be agreed evidence based policies covering management of individuals with diagnosed disease. This should be based on reasonable evidence. For inherited disorders the potential benefits to family members should be clearly set out with agreed policies on how relevant prevention and care will be provided.	
		Appropriate management of individuals with established disease should be available and accessible for all patients and their family members.	
12	Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.	Clinical management of the condition and patient outcomes should be optimised in healthcare providers as far as practicable before participation in the screening programme. For rare conditions the health system must be able to offer diagnosed patients specialised timely advice, although in the early stages it is acknowledged that new patient diagnosis and provision of treatment will drive appropriate service configuration.	

	Current NSC criterion	Proposed amendment	Comment and clarification
13	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (*e.g.* Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	For common complex disorders, there should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality and/or morbidity. For rare disorders reasonable level evidence on effectiveness, based on clinically detected and screen detected cohorts would normally be required. This may be based on good quality aggregated outcome studies linked to existing international screening programmes. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (*e.g.* antenatal screening) there must be evidence that services to enable such informed choice are effective (*e.g.* good patient information and communication) and there is adequate follow up support for the chosen options.	
14	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	There should be evidence that the complete screening programme (purpose, target population, test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public as judged against issues outlined in Table 5.	We suggest an appendix that sets out the range of ethical, legal and social factors to consider (See Table 5).
		Universal screening is preferred to ethnically targeted screening. However, if there are sound reasons for targeted screening on the basis of ethnicity, efforts should be made to avoid stigmatisation.	New criterion*. *See Table 1, Criteria A3
15	The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).	The benefit from the screening programme should outweigh the physical and psychological harm.	

	Current NSC criterion	Proposed amendment	Comment and clarification
16	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (*i.e.* value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.		
17	All other options for managing the condition should have been considered (*e.g.* improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.		
18	There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.		
19	Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme. For rare disorders, the initiation of a screening programme may provide both the knowledge and the impetus to improve services.	
20	Evidence based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	Evidence based information, explaining the purposes of testing, test results, investigation, treatment and potential benefits and harms consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	

	Current NSC criterion	Proposed amendment	Comment and clarification
21	Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.		
22	If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.		Consider removing this criterion as it is included in criterion 14. See Table 5 on ethical, legal and social aspects.

Table 5 Checklist of ELS issues

Ethical issues	**Ultimate aim**	Do the aims of the screening programme fit with broad objectives of a public health programme? Are the principles underpinning the evaluation of screening purpose with respect to informed choice in reproduction or the value of information for the individual or family members acceptable?
	Adult onset conditions	Has the impact of this knowledge on patients been assessed, particularly in relation to conditions with variable penetrance?
		Who should have access to this information?
		Have the rights of children 'not to know' been considered in the context of prenatal or newborn screening?
		Is such information inadvertently provided by prenatal screening programmes in circumstances where the pregnancy continues?
	Carriers	Will the screening programme detect carriers?
		What is the psychosocial impact on these individuals?
		How and when will information on carrier status be communicated?
		How will data be stored?
	False positives/ false negatives	Are levels of false positives and false negatives at an acceptable level?
		Has the impact of false positives and false negatives been considered in relation to the particular screening scenario?
		Are there plans on how to communicate and minimise harm from false positives and false negatives?
	IFs and VOUS	Is there a potential for discovering IFs and VOUS?
		If so, which IFs and VOUS should be communicated? Who should decide?
		Does the screening programme make people aware of the potential for generating IFs and VOUS? Are procedures for informed consent adequate?
		Does the service have the capacity to provide appropriate counselling and ongoing treatment and management for people whose screening has identified IFs and VOUS?
		Are systems in place to minimise the number of VOUS? (*e.g.* data sharing, targeted interpretation, automation or use of expert committees?)

Social issues	**Familial impact**	Has the impact on relatives been considered in the decision to screen?
		Has the impact on the screened individual been considered in terms of duty to disclose information to the wider family?
		Are there sufficient services in place to manage and treat any family members who are detected through screening?
	Non-paternity	For genetic screening programmes, has the aggregate impact of non-paternity been considered on test accuracy?
	Equity	Is the proposed screening programme likely to present any negative connotations in terms of equity/solidarity?
		Will proposed changes result in reasonable healthcare allocation?
		What is the opportunity cost of the new screening programme? *e.g.* in terms of resources for primary prevention measures.
	Routinisation and over-diagnosis	Would implementation of a large scale screening programme impact on the public's perception of the seriousness of the test? Can informed consent be achieved in this context?
		Has the screening programme been assessed in terms of over-diagnosis? What is the likely impact on participants of over-diagnosis? How can this be mitigated?
Legal issues	**Confidentiality**	Has the screening programme considered the burden on individuals in terms of non-disclosure within the family?
		Will data from screening be assessable for secondary users including employers or insurers? What safeguards are in place to protect against this?
	Discrimination	If screening is routine, how likely is it that those that chose not to participate in the screening programme might be discriminated against? What protections have been put in place to prevent/reduce this occurring?
		If certain genetic variants are more common in certain ethnic groups, have measures been put in place to avoid discrimination on this basis?
	Consent/ informed choice	Does the screening programme have adequate information and resources to ensure that properly informed consent is sought from participants?
		Are the potential risks and harms presented in a balanced way?
		Where screening incorporates clinical and research elements, are consent procedures such that participants can make an informed choice?
	Storage	Will samples or data be stored for future or secondary use? Do consent procedures adequately cover these possibilities?

2 Introduction

2.1 Background

Large scale screening was implemented to improve population health at the same time as Wilson and Jungner[2] published their recommendations on screening criteria in the 1960s. The scope of screening, in terms of the range of conditions covered and technologies used, has evolved along with our aetiological understanding of disease, and technical capabilities. To ensure an equitable and evidence based approach to decision making and quality assured screening provision, the UK National Screening Committee (NSC) was formed in 1996 with responsibility for appraising new screening programme proposals in the UK, periodically assessing new evidence for programmes, and overseeing implementation of new programmes.

As part of its terms of reference, a triennial review of the NSC's policies is carried out, which includes a review of the criteria used to appraise screening programmes. The NSC's remit covers a broad range of conditions in different clinical specialties, with different types of test, and modes of programme delivery. Cutting across this matrix, genetic testing forms a significant part of the NSC's considerations. With this in mind, and with expansion in technological capability and understanding in genomics, the 2014 NSC Review Group considered that it would be timely to include an examination of the issues specific to genetic screening in the NSC review. Particular reference would be made to screening criteria, decision making in screening, and ethical, legal and social issues (ELS).

Based on the methodology applied by Farah Seedat (FS) and Sian Taylor-Phillips (ST-P) in their international review of screening procedures in other countries (personal communication, 2014) we identified sources describing criteria used for appraising genetic screening programmes, and noted any variance between this body of literature and the NSC criteria. For a greater understanding of the decision making process, a brief examination of the systems in other countries was conducted, to illuminate the background regulatory environment in which the decision making bodies function.

We examined the literature to identify and analyse key ELS issues to be considered in formulating criteria for assessing genetic screening programmes, and highlighted potential issues.

We included information on screening programmes harnessing genetic and genomic technologies in our review thereby including screening aimed at identifying heritable diseases as well as screening based on technologies examining variation in multiple genes or even across the whole genome (see HGSG Report for definition of genomics)[3].

...the 2014 NSC Review Group considered that it would be timely to include an examination of the issues specific to genetic screening in the NSC review.

2.2 Objectives

The key objectives of the review were:

- To identify and compare the criteria used by other countries or proposed in the literature to appraise genetic screening programmes and compare this specifically to the current NSC criteria
- To summarise the key ELS issues identified in UK and other countries which may inform appraisal of genetic screening programmes
- To summarise the regulatory structures responsible for decision making in the UK and other countries, with particular reference to genetics
- To make recommendations for the UK NSC Review Committee

3 Methods

3.1 Search strategy

Four databases: Medline; Embase; Applied Social Science Index and Abstracts (ASSIA); Social Science Citation Index (SSCI), were searched based on the methodology set out by FS and ST-P in their review of screening policy. In order to capture articles specifically concerned with appraisal of genetic / genomic screening, the initial search terms relating to policy and screening were combined with genetic / genomic search terms (search terms are listed in Appendix 1). The searches and data extraction were carried out by one reviewer, Louise Cameron (LC), in January 2014. Titles and abstracts were reviewed to identify papers which focused on genetic screening programmes. We excluded articles that did not refer to genetic screening policy or appraisal, or those that did not contain sufficient information.

Further sources were identified from the articles cited within the systematic review of screening criteria by FS and ST-P. This list was scrutinised for references to genetic screening amongst the general screening articles identified in their search. Reference lists from included articles were also examined for further sources, and hand-searching provided additional articles.

After finalising a list of included articles, Hilary Burton (HB) was consulted to see if there were any significant omissions from the list.

Number of articles:

A total of 3582 articles were identified from the searches, and 87 abstracts or full texts were examined. Seventeen of these were included in the final analysis. Three articles were included from FS and ST-P's systematic review and a further 15 from websites and hand-searching. The final number of included articles was 35.

Whilst the included articles should be representative of the wider literature, the extent of the review was influenced by resource considerations, and further time would have allowed increased identification of articles through hand-searching. In particular the search for papers on ELS was restricted to those papers primarily focused on criteria and decision making in screening. A more general review of the literature on ELS and screening would have led to a more extensive collection of papers. Although strict criteria were applied for article inclusion, some degree of subjectivity may have resulted from the use of a single reviewer in article selection. In addition, the nuances of terminology as applied to genetic screening in the literature must be considered: the term 'screening' is used in reference to many varied activities, including individual screening in the context of clinical care and opportunistic screening, as well as population screening and so it is possible that some relevant papers may have been wrongly excluded because of a perception that they did not describe population screening.

...the initial search terms relating to policy and screening were combined with genetic / genomic search terms.

3.2 Data extraction and synthesis

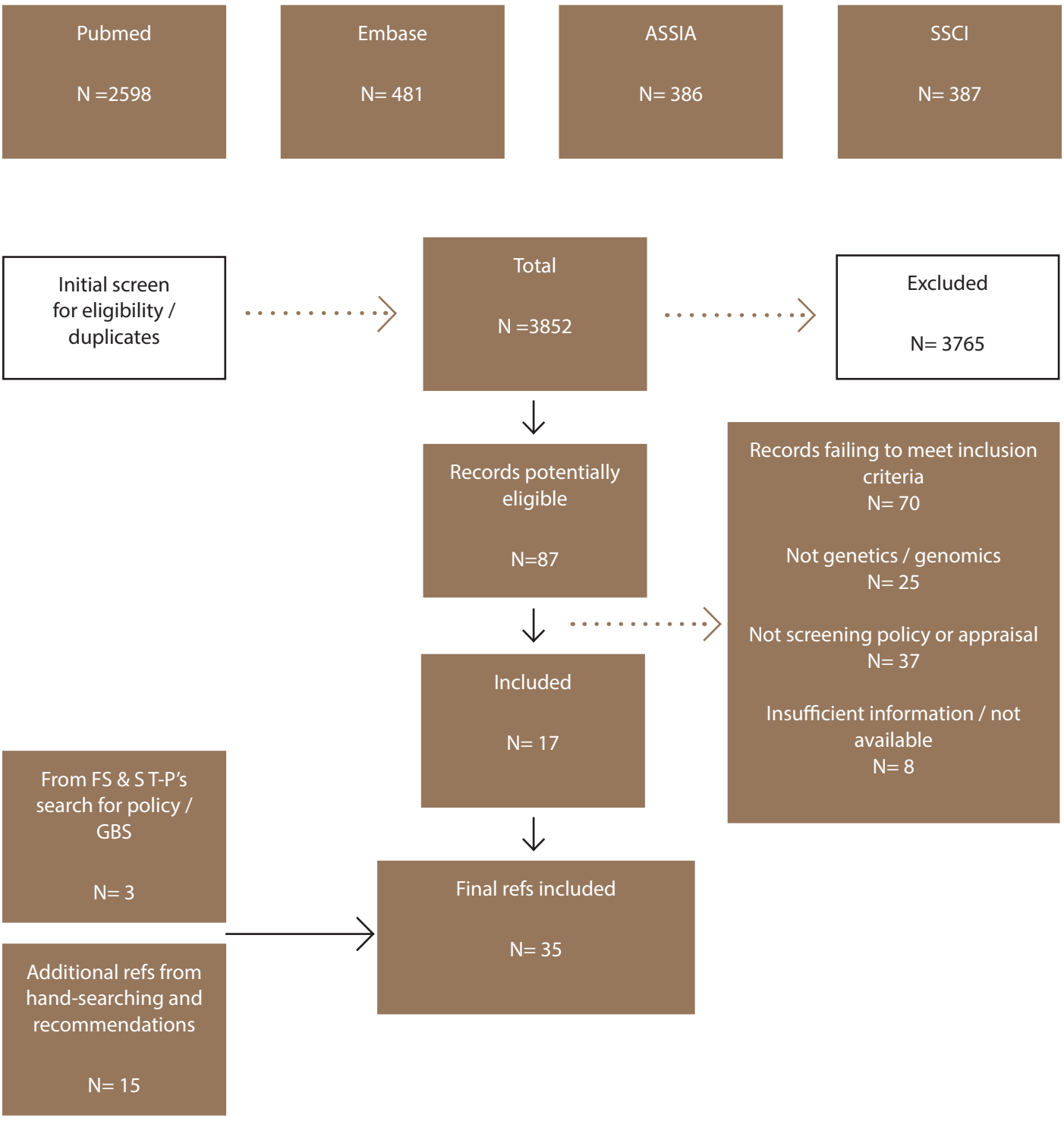
The final list of included articles was not assessed for quality due to the descriptive nature of the review. The data was extracted with customised extraction forms (Appendix 2) which included: author; title; year; country; type of article; purpose of article; the area of genetic testing; source / participants; main findings / criteria / ELS issues.

We synthesised the data extracted by organising the included articles into two groups: those that discussed screening criteria explicitly, and those that discussed ELS issues in the context of genetic screening policy or appraisal.

The criteria from the first group of articles were mapped on to the original Wilson and Jungner criteria and the current (2003) NSC criteria. The key differences are shown in Table 1 (table with full listing of criteria available on request). The ELS articles were examined for inclusion of relevant themes and this information is summarised in Table 2 (table showing full extraction of information available on request). Sources of information on international decision making structures, provided from the review by FS and ST-P were scrutinised for information on genetic / genomic screening appraisal and any special arrangements for undertaking decision making in this area, particularly delegation of decision making arrangements with regard to genetics. This information is summarised in Table 3.

4 Results

Figure 1 Flow Chart showing yield of included articles



4.1 Description of articles found

A total of 35 articles were included in the final analysis, eight articles explicitly discussed criteria for appraising genetic screening programmes, and a further 27 primarily discussed ELS issues in the context of appraisal of genetic / genomic screening programmes. Eighteen of the articles gave a worldwide perspective [1, 4-20], while three were concerned with issues in the UK[21-23], seven with the US[24-30] and seven with Europe[31-37].

Type of articles:

Four workshop reports were included; four reports from non-governmental organisations; five articles describing guidelines or recommendations, one needs assessment, along with twenty-one review articles, including literature reviews and reviews of specific recommendations and criteria.

5 Criteria

5.1 Criteria characteristics

From the included articles describing criteria, the number of discrete criteria discussed varied from three for the PHG Foundation[14] report and the paper by Bonham[8] to 21 for the Health Council of the Netherlands[37]; this compares with the NSC's 22 criteria. Some discrete criteria in the sources were encompassed within one criterion listed by the NSC. Table 1 shows the variance between the UK NSC's criteria and other international models or proposed systems in the literature.

Table 1 Summary of variation in criteria for genetic screening programmes

Divergence	Criterion number	Criteria	Source
Criteria unique to NSC	4	If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.	NSC
	6	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	NSC
	9	If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.	NSC
	21	Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.	NSC
	22	If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.	NSC

Divergence	Criterion number	Criteria	Source
Criteria with proposed modifications or not explicitly stated in the NSC criteria	1	'The overall burden of disease due to genetic conditions should be considered. EURORDIS advocates that this should be a global approach - rather than a piecemeal policy for each disorder separately.'	PHGF (2010)[14]
	2	Level of risk, assessed through penetrance is important.	Goel *et al.* (2001)[13]
	2	'The rarity of inherited metabolic conditions means that the methods in standard epidemiological research, which rely on a population based assessment of disease comparing populations with and without disease, will be unlikely to provide sufficient statistical power to provide classical evidence on incidence, causation, risk factors and natural history. The question at issue thus becomes: do we understand the underlying pathology and expected natural history well enough to recommend treatment that we believe to be beneficial?'	PHGF (2010)[14]
	12	Regarding optimised clinical management prior to implementation of screening programmes: 'the introduction of screening often provides the necessary stimulus to agree national professional treatment guidelines and frequently leads to the improved organisation of services for patients detected.'	Bonham (2013)[8]
	13	'It is impossible to obtain evidence of effectiveness of screening programmes from randomized trials because of the rarity, complexity and heterogeneity of the conditions. Not only will there be insufficient patients to generate the necessary statistical power, but also there would be significant ethical considerations in allocating patients to a non-screening group in the light of rapid advances in dietary and other aspects of management. Therefore recommend the 'next best' study design (observational cohort) in which screened and clinically detected cohorts are compared in nearby geographic areas with similar services or sequentially with groups closely related in time before and after a screening programme is put in place.'	PHGF (2010)[14]
	13	'The demand for evidence from high quality randomised clinical trials (RCT) is very difficult to satisfy. The rarity of the conditions linked to their intrinsic heterogeneity would demand multinational studies over many years to demonstrate benefit in some cases and the ethics of withholding screening to establish valid comparator groups may be difficult to justify in the face of mounting public pressure. This does not deny the need to establish good quality outcome studies linked to existing screening programmes based upon agreed case definitions and consensus approaches to treatment. Indeed, this is a pressing priority for existing programmes and could be viewed as a pre-requisite for future development. Nevertheless, the lack of RCT evidence in itself cannot be viewed as a barrier to the introduction of screening.'	Bonham (2013)[8]
	15	A programme should only be considered if benefits clearly outweigh harm. Screened patients, before relatives.	ESHG PPPC (2003)[31]
	16	Economic criteria alone cannot be used to justify a screening programme.	ESHG PPPC (2003)[31]

Divergence	Criterion number	Criteria	Source
	19	Regarding staffing and facilities for testing and diagnosis prior to screening programme implementation: 'this proves difficult to satisfy, as facilities for the effective diagnosis and treatment of rare disorders are not optimal even in highly developed countries. In addition, relatively few agreed international guidelines for treatment exist and there are very few agreed case definitions to guide classification.'	Bonham (2013)[8]
Criteria in addition to those used by NSC	A1	'Systematic case finding followed by systematic cascade testing is intermediate between population screening and testing of high-risk individuals and should also be considered, according to the same criteria as population genetic screening.'	ESHG PPPC (2003)[31]
	A2	'Rapid advances in technology may make it possible to screen large numbers of disorders or traits simultaneously. It will then become difficult if not impossible to provide proper information about each of the conditions and traits screened. Our recommendation is to authorise packages only when there is enough consistency in the characteristics of the conditions screened to allow properly informed consent from the consumer.'	ESHG PPPC (2003)[31]
	A3	'As the prevalence of genetic traits often varies among populations, screening programmes may be better targeted to subpopulations with high prevalence if the community agrees to have a focused health-care programme. In populations composed of subpopulations with different genetic backgrounds, the test should be selected according to population substructure.'	ESHG PPPC (2003)[31]

5.2 Criteria unique to NSC

The majority of the criteria listed by the NSC are also described in the eight included sources, but five criteria are exclusive.

Three of the unique NSC criteria focus on genetic screening programmes: criterion 4 considers the needs of genetic mutation carriers, in terms of the natural history of this group and in particular the psychological implications of screening; criterion 9 highlights the importance of defining and explaining the subset of mutations which will be tested for if this does not cover all known mutations; criterion 22 highlights the importance of acceptability of the programme for carriers of a mutation and their families.

A further two criteria were unique to the NSC but were not specifically related to genetics. In criterion 21, the NSC explicitly mentions public pressure for widening eligibility criteria. Criterion 6 highlights the need to understand the distribution of test values in the population, to allow determination of suitable cut-off values.

5.3 Criteria with proposed modifications or not explicitly stated in NSC list

Although the NSC criteria discuss the need to understand the epidemiology, a detectable risk factor and disease marker, there is no explicit mention of the level of risk assessed through penetrance as the Canadian Crossroads Workshop described by Goel *et al*.[13] In the context of the natural course of disease, Goel *et al.* explicitly address the question of genetic risk and susceptibility, and advise an extension of the original evaluation framework to include the natural history of evolution from susceptibility to clinical presentation.

The criteria proposed by the European Society for Human Genetics (ESHG) Public and Professional Policy Committee (PPPC)[31] make mention of benefits and harms to screened patients before relatives, which is not explicitly mentioned by the NSC (although the NSC may consider this implicit in its assessment of benefits and harms). The ESHG recommendations also state that economic criteria alone cannot be used to justify a screening programme. The NSC approach balances the economic impact of new screening programmes with health benefits and issues such as acceptability, but does not explicitly caution against the over emphasis of economic considerations.

The PHG Foundation's report[14]...proposals emphasise the need to consider the overall burden of rare diseases, rather than considering the prevalence of each condition separately.

The PHG Foundation's report[14] on expanded newborn screening for inherited metabolic disorders proposes modifications to the NSC criteria which would assist in the evaluation of screening programmes for rare diseases. The proposals emphasise the need to consider the overall burden of rare diseases, rather than considering the prevalence of each condition separately. In relation to epidemiological studies, they note that, due to the rarity of these conditions, population based assessments are unlikely to provide sufficient statistical power and that decision making with regard to screening programme implementation should be based on an understanding of the underlying pathology and expected natural history of the disease. They suggest that observational cohorts be used as evidence for the efficacy of a screening programme in place of RCT evidence which cannot be attained due to the rarity of the conditions and ethical concerns about withholding potentially beneficial treatment.

The issue of RCT data was also referred to in the report by Bonham[8] along with proposed modifications to two further NSC criteria. These criteria stipulate that clinical management of the condition and patient outcomes should be optimised along with facilities and staffing for testing and treatment before the implementation of a screening programme. Bonham argues that this is difficult to achieve in the rare disease sphere, and questions whether it is right to penalise this group of patients further by not introducing screening. He notes that, in practice, the implementation of a screening programme often provides the necessary stimulus to agree national professional treatment guidelines and frequently leads to the improved organisation of services for patients detected through screening.

5.4 Additional criteria

Whilst the criteria relating to the condition, test and treatment were largely the same amongst the different sources, the greatest divergence was seen in the criteria relating to programme organisation. The ESHG PPPC criteria discuss the impact of new technologies, and caution against introducing screening because it is technologically possible, but advise waiting until there is 'enough consistency in the characteristics of the conditions screened to allow properly informed consent from the consumer.' [31] The ESHG PPPC criteria set out some issues with regard to working definitions: stating that systematic case finding followed by cascade testing is intermediate between population and high-risk screening. The report recommends that this type of screening should not be done ad hoc but is subject to the same decision making processes as population screening programme proposals (focusing on benefits and harms and implementation). The ESHG PPPC also introduces the concept of heterogeneity of populations with respect to their genetic background in the consideration of genetic screening programmes. It notes that, as the prevalence of genetic traits often varies among populations, it may be beneficial if the community agrees, to target screening programmes within subpopulations with high prevalence. In populations composed of subpopulations with different genetic backgrounds it recommends selecting the tests according to population substructure.

5.5 Systems for applying criteria

In addition to considerations about the criteria themselves, there is discussion in the literature about decision making systems and optimal methods of applying the criteria. Although it is beyond the scope of this review to discuss these studies in detail, one of the papers included in this review, by Blancquaert *et al.*[1] proposes a decision support guide for population genetic screening which is highly relevant to this review.

Blancquaert *et al.* suggest improving the transparency of the evaluation and decision making process by being explicit about the tensions and trade-offs in the process as well as the underlying reasoning and evidence considered in screening appraisal. An iterative approach to decision making is proposed and emphasis is placed on facilitating an interdisciplinary approach. In the resulting decision support guide, the evaluation of evidence is not measured against predefined thresholds but rather recommendations are formulated on the basis of the evidence regarding the overall benefits and risks of screening, while taking into account the knowledge gaps and the trade-offs between potentially conflicting considerations. The decision support guide can be

employed at different stages of screening programme implementation; for example, at the pilot phase, when expanding to a large scale population programme or when modifying an existing programme. The level of evidence available will depend on the progress of the proposal along an implementation pathway with emerging evidence being added during the process.

The decision support guide is underpinned by eight screening principles concerned with key issues such as equity. These principles are evaluated by twenty criteria organised into clusters at each of the three decision nodes. Each node is focused on a specific aspect of the programme such as the impact on individuals and families. For each criterion, different types of evidence can be called upon to substantiate whether the criterion has been fulfilled.

The decision nodes are nested in each other like a series of Russian dolls, with the evidence considered for the first being subsequently integrated into the analysis for the second, and so on. At the first decision node the criteria pertain to the nature of the disease and the capacity to detect and treat it (do benefits outweigh harms for individuals?); at the second decision node the needs and values of the target population are considered (how will the programme work in a given setting?); and at the third decision node a societal perspective is included in evaluating the priorities of the population, allocation of resources and whether the programme aligns with fundamental screening principles.

The guide aims to provide a transparent account of the decision making process and incorporates a broad range of evidence to represent the key elements of the programme including the condition and test, the programme and the wider social values and priorities which must be taken into account. The guide has been accessed by a variety of groups internationally, but there is, as yet, no feedback on its implementation.

The decision nodes are nested in each other like a series of Russian dolls, with the evidence considered for the first being subsequently integrated into the analysis for the second, and so on.

6 ELS issues in genetic screening policy

6.1 Introduction

Ethical, legal and social issues in screening have been recognised as integral to decision making and policy, from the initial criteria listed by Wilson and Jungner[2] who noted that the test must be 'acceptable to the population' (Criterion 6). More recently, the NSC criteria have enlarged on various aspects of this to cover clinical, social and ethical acceptability (Criterion 14), including physical and psychological harm (Criterion 15) and explicitly relating to family members as well as the individual screened (Criterion 22).

A number of general ethical, legal and social issues arise from the fundamental differences between screening and other forms of healthcare. Typically screening comprises an unsolicited offer to an asymptomatic individual, of an intervention that can help to determine their risk of present or future disease. Screening people for disease they were not aware of is clearly different from treating those with symptoms who have sought treatment. Any screening programme must therefore carefully balance the benefits of screening with harms for both the individual and the population.

Genetic screening programmes share many of the ELS issues identified by Wilson and Jungner but there are in addition some unique issues arising from the specific assay used (examination of DNA) and the new possibilities that are raised (such as prenatal testing or implications for family members). The articles examined in this review discussed the range of ELS issues that may arise in association with genetic screening. These issues are summarised in Table 2 and discussed below.

Screening people for disease they were not aware of is clearly different from treating those with symptoms who have sought treatment. Any screening programme must therefore carefully balance the benefits of screening with harms for both the individual and the population.

A total of 27 articles describing the ELS issues particularly arising in genetic screening programmes were included in our review.

The group of articles covered a broad range of genetic screening including preconception screening; prenatal screening, newborn screening and screening of children and adults. Discussion ranged from current technical realities such as screening for single gene disorders *e.g.* cystic fibrosis, or inherited metabolic disorders, to the possible implications of whole genome sequencing (WGS) in screening programmes, either to screen for a larger number of disease-causing variants, or to inform rationalisation of screening programmes through risk profiling.

6.2 Ethical issues in genetic screening

The purpose or aim of genetic screening

Several commentators have used the ultimate aim of genetic screening as a starting point for discussing ELS issues. For programmes such as the newborn bloodspot screening programmes and screening of individuals for adult onset disease the principle aims are to reduce morbidity and mortality for the person screened (Wilcken[18]), to reduce the emotional and financial burden on families of caring for a child with a genetic illness (Andermann *et al.*[6]) and to 'prevent needless suffering and human and economic waste (Simopoulous[28]). Holland, Stewart & Masseria[33] also note that it could be suggested that this type of screening may also be useful to identify those at risk even 'if nothing can be done to alter the finding, the need for and use of such information must be very carefully considered'.

Genetic screening may also be used to identify carriers of serious inherited conditions or prenatally to identify seriously affected fetuses. These new contexts have led to discussion on various ethical aspects of wider aims for screening and adverse consequences that might arise. Holland, Stewart & Masseria[33] talk about the aim of informing reproductive choice of individuals and couples at risk, but also cite a second possible aim of screening 'to reduce the prevalence of the disorder'. Potter *et al.*[16] noted that this should not be a stated purpose but that there are 'inherent tensions between the goals of enhancing reproductive choice and preventing the births of children who would have disabilities'. Godard *et al.*[34] warn that the reduction in population prevalence for a condition may lead to the adverse effect of reducing acceptance of such disorders in the population and also of the danger of stigmatisation as some minority ethnic groups have higher frequencies of a particular gene (variant). Simopoulos[28] warns against the possibility 'of a mistaken impression that the program is intended to be an instrument of discrimination or is devoted to any eugenic cause'. Van El *et al.*[35] note that there may be a tension between the aim of reproductive screening (enhancing autonomy by providing meaningful reproductive options) and the fact that widening the scope of testing will make counselling and decision making extremely difficult.

Finally, John[38] examines the controversial issue of using a cost-effectiveness or 'savings argument' in making policy decisions about prenatal screening programmes. He argues that this consideration may not be as unacceptable as is often assumed as long as the outcomes, such as parental autonomy and the permissibility of abortion are morally acceptable and there is continuing support for meeting costly obligations such as care for those with disabilities and for protection of those with disabilities from discrimination.

The consequences of false positives and false negatives are particularly important when considered in the context of prenatal screening as such information may inform choices regarding continuation of pregnancy.

Screening for adult onset conditions

Genetic screening can predict serious disease that may only arise in adult life, by identifying genetic variation (mutations), most frequently single gene (or Mendelian) disorders. Depending on the penetrance of these mutations the probability for future disease may be extremely high although the precise presentation and clinical course may vary. Khoury, Janssens & Ransohoff[12] comment that this information can be obtained at any stage in life, even prenatally, predating the onset of disease by several decades. This gives rise to a number of ethical issues, particularly when testing children including that 'disclosing such information to parents may contravene the child's right not to know the information' (Patenaude, Sénécal & Avard[27]) and many commentators argue that this should only be done when it is in the best interests of the child. On the basis that carrier status is rarely of clinical relevance, until it is used to guide reproductive decision making, in Germany parents are legally prohibited from knowing the carrier status of their 'infant.'[39] Wilcken[18] comments that the current focus on personalised medicine will mean that there will be much pressure to screen for adult-onset disorders and risk assessment. Van El *et al.*[35] highlight an issue of current concern in prenatal testing where screening for serious adult-onset disorders might be offered in the interests of reproductive choice, but the outcome is a pregnancy which continues to term. In this case the child has lost his or her right to an 'open' future and may be unwillingly burdened with knowledge of future disease risk.

Carrier status

The Nuffield Council[23] note that some genetic screening programmes detect carriers, even when the aim of the programme is to identify only the affected homozygotes. There has been debate in the literature as to whether identification of carrier status represents a benefit or cost of newborn screening. In effect, the identification of carrier status is an incidental finding, and it is important that the ethical issues are adequately considered. These include the psychosocial impact of learning about carrier status, and issues of disclosure with regard to children being identified as carriers. Potter *et al.*[16] note this as being particularly important and refer to prenatal, preconceptional and newborn screening. The HGC[22] recommend providing information on carrier status to general practitioners so this information can be stored in a secure and accessible format, and returned / made available at a suitable stage. Whether or not this occurs in practice is likely to be dependent on GPs setting a suitable mechanism to alert them when important information is available.

False positives and false negatives

All screening programmes must address the issue of false positives and false negatives, and aim to reduce these to an acceptable level. Determining what is an 'acceptable' level will depend on the further interventions that flow from a positive or negative test result. The consequences of false positives and false negatives are particularly important when considered in the context of prenatal screening as such information may inform choices regarding continuation of pregnancy. The issue of false positives and false negatives is considered very carefully in the appraisal of biochemical screening programmes for inherited metabolic disorders as the choice of timing and cutoffs together with the variability and rarity of these conditions must be optimised to reduce the false positive and false negative rates to the minimum achievable, whilst maintaining high detection rates.

Burke *et al.*[26] comment that 'false positives are an inevitable feature of a screening process that seeks to maximise sensitivity, and as more independent tests are added to screening panels, the overall number of false positives increases.' With this in mind, Burke *et al.* also describe the need for further evaluation of the impact of false positives, in terms of economic and psychosocial consequences. Cited in the same paper, a study by Gurian *et al.* has observed persistent psychosocial distress in a proportion of parents of false positive cases, particularly where urgent or invasive treatment may have been required. They propose that where this is observed, it may be linked to failing to understand that newborn screening is generally a probabilistic rather than a diagnostic test and so false positives are an inevitable consequence. Holland, Stewart & Masseria[33] note that 'there is the unpalatable certainty that some individuals with false negative results will be given unfounded reassurance and that some with false positive results will experience, at the very least, unnecessary anxiety and, at the worst, inappropriate treatment.'

Incidental findings (IFs) and variants of uncertain significance (VOUS)

Whilst incidental findings and ambiguous clinical information are not new medical concepts, or indeed unique to genetic testing, the scale of this issue would warrant major consideration if higher resolution technologies (such as arrays or whole genome sequencing) were to be implemented as screening tests at a population level.' Burke *et al.*[26] describe the potential impact of genome-scale tests in newborn screening which would greatly increase the risk of incidental findings including identification of carriers' genetic susceptibilities to common adult-onset disorders, and findings of uncertain significance.

Hall *et al.*[9] emphasise the importance of the consent process in encompassing the possibility of incidental or unsolicited findings, and note that there is an 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. Wider issues of service provision come into this debate as, if reporting were to become the norm in clinical settings, the system would have to cope with a greatly increased workload in terms of communicating results and counselling recipients of the newly available information

Within a population screening programme it would be essential that testing of the genome was targeted to minimise VOUS as far as possible and that systems, such as the occasional use of expert committees were in place to deal with them.

Regarding familial impact, three main issues were highlighted from the literature included in our review: psychosocial sequelae, confidentiality and the role of education in mitigating these issues.

6.3 Social issues in genetic screening

Familial impact

With regard to the possible impact on families, genetic testing may be regarded as in some way exceptional. Unlike other screening methods, the information arising from genetic screening can be used directly to screen other members of the family. Three main issues were highlighted from the literature included in our review: psychosocial sequelae, confidentiality and the role of education in mitigating these issues. Simopoulos[28] discusses the psychosocial impact and comments that 'genetic screening discovers something within a person's own make-up that may threaten his / her self-esteem or cause him / her to feel guilty of transmitting some 'blight' to his / her children.' Godard *et al.*[34] refer to the tension which may develop between the individual's right to confidentiality

Chowdhury et al. *suggest that the wider use of genetic variants in multiple preventive programmes may diminish issues of distributive justice.*

and the right of other individuals to avoid potential harms. The HGC[22] note that the moral obligations regarding disclosure fall on patients and professionals alike. They propose better public understanding as a possible solution to this problem, as this may 'normalise the issues surrounding the inheritance of recessive conditions and the sharing of carrier status information.' A better understanding that every individual carries genes for a few recessive conditions, which genetic testing can uncover, may help to alleviate some of these issues.

McQueen *et al.*[10] state that 'there is also a need to be sensitive to the possibility that in some cultural contexts, individuals freely put aside their personal autonomy in favour of the values, needs and concerns of the community or family group. Screening programmes must demonstrate sensitivity to such issues.'

Bailey *et al.*[7] describe 'genealogical ethics': a moral decision making process of whom in the extended family to tell, what genetic information to reveal, when to disclose and who should do the telling. The authors also raise the issue of conveying accurate information.

Non-paternity

One review considers the way in which policy makers may need to consider the impact of non-paternity in decision making about genetic screening programmes (Asch *et al.*[24]). When considering policy for carrier screening for a recessive condition such as cystic fibrosis they note that test performance for a whole population is reduced by non-paternity. This arises because, within a decision model, the result from the male partner is not informative. The higher the rate of non-paternity in the population, the more the test performance will be reduced. Strategies that screen the woman first and then use further information and choices from the woman to decide on next steps will be more efficient. However the authors note that such strategies do not 'evenly distribute the burden of genetic screening between the genders', potentially giving rise to more women than men bearing stigma and discrimination in social, employment and insurance settings.

Equity

The use of genomic information to inform population based stratified screening programmes has the potential to undermine 'genetic solidarity' and two reviews have commented on these issues. Chowdhury *et al.*[19] note the need for robust communication strategies to convey genetic information to the public, to prevent the exacerbation of existing inequalities which could result from a lack of engagement and uptake amongst certain ethnic or socioeconomic groups. Chowdhury *et al.* suggest that the wider use of genetic variants in multiple preventive programmes may diminish issues of distributive justice. Hall *et al.*[9] raise the issue with regard to research in non-Caucasian populations since the current research on risk stratification has been almost exclusively carried out in Caucasian populations, meaning that other ethnic groups may be excluded from the advantages of a stratified programme.

Khoury, Janssens & Ransohoff[12] query the acceptability of a risk-stratified approach in a time of limited healthcare resources, and question whether stratification on a genetic basis would be more or less favourably received than other methods such as age, income or other population subgroups. In particular the acceptability of such programmes, which offer reduced or even no preventive intervention to those at lower risk may be compromised.

The WHO note in Andermann, Blancquaert & Déry[20] that there may be additional concerns regarding the utility of new and costly technologies to improve population health, and the opportunity cost of drawing resources away from other interventions.

Routinisation and over-diagnosis

As the use of genetic testing moves from a specialised clinical service to a wider population based screening programme, the issue of routinisation becomes important. Some authors consider how the time, care and expertise that goes into helping a patient make an informed choice about testing in a clinical setting may be transferred to a screening setting. Whilst recognising that some types of screening are already becoming normal practice rather than a considered choice, The Nuffield Council[23] caution against informed consent being lost in the ubiquity of screening, and the workload volume diluting the time available for proper consideration of results with patients. Potter *et al.*[16] in their workshop report raise professional concerns regarding routinisation specifically in the context of prenatal screening.

Overdiagnosis, whilst not unique to genetic screening, can result from the variable penetrance of many genetic variants and from the heterogeneity of rare genetic disease with the existence of mild forms of disease that may have no clinical impact. Burke *et al.*[26] comment that genetic screening will inevitably identify a proportion of individuals with disease or genetic risk of disease who would not, in fact, have gone on to experience ill-health. In the context of newborn screening programmes, the consequences in terms of intervention for infants who test positive and are subsequently diagnosed either through genetic or phenotypic biomarkers as having the disease, but who would have remained asymptomatic, differ according to the disease. Burke *et al.*[26] highlight this with respect to two disorders that are, or have been, included in newborn screening panels in some US states. Around 25% of infants with MCADD will remain asymptomatic but treatment primarily involves dietary measures. In contrast, Krabbe disease, a rare neurodegenerative disorder, has a more variable course and clinical follow up is required to monitor all with a positive test, with possible treatment involving bone marrow transplant. This demonstrates that the burden of over-diagnosis is much higher for the latter condition.

Bailey *et al.*[7] talk about Fragile X in a newborn screening context and the likelihood of identifying a number of males and females with the full (normally pathogenic) *FMR1* gene expansion who would never otherwise have been detected because of their normal or near normal intellectual functioning. The paper also describes a study by Whitmarsh *et al.* in which families with a child affected with sex chromosome aneuploidies were largely in favour of newborn screening for such conditions but families of children with milder symptoms were more ambivalent.

Direct to consumer (DTC) testing

The potential availability of genetic screening and testing on a direct-to-consumer basis has led to concerns that genetic risks may not be communicated accurately of effectively to consumers. There is disquiet amongst genetic professionals about the potential for the public to be harmed by accessing these tests and a belief that the nature of information provided by DTC genetic tests is best communicated to patients via experienced health professionals. Seven articles in our review commented on these issues. The HGC[22] and The Nuffield Council[23] recommend that those offering screening in the private sector follow the guidelines set out by the NSC, and the code of practice set out by the ASA with regard to marketing information. Burke *et al.*[26] quote one such company's material: 'you can start looking at your health in a new way. You can also learn if certain medications work with your genetic makeup.' The HGC[22] raise the complex ethical issue of tacit support (if only financial) for non-stated ideological aims of commercial companies with regard to genetic conditions within a population.

The relative impact of DTC testing in different countries is discussed, and Zimmern & Kroese[21] note that the impact is likely to be greatest in US (and lower in the UK), whilst Simopoulos[28] estimates the impact of DTC to be lower in European countries where access to healthcare is organised as a public service. Hall *et al.*[9] look at the equity issues associated with DTC testing and raise the prospect of private provision undermining genetic solidarity and potentially exacerbating health inequalities; the HGC highlights the consequent burden on the NHS in counselling patients following a DTC test result, including a need for general practitioners and those in front-line services to have improved genetic literacy.

6.4 Legal issues in genetics screening

Confidentiality

Confidentiality is an issue that is often raised with regard to genetic screening tests, where the information is often thought to be particularly sensitive. The question of confidentiality has been raised in the familial context by The Nuffield Council[23] who discuss disclosure within families and the burden this can place on health professionals in considering the best interests of the patient and balancing this against the interests of other family members.

Simopoulos[28] discusses confidentiality in a societal context and potential concerns with regard to employers gaining access to sensitive genetic information, which could impact on a person's employment prospects.

Abel *et al.*[4] emphasise the wider 'costs' of increased legislation and regulation to maintain genetic privacy. They question where these costs will be met: in the private sector in terms of higher costs for goods and services or the public sector, in the form of taxpayer contributions? The authors ask what price individuals are prepared to pay to protect their right to genetic privacy; would they forfeit their health insurance for example?

Hall *et al.*[9] outline different scenarios in stratified screening and the relative complexities of maintaining confidentiality. They describe the process by which confidentiality breaches may arise, with the threats increasing where genomic data is held in a central database; where there is linkage of multiple datasets

including phenotypically rich data sets, and long term storage over the lifetime of an individual. In contrast, the threats to confidentiality may be reduced if targeted genetic information is obtained through near-patient testing, incorporated into a risk or test algorithm with the final result being used for stratification in relation to a single disease.

Discrimination

Genetic information is regarded as sensitive because of the potential to discriminate on the basis of differences between individuals. Andermann, Blancquaert & Déry[20] describe the potential for discrimination on the basis of genetic differences and ethnicity, while Godard *et al.*[34] point to the potential for discrimination against individuals who choose not to participate in genetic screening programs. Khoury[11] discusses the potential for employment discrimination based on an individual's susceptibility to disease. Chowdhury *et al.*[19] comment on the special status of genetic information, and compare it to the sensitive nature of HIV status. A moratorium is in effect until 2017 (with a review due in 2014), to prevent predictive genetic information being used by insurers but the authors caution that in the longer term, as this type of information becomes more predictive and its clinical utility increases, there may be increasing demand for insurers to be able to use this type of information. The HGC[22], whilst recognising the risks of discrimination, suggest a pragmatic approach in that steps should be taken to avoid discrimination, but the prospect should not preclude implementation of a screening programme. Bailey *et al.*[7] describe examples of discrimination occurring in practice, one study citing a third of families known to be at risk of Fragile X syndrome suffering discrimination, most commonly from health insurance providers. Abel *et al*[4] cite examples of misuse of genetic testing to limit insurance payments by employers in the US, countered by assertions from the insurance industry about benign intentions such as lowering insurance premiums. Joly *et al*[40] consider the issue of genetic susceptibility information obtained as part of a screening programme potentially being requested by insurance companies. They note that the impact on a person's risk profile of currently available genetic data would be relatively small, but this may increase in time. There remains a great deal of concern among the public which the authors felt might best be alleviated by the insurance industry providing easily accessible information on their use of genetic information and appointing an independent ombudsman to deal with complaints.

Godard et al. describe the conditions which must be met for informed consent to be achieved such as sufficient understanding, freedom of choice and legal capacity, but question whether this is truly achieved because of the unfamiliarity of the subject matter.

Consent / informed choice

Godard *et al.*[34] describe the conditions which must be met for informed consent to be achieved such as sufficient understanding, freedom of choice and legal capacity, but question whether this is truly achieved because of the unfamiliarity of the subject matter. Many writers have expressed concerns about the consent processes themselves and have suggested ways in which they could be improved. Cornel *et al.*[39] recommend initiating information provision regarding newborn screening in pregnancy to improve the consent process. Burke *et al.*[26] argue that there are shortfalls in the manner in which informed consent is sought and documented, and raise this issue in reference to newborn screening. Burke *et al.* also describe specific information which should be provided to those undergoing prenatal screening, and state that 'prospective parents have a right to receive complete and balanced information about persons with disabilities, including their potential for a good quality of life, to ensure that decisions are not based on inappropriately negative views of genetic disorders.'

The HGC[22] discusses consent with particular emphasis on young people, and notes that carrier testing is not normally offered to young people below the age of 15-16 years, as such information has limited utility at this stage of life, and may be of most use later for reproductive decision making.

Storage

The storage of genetic samples raises important ethical issues, including the conditions under which samples may be re-analysed, and destroyed. In their paper on genotyping in risk stratification for common cancers, Hall *et al*.[9] discuss the complexities of storage of genetic material and personal and phenotypic data. They propose two possible models of data collection and storage: the first model essentially looks at a very small number of genetic variants known as single nucleotide polymorphisms (SNP) for risk calculation of a single disease, the sample is destroyed immediately, personal data is retained (but not linked to the sample). The second model, with broader scope, involves examining a larger number of SNPs for risk calculation for several diseases, the sample is retained, but personal data is kept as linked anonymised data. Implementation of the second model, whilst potentially providing enhanced information for disease risk, is more likely to result in incidental findings than the first more targeted approach. It also requires careful consideration regarding access not only in terms of family members, but also employers and insurance companies. Consent to storage would also have to cover the potential for the individual to withdraw their consent, consider the possibility of re-contact with updated risk profiling, and factor in changes in capacity throughout an individual's lifetime.

Table 2 Summary of ELS themes in genetic screening

Highlighted in green are new ELS issues resulting from new genomic technologies in screening

Highlighted in blue are existing ELS issues, albeit with some new implications

Author (year)	Title	Genetic application	Ethical				Legal					Social			
			Ultimate aim	Adult onset	FPs, FNs, carrier	IFs, VOUS	Familial impact	Non-paternity	Equity	Routiniation, over-diagnosis	DTC testing	Confidentiality	Discrimination	Consent/ inf choice	Storage
Khoury (1996)[11]	From Genes to Public Health: The Applications of Genetic Technology in Disease Prevention	Genetic screening in preventative measures	X	X	X							X	X	X	
WHO (1998)[17]	Proposed International Guidelines on ethical issues in medical genetics and genetics services	General genetic screening		X			X	X	X			X	X	X	X
McQueen (2002)[10]	Some ethical and design challenges of screening programs and screening tests	General genetic screening			X		X		X		X	X	X	X	
Godard *et al.* (2003)[34]	Population genetic screening programmes: principles, techniques, practices, and policies	Prenatal and postnatal population genetic screening	X	X	X		X		X		X	X	X	X	
Abel *et al.* (2005)[4]	The impact of Genetic Information on Policy and Clinical Practice				X		X					X	X		
Asch *et al.* (2006)[24]	Genetic Screening for Reproductive Planning: Methodological and Conceptual Issues in Policy Analysis	CF screening in reproductive planning	X		X		X	X	X				X	X	

Author (year)	Title	Genetic application	Ethical				Legal				Social					
			Ultimate aim	Adult onset	FPs, FNs, carrier	IFs, VOUS	Familial impact	Non-paternity	Equity	Routiniation, over-diagnosis	DTC testing	Confidentiality	Discrimination	Consent/ inf choice	Storage
Holland, Stewart & Masseria (2006)[33]	Policy Brief: Screening in Europe	Genetics as specific area of screening	X		X				X		X			X	
Nuffield Council (2006)[23]	Genetic Screening: a Supplement to the 1993 Report by the Nuffield Council on Bioethics	General genetic screening	X	X	X		X			X	X	X	X	X	
Patenaude, Sénécal & Avard (2006)[27]	Whither Pediatric Research and Predisposition Genetic Testing	Research: Pediatric predisposition testing	X	X			X					X		X	
Zimmern & Kroese (2007)[21]	The evaluation of genetic tests	Genetic tests	X				X		X		X	X	X		
Bailey *et al.* (2008)[7]	Ethical , Legal and Social Concerns about expanded newborn screening: Fragile X as an example.	Expansion of newborn screening	X		X	X	X			X		X	X	X	
Michigan Department of Community Health (2009)[30]	Genetics Through the Life Cycle: Improving Health and Preventing Disease	General genetic screening										X			
Potter *et al.* (2009)[16]	Ethical, Legal, and Social Issues in Health Technology Assessment for Prenatal/Preconceptional and Newborn Screening: A Workshop Report	Prenatal, pre-conceptional, newborn screening	X	X	X	X	X		X	X		X	X	X	

Author (year)	Title	Genetic application	Ethical				Legal		Social						
			Ultimate aim	Adult onset	FPs, FNs, carrier	IFs, VOUS	Familial impact	Non-paternity	Equity	Routiniation, over-diagnosis	DTC testing	Confidentiality	Discrimination	Consent/ inf choice	Storage
Simopoulos (2009)[28]	Genetic Screening: Programs, Principles, and Research – Thirty Years Later	Newborn screening: IMDs	X	X	X		X		X		X	X	X	X	
Andermann, Blancquaert & Déry (2010)[20]	Genetic screening: a conceptual framework for programmes and policy-making	General genetic screening	X				X		X		X	X	X		X
Zwahlen *et al.* (2010)[36]	Population-based screening – the difficulty of how to do more good than harm and how to achieve it	General genetic screening		X	X		X			X				X	
Andermann *et al.* (2011)[6]	Guiding policy decisions for population-based genetic screening: an evidence based and interdisciplinary approach	General genetic screening	X						X			X	X	X	
Burke *et al.* (2011)[26]	Genetic Screening	General genetic screening	X	X	X	X	X		X	X	X		X	X	
HGC (2011)[22]	Increasing options, informing choice: A report on preconception genetic testing and screening	Preconception genetic screening	X		X	X	X		X		X	X	X	X	
Wilcken (2011)[18]	Newborn screening: how are we travelling, and where should we be going?	Genomics in newborn sceening	X	X	X						X			X	
Bowen *et al.* (2012)[25]	Public Health Action in Genomics Is now needed beyond Newborn Screening	Screening for adult-onset conditions		X			X								

Author (year)	Title	Genetic application	Ethical		Legal				Social						
			Ultimate aim	Adult onset	FPs, FNs, carrier	IFs, VOUS	Familial impact	Non-paternity	Equity	Routiniation, over-diagnosis	DTC testing	Confidentiality	Discrimination	Consent/ inf choice	Storage
Oldman (2012)[15]	Ethical issues in screening	General genetic screening			X	X	X	X	X	X		X	X	X	
Tarini & Goldenberg (2012)[29]	Ethical Issues with Newborn Screening in the Genomics Era	WGS in newborn screening	X		X				X					X	
Chowdhury *et al.* (2013)[19]	Incorporating genomics into breast and prostate cancer screening: assessing the implications	Screening for common complex disorders		X	X	X	X		X			X	X	X	
Hall *et al.* (2013)[9]	Implementing risk-stratified screening for common cancers: a review of potential ethical, legal and social issues	Cancer screening: inclusion of genotype in stratified screening rationale		X			X	X	X		X	X	X	X	X
Khoury , Janssens & Ransohoff (2013)[12]	How can polygenic inheritance be used in population screening for common diseases?	Screening for common complex disorders		X	X					X	X		X		
Van El *et al.* (2013)[35]	Whole-genome sequencing in healthcare	WGS in healthcare		X		X	X					X	X	X	X

7 International organisations resonsible for screening and genetic screening

To provide background information on the regulatory structures in place in different countries for appraising genetic screening programmes, a qualitative assessment of the organisational structures in countries listed in FS and ST-P's review was conducted with specific emphasis on the arrangements and practices relevant to genetic screening.

The structure and function of the decision making bodies varied amongst different countries, but some fundamental similarities with the UK situation were observed. Many countries have devolved responsibility for appraising screening programmes to a specialist body which produces recommendations which are then acted upon at a national or regional level. Bonham (2013)[8] notes in relation to expanded newborn screening panels, that countries where decision making is dominated by the 'professional genetics' community, include a larger range of conditions, as opposed to those countries where the responsibility rests mainly with the public health specialists and epidemiologists.

The non-uniform approach to governance and decision making can result in regional variation in screening, a situation which has been avoided in the UK through national implementation of programmes. In the course of our review, we found no current evidence of any genetic screening authorities acting independently from generic screening or healthcare bodies in other countries, but some countries such as the Netherlands do have input from a specialist sub-committee on this topic. Some countries partition responsibility for different aspects of genetic screening such as cancer, prenatal screening or reproductive genetic testing.

Other professional bodies contribute to the decision making process by making recommendations and statements on screening, and in the case of genetic screening, such organisations tend to include genetic organisations, and other involved clinical groups such as obstetrics & gynaecology, cancer and rare disease groups.

Table 3 Summary of bodies responsible for decision making in genetic screening appraisal (information from FS and S T-P's review, personal communication)

Country	Screening body	Mode of operation	Other advisory organisations
Australia	Australian Population Health Development Principal Committee	National recommendations, regional implementation	Re newborn screening: A joint committee of the Human Genetics Society of Australasia and Royal College of Physicians of Australasia advises on policy, quality assurance, and other matters
Belgium	Superior Health Council	National	Higher Council on Human Genetics
Canada	Canadian Task Force on Preventive Health Care	National recommendations, regional implementation	
Denmark	National Board of Health	National recommendations, regional implementation	Danish Council of Ethics, Danish Centre for Human Rights
Finland	National Screening Committee, Ministry of Health and Social Affairs, National Institute for Health and Welfare	National recommendations, regional implementation	Society for Medical Genetics
France	Haute Authorite de Santé	National	National Ethical Consultative Committee for the Life and Health Sciences in France, Genetics and Medicine National Advisory Committee on Bioethics National College of Gynaecologists and Obstetricians
Germany	The Federal Joint Committee	National	The German Society of Human Genetics
Italy	National Observatory Screening	National	The Italian Committee on Bioethics
Japan	Ministry of Health, Labour and Welfare	Not stated	
Netherlands	National Institute for Public Health and Environment Health Council of the Netherlands, with Committee on Genetic Screening	National	
New Zealand	Ministry of Health, National Screening Advisory Committee, National Screening Unit	National	
Spain	Ministry of Health, Social services and Equality	Regional	
Sweden	The National Board of Health and Welfare	National	Swedish Society for Medical Genetics

Country	Screening body	Mode of operation	Other advisory organisations
Switzerland	Responsibility of Swiss Medical Board	National	The Swiss Academy of Medical Sciences
UK	UK National Screening Committee	National	
USA	US Preventative Services Task Force, US Dept of Health and Human Services	National recommendations, regional implementation	American Medical Association (AMA); American College of Medical Genetics (ACMG); American Society for Human Genetics (ASHG); American Academy of Pediatrics (AAP)
WHO	WHO Consultation Group	International recommendations, regional implementation	Committee on Genetic Screening
European Council	Council of European Union	International recommendations, regional implementation	

8 Discussion

The criteria that are currently in place in the UK and other countries have largely evolved from the original Wilson and Jungner criteria and were developed in the context of common chronic diseases of major public health importance. Review of the literature concerned with criteria and decision making for genetic screening shows that many authors have grappled with the 'fit' of traditional screening criteria for decision making on new screening programmes for genetic conditions. They have variously concluded that the criteria do not work well and suggested amendments, some of which have been included in more recent iterations of the Wilson and Jungner criteria, such as the current NSC list. Although the criteria mention ethical, legal and social issues in general terms of public and professional acceptability, physical and psychological harm, the various domains are not elaborated further. Our report shows that, particularly in the area of genetic screening, researchers, clinicians and policy-makers have felt the need to describe the various parameters in more detail. We summarise here some of the main areas where amendments and clarifications to criteria may be necessary and make suggestions for an ELS checklist to assist decision makers in assessing the criteria.

We start with the issue of the scope of screening programmes. In the UK opportunities for genetic screening have enabled widening of original scope to include antenatal population screening for risk of disease in the fetus and for carrier status in parent(s). Discussions in the literature raise important questions about whether the scope should be further widened to include carrier status in the non-pregnant population. Also relevant to consideration of scope are firstly: screening aimed at genetically determined subpopulations (for example ethnic groups who have increased genetic risk for rare disease) (Table 1, criterion A3) and secondly the inclusion of systematic cascade testing of relatives of individuals with inherited conditions such as familial hypercholesterolaemia (Table 1, criterion A1).

We summarise here some of the main areas where amendments and clarifications to criteria may be necessary and make suggestions for an ELS checklist to assist decision makers in assessing the criteria.

Whether or not a genetic disease fulfils the criterion of being a sufficiently 'important health problem' is a vital initial question. For screening programmes this is usually judged on the basis of disease prevalence and severity. Many genetic conditions, such as inherited metabolic conditions, are extremely rare and exhibit a high degree of heterogeneity with milder and more severe forms. These very factors also make basic epidemiological work difficult so that the evidence available about population prevalences may be much less robust than would normally be available for common chronic disease. However, many judge that this criterion should be moderated in situations where technological advances make it possible to 'multiplex' the screening test, thereby adding extra conditions at minimal cost. In addition to having a major impact on the small number of affected individuals and their families, this can potentially increase the cost effectiveness and further reduce the population health burden. Although there is a general resistance to the idea that increasing the breadth of screening should be technology led this may be suitable in some circumstances and groups of conditions. For example in newborn screening, once tandem mass spectrometry is in place, it is suggested that it would be reasonable to consider the addition of further conditions provided that test performance is good, the condition is severe enough for the individual, there are few adverse effects on the unaffected population and adequate treatment services are in place. However, strict arguments against inclusion

Genetic screening programmes which function in the prenatal domain must be clear about their aims and how these will be measured and valued.

would be disease specific and may include conditions where it is impossible to differentiate between those with mild disease and others requiring rigorous and potentially harmful treatment.

For rare genetic conditions the standards for evidence of natural history and effectiveness of clinical strategies including, as for common chronic disease, the requirement for RCT evidence, are judged to be generally impossible to meet. Moreover the heterogeneity of these diseases, with subsets that can be differentiated on a molecular basis, further complicates this. Many authors recommend that 'reasonable level' evidence, with a requirement for prospective monitoring and collection of data through the screening programme should be required. Indeed to do otherwise for rare diseases would be inequitable and result in injustice.

As well as determining latent or early disease, screening programmes may also encompass the detection of disease risk. Genetic screening may be used to determine the presence of a disease or condition (for example Down's syndrome or inherited disease) and may be undertaken through analysis of DNA (for example Down's syndrome screening), or by testing for the phenotype (for example newborn screening for inherited metabolic disease). It also includes the identification of genetic variations that are associated with disease risk (for example, preconception carrier screening, where there is presence or risk of disease for potential offspring), or testing for risk of adult onset disease (for example cascade screening for familial hypercholesterolaemia or screening using genetic susceptibility to stratify risk for common chronic diseases such as breast cancer). Within the current screening criteria the two different categories are conflated, making explicit judgements more problematic.

Widening the scope of genetic screening to include susceptibility to chronic disease, as considered by the PHG Foundation in the work on breast and prostate screening[19] means that a more inclusive term for DNA differences that may be sought through the screening test is appropriate. The term 'mutation' is appropriate in the context of single gene, or Mendelian disease where a single mutation in a particular gene leads, almost invariably to disease (for example mutations in the CFTR gene in cystic fibrosis). Conversely, for disease susceptibility to common chronic disease it is accepted that the cumulative effect of many commonly occurring differences in DNA (known as variants) each increasing risk of disease by only a small amount, may combine to significantly increase susceptibility to disease. For example more than 60 variants are currently associated with breast cancer.[19]

Looking for variants across the entire genome is now regarded as an ongoing exercise and for both rare and common disease it is accepted that data obtained through research and clinical practice will be retained in databases and used to augment the knowledge base and optimise future testing. This may mean sometimes adding variants, or removing them from a test panel as knowledge accrues. In screening programmes it will be important to strike the right balance in oversight of genetic and genomic tests at the detailed level of individual variants. We would suggest that the criteria should require a description of how the set of variants were initially selected, how the panel would be kept under review and new evidence incorporated and what would trigger a full reassessment of the test. This acknowledges that the detailed evidence of test performance, and utility of including particular variants, will be largely in the hands of test providers and that the screening committee is unlikely to have the capacity or detailed expertise to undertake a full-scale test review every time a change in the screening panel is proposed.

The potential to determine disease risk for a fetus at the prenatal stage or even preconception has brought an added complexity to decision making on screening which many have sought to clarify. In particular, there is a requirement to consider the benefit of screening, which may be said to guide management or treatment during pregnancy and also include giving parents the option to terminate the pregnancy with an affected fetus. Genetic screening programmes which function in the prenatal domain must be clear about their aims and how these will be measured and valued. Prenatal genetic screening programmes such as the Down's syndrome screening programme should be recognised as a means of providing choice to parents, and not be confused with the aims of other public health screening programmes which are implemented to reduce morbidity and mortality. However, once that is established, there is an argument that other supporting evidence, such as cost effectiveness should not be inadmissible.

The concern for how the various dimensions of benefit might be valued also arises when screening programmes are proposed to provide information about disease even when there is no effective treatment. This may be of value if the patient or parents can be spared the 'diagnostic odyssey', an often lengthy period between onset of symptoms and achieving a diagnosis. This is linked to a group of criteria concerned with optimisation of treatment services prior to instigation of the screening programme. Again, many commentators argue that this may be unlikely or even impossible to achieve for rare conditions. An important value of screening may be early diagnosis when the patient is still asymptomatic so that those with disease (or severe risk of disease) can be fast-tracked to whatever specialist services are available. Thus it is considered legitimate that the identification of patients through screening may drive the development of services, at least in early stages of the programme.

The burgeoning ELS issues that arise from genetic / genomic screening also need to be addressed more explicitly in decision making. This arises because of a) the complexity of genetic tests that may be offered, b) the increased potential for screening at different stages in the disease natural history and c) because of a tangible sense that genetic material and data is considered differently to other samples and information.

Many of the fundamental ethical, legal and social issues are general to screening, but genetic screening increases their scale and complexity. For example, false positives, false negatives and incidental or uncertain findings arise in other programmes, but in genetic testing they may acquire greater significance. This may be because of the decision making that the test underpins (for example, prenatal screening); because of the uncertainty of interpreting findings (*e.g.* rare subsets of inherited metabolic diseases); or because of the large amount of information that may be produced by 'multiplexed' testing or genome wide analysis and the potential for incidental or uncertain findings

Many of the fundamental ethical, legal and social issues are general to screening, but genetic screening increases their scale and complexity.

Genetic testing before or after birth has the potential to give parents unprecedented information about their child's health. Such information may extend into adulthood. This raises key ethical issues about the rights of parents versus the rights of the child to have an 'open future'. Similar issues arise more generally within families where genetic testing of one individual may lead to knowledge of disease or health risks for other family members that they may, or may not wish to know. Non-paternity is a further potential incidental finding of genetic screening and one that may have major impact within families.

Genetic material and data have the potential to be more predictive of future health than other types of samples and data, and some would argue deserve increased protection or safeguards. Undoubtedly there are sensitivities surrounding the use, storage and communication of results from genetic testing, particularly with regard to potential discrimination by employers or insurers. Therefore ensuring informed consent is critical to safeguarding the public and the integrity of screening programmes.

All of the above issues make accurate information provision extremely important to avoid routinisation of genetic testing and allow for informed consent (as highlighted in Table 1, criterion A2).

Finally there is a set of issues around equity, which again are general issues for screening programmes but may be particularly problematic in genetic testing. These include prioritisation against other health services, where costly new genetic technologies may draw resources from other interventions. For decision making within screening programmes, policy makers need to ensure that resources are provided fairly and with equal effectiveness to different societal groups, such as ethnic minorities, or those from lower socioeconomic or educational groups. Again this may be more complex for genetic testing because of deficiencies in the underlying evidence base for some populations and because the complexities in information provision and consent may deter some groups from accessing screening.

9 Conclusions and recommendations

This literature review has examined international opinions relevant to the suitability of current screening criteria used by the NSC in making judgements about new genetic screening programmes and the ways that these are applied by policy makers in decision making. It highlights how problems arise, firstly with the scope of genetic screening to which screening criteria might be applied, and secondly with the screening criteria themselves because of the rarity and heterogeneity of inherited disorders, the potential to identify risk of disease from preconception to adult life, and the added complexity of obtaining, using and storing genetic information. These problems are technical in nature and involve consideration of a wide range of ethical, legal and social issues. As screening programmes utilising new genomic technologies begin to comprise a greater proportion of the screening programmes in the UK, consideration of these issues should form an increasingly significant part of screening programme appraisal.

We have concluded that the existing NSC criteria are not congruous with the needs of decision makers for genetic screening programmes including those for inherited disease and those that incorporate genetic susceptibility into risk assessment. Such screening applications are likely to become an increasingly significant part of the NSC remit over the next decade, and we have therefore suggested some modifications to the existing criteria to account for this. The ethical legal and social issues that arise from genetic screening are too complex to be dealt with in the simple, 'catch-all' statements made in the current screening criteria and we therefore propose modifications to the current criterion 14 to make more explicit consideration of ELS issues. We also query whether the current NSC structures and processes are suitable for the complexity of decision making regarding genetic / genomic screening programmes, and suggest an appraisal of alternative models which might embrace this and facilitate the decision making process.

Recommendations

1. **The NSC review committee should determine the scope of genetic screening that falls under its remit, with particular reference to preconception carrier screening, cascade testing, and screening of subpopulations defined by genetic risk.**

2. **Consideration should be given to modifying current screening criteria in accordance with the recommendations in Table 4.**

3. **A supportive checklist of ethical, legal and social aspects to consider should be developed as a reference resource to support the screening criteria. An initial set is included in Table 5.**

4. **Consideration should be given to developing more robust and systematic processes to appraise new applications against amended NSC criteria, such as the iterative approach proposed by Blancquaert *et al.*[1] which allows for greater interaction between opposing concerns and priorities.**

5. **The NSC should make arrangements to ensure that it possesses or can gain access to the necessary capability and capacity to assess new genetic screening programmes. In particular it should consider how it obtains the necessary scientific, epidemiological, clinical, ethical, legal and social advice to support decision making.**

Table 4 Amended criteria

	Current NSC criterion	Proposed amendment	Comment and clarification
		There should be an agreed case definition for the condition.	New criterion.
1A	The condition should be an important health problem.	The condition should be an important health problem as judged by its frequency and severity OR The conditions should together constitute an important health problem.	
1B		For rare diseases, it may be appropiate to consider groups of conditions.	This may be particularly suitable for conditions where testing can be multiplexed.
2	The epidemiology and natural history of the condition including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.	The incidence and prevalence of the conditions should be understood.	This criterion merges several ideas. If judgments are to be made it is more transparent to separate them. With regard to natural history of rare disorders best level evidence should be used and there may need to be a commitment to build up this knowledge through international cohorts of screened and clinically presenting cases.
		There should be robust evidence about either: • The association between risk factors and disease (for inherited disease the penetrance and expressivity of gene mutations should be known) • The association between disease marker and serious / treatable disease	
		The natural history of treated and untreated disease should be known. However, it is recognised that for rare disease best available evidence should be used and there may need to be a commitment to build up this knowledge through international cohorts of screened and clinically presenting cases.	
3	All the cost-effective primary prevention interventions should have been implemented as far as practicable.		

	Current NSC criterion	Proposed amendment	Comment and clarification
4	If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.		This may not be possible. Evidence should be used with prospective data collection.
5	There should be a simple, safe, precise and validated screening test.		
6	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.		
7	The test should be acceptable to the population.	The test and subsequent handling of resulting samples, data and results should be acceptable to the population.	
8	There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.		
9	If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.	If the test is for a set of mutations or genetic variants, the method for selection of variants and the means through which these will be kept under review should be clearly set out.	The term mutations is more appropriately used when considering changes in DNA sequence that are rare (frequency less than 1%) and strongly related to severe disease as in most single gene or 'inherited disorders'; 'variants' is the more commonly used term in the context of susceptibility to common chronic disease where differences occur with greater frequency but the association with disease is much weaker. Used with the term 'genomics' it reflects the fact that the whole genome has been scrutinized rather than particular genes.

	Current NSC criterion	Proposed amendment	Comment and clarification
10	There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.	Whilst accepting that the primary benefit should be to the child screened, evaluation of effectiveness of management options should be broadened to include avoiding the diagnostic odyssey and providing information to enhance reproductive choices for family members.	
11	There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.	There should be agreed evidence based policies covering management of individuals with diagnosed disease. This should be based on reasonable evidence. For inherited disorders the potential benefits to family members should be clearly set out with agreed policies on how relevant prevention and care will be provided.	
		Appropriate management of individuals with established disease should be available and accessible for all patients and their family members.	
12	Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.	Clinical management of the condition and patient outcomes should be optimised in healthcare providers as far as practicable before participation in the screening programme. For rare conditions the health system must be able to offer diagnosed patients specialised timely advice, although in early stages it is acknowledged that new patient diagnosis and provision of treatment will drive appropriate service configuration.	

	Current NSC criterion	Proposed amendment	Comment and clarification
13	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (*e.g.* Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	For common complex disorders, there should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality and / or morbidity. For rare disorders reasonable level evidence on effectiveness, based on clinically detected and screen detected cohorts would normally be required. This may be based on good quality aggregated outcome studies linked to existing international screening programmes. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (*e.g.* antenatal screening) there must be evidence that services to enable such informed choice are effective (*e.g.* good patient information and communication) and there is adequate follow up support for the chosen options.	
14	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment / intervention) is clinically, socially and ethically acceptable to health professionals and the public.	There should be evidence that the complete screening programme (purpose, target population, test, diagnostic procedures, treatment / intervention) is clinically, socially and ethically acceptable to health professionals and the public as judged against issues outlined in Table 5.	We suggest an appendix that sets out the range of ethical, legal and social factors to consider (See Table 5).
		Universal screening is preferred to ethnically targeted screening. However, if there are sound reasons for targeted screening on the basis of ethnicity, efforts should be made to avoid stigmatisation.	New criterion*. *See Table 1, Criteria A3
15	The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).	The benefit from the screening programme should outweigh the physical and psychological harm.	

	Current NSC criterion	Proposed amendment	Comment and clarification
16	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (*i.e.* value for money). Assessment against this criterion should have regard to evidence from cost benefit and / or cost effectiveness analyses and have regard to the effective use of available resource.		
17	All other options for managing the condition should have been considered (*e.g.* improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.		
18	There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.		
19	Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme. For rare disorders, the initiation of a screening programme may provide both the knowledge and the impetus to improve services.	
20	Evidence based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	Evidence based information, explaining the purposes of testing, test results, investigation, treatment and potential benefits and harms consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.	

	Current NSC criterion	Proposed amendment	Comment and clarification
21	Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.		
22	If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.		Consider removing this criterion as it is included in criterion 14. See Table 5 on ethical, legal and social aspects.

Table 5 Checklist of ELS issues

Ethical issues	**Ultimate aim**	Do the aims of the screening programme fit with broad objectives of a public health programme? Are the principles underpinning the evaluation of screening purpose with respect to informed choice in reproduction or the value of information for the individual or family members acceptable?
	Adult onset conditions	Has the impact of this knowledge on patients been assessed, particularly in relation to conditions with variable penetrance?
		Who should have access to this information?
		Have the rights of children 'not to know' been considered in the context of prenatal or newborn screening?
		Is such information inadvertently provided by prenatal screening programmes in circumstances where the pregnancy continues?
	Carriers	Will the screening programme detect carriers?
		What is the psychosocial impact on these individuals?
		How and when will information on carrier status be communicated?
		How will data be stored?
	False positives / false negatives	Are levels of false positives and false negatives at an acceptable level?
		Has the impact of false positives and false negatives been considered in relation to the particular screening scenario?
		Are there plans on how to communicate and minimise harm from false positives and false negatives?
	IFs and VOUS	Is there a potential for discovering IFs and VOUS?
		If so, which IFs and VOUS should be communicated? Who should decide?
		Does the screening programme make people aware of the potential for generating IFs and VOUS? Are procedures for informed consent adequate?
		Does the service have the capacity to provide appropriate counselling and ongoing treatment and management for people whose screening has identified IFs and VOUS?
		Are systems in place to minimise the number of VOUS? (*e.g.* data sharing, targeted interpretation, automation or use of expert committees?)

Social issues	**Familial impact**	Has the impact on relatives been considered in the decision to screen?
		Has the impact on the screened individual been considered in terms of duty to disclose information to the wider family?
		Are there sufficient services in place to manage and treat any family members who are detected through screening?
	Non-paternity	For genetic screening programmes, has the aggregate impact of non-paternity been considered on test accuracy?
	Equity	Is the proposed screening programme likely to present any negative connotations in terms of equity / solidarity?
		Will proposed changes result in reasonable healthcare allocation?
		What is the opportunity cost of the new screening programme? *e.g.* in terms of resources for primary prevention measures.
	Routinisation and over-diagnosis	Would implementation of a large scale screening programme impact on the public's perception of the seriousness of the test? Can informed consent be achieved in this context?
		Has the screening programme been assessed in terms of over-diagnosis? What is the likely impact on participants of over-diagnosis? How can this be mitigated?
Legal issues	**Confidentiality**	Has the screening programme considered the burden on individuals in terms of non-disclosure within the family?
		Will data from screening be assessable for secondary users including employers or insurers? What safeguards are in place to protect against this?
	Discrimination	If screening is routine, how likely is it that those that chose not to participate in the screening programme might be discriminated against? What protections have been put in place to prevent / reduce this occurring?
		If certain genetic variants are more common in certain ethnic groups, have measures been put in place to avoid discrimination on this basis?
	Consent / informed choice	Does the screening programme have adequate information and resources to ensure that properly informed consent is sought from participants?
		Are the potential risks and harms presented in a balanced way?
		Where screening incorporates clinical and research elements, are consent procedures such that participants can make an informed choice?
	Storage	Will samples or data be stored for future or secondary use? Do consent procedures adequately cover these possibilities?

10 References

1. Blancquaert I, Beauchamp S, Andermann A. Decision support guide for population-based genetic screening. 2008. Available from: www.cangenetest.org/en/publications.html

2. Wilson J, Jungner G. Principles and Practice of Screening for Disease. WHO, 1968. Available from: www.who.int/bulletin/volumes/86/4/07-050112BP.pdf

3. Department of Health. Genomic Technology in Healthcare: building on our inheritance. 2012. Available from: www.gov.uk/government/uploads/system/uploads/attachment_data/file/213705/dh_132382.pdf

4. Abel E, Horner SD, Tyler D, *et al.* The impact of genetic information on policy and clinical practice. Policy Polit Nurs Pract. 2005;6(1):5-14.

5. Andermann A, Blancquaert I, Beauchamp S, *et al.* Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008;86(4):317-9.

6. Andermann A, Blancquaert I, Beauchamp S, *et al.* Guiding policy decisions for genetic screening: developing a systematic and transparent approach. Public Health Genomics. 2011;14(1):9-16.

7. Bailey DB, Jr., Skinner D, Davis AM, *et al.* Ethical, legal, and social concerns about expanded newborn screening: fragile X syndrome as a prototype for emerging issues. Pediatrics. 2008;121(3):e693-704.

8. Bonham JR. Impact of new screening technologies: should we screen and does phenotype influence this decision? J Inherit Metab Dis. 2013;36(4):681-6.

9. Hall A, Chowdhury S, Hallowell N *et al.* Implementing risk-stratified screening for common cancers: a review of potential ethical, legal and social issues. Journal Of Public Health. 2014;36(2):285-91.

10. McQueen MJ. Some ethical and design challenges of screening programs and screening tests. Clin Chim Acta. 2002;315(1-2):41-8.

11. Khoury MJ. From genes to public health: the applications of genetic technology in disease prevention. Am J Pub Health. 1996;86(12):1722.

12. Khoury MJ, Janssens AC, Ransohoff DF. How can polygenic inheritance be used in population screening for common diseases? Genetics in Medicine. 2013;15(6):437-43.

13. Goel V. Appraising organised screening programmes for testing for genetic susceptibility to cancer. *BMJ.* 2001;322(7295):1174-78.

14. Burton H, Moorthie S. Expanded newborn screening, a review of the evidence. PHG Foundation, 2012. ISBN 978-1-907198-03-8 Available from: www.phgfoundation.org/reports/5504/

15. Oldman A. PHG Foundation (2012) Ethical, legal and social issues in screening.

16. Potter B, Avard D, Entwistle V, *et al.* Ethical, legal, and social issues in health technology assessment for prenatal / preconceptional and newborn screening: A Workshop Report. Public Health Genomics. 2009;12:4-10.

17. WHO. Proposed international guidelines on ethical issues in medical genetics and genetic services. 1998. Available from: whqlibdoc.who.int/hq/1998/WHO_HGN_GL_ETH_98.1.pdf

18. Wilcken B. Newborn screening: how are we travelling, and where should we be going? J Inherit Metab Dis. 2011;34(3):569-74.

19. Chowdhury S, Dent T, Pashayan N, *et al.* Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med. 2013;15(6):423-32.

20. Andermann A, Blancquaert I, Déry V. Genetic screening: a conceptual framework for programmes and policy-making. Journal of Health Services Research & Policy. 2010; 15(2):90–7.

21. Zimmern RL, Kroese M. J Pub Health. The evaluation of genetic tests. J Pub health. 2007;29(3):246-250.

22. Human Genetics Commission. Increasing options, informing choice: A report on preconception genetic testing and screening. 2011. Available from: f.hypotheses.org/wp-content/blogs.dir/257/files/2011/04/2011.HGC_.-Increasing-options-informing-choice-final1.pdf

23. Nuffield Council on Bioethics. Genetic screening: a supplement to the 1993 report by the nuffield council on bioethics. 2006. Available from: nuffieldbioethics.org/wp-content/uploads/Genetic-Screening-a-Supplement-to-the-1993-Report-20061.pdf

24. Asch DA, Hershey JC, Pauly MV, *et al.* Genetic screening for reproductive planning: methodological and conceptual issues in policy analysis. Am J Pub Health. 1996;86(5):684-690.

25. Bowen MS, Kolor K, Dotson WD, *et al.* Public health action in genomics is now needed beyond newborn screening. Public Health Genomics. 2012;15(6):327-334.

26. Burke W, Tarini B, Press NA, *et al.* Genetic screening. Epidemiol Rev. 2011;33(1):148-64.

27. Patenaude A, Sénécal K, Avard D. Whither pediatric research and predisposition genetic testing? GenEdit. 2006;4(2):1-9.

28. Simopoulos A. Genetic Screening: Programs, principles, and research - thirty years later. Public Health Genomics. 2009;12:105-11.

29. Tarini B, Goldenberg A. Ethical issues with Newborn Screening in the Genomics Era. Annual Review of Genomics and Human Genetics. 2012;13:381-93.

30. Michigan Department of Community Health. Genetics through the life cycle: Improving health and preventing disease. 2009. Available from: www.michigan.gov/documents/MIgeneticsplanandassessment__118168_7.pdf

31. On behalf of the European Society of Human Genetics' PPPC. Population genetic screening programmes: technical, social and ethical issues. European Journal of Human Genetics. 2003;11:903-5.

32. European Commission. EUR 21120 – 25 recommendations on the ethical, legal and social implications of genetic testing. 2004. ISBN 92-894-7308-8 Available from: ec.europa.eu/research/conferences/2004/genetic/pdf/recommendations_en.pdf

33. Holland W, Stewart S, Masseria C. European observatory on health systems and policies (2006). Policy Brief: screening in Europe. Available from: www.euro.who.int/__data/assets/pdf_file/0007/108961/E88698.pdf

34. Godard B, ten Kate L, Evers-Kiebooms G, *et al.* Population genetic screening programmes: principles, techniques, practices, and policies. European Journal of Human Genetics 2003; 11 (Suppl 2): S49–S87.

35. van El CG, Cornel MC, Borry P, *et al.* Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;21(6):580-4.

36. Zwahlen M, Low N, Borisch B, *et al.* Population based screening - the difficulty of how to do more good than harm and how to achieve it. Swiss Med Wkly. 2010;140:w13061.

37. Health Council of the Netherlands: Committee Genetic Screening. Genetic screening. The Hague: Health Council, 1994. ISBN: 90-5549-073-3 Available from: www.gezondheidsraad.nl/sites/default/files/9422E.pdf

38. John S. Efficiency, responsibility and disability: philosophical lessons from the savings argument for pre-natal diagnosis. University of Cambridge, 2013. Available from: ppe.sagepub.com/content/early/2013/10/11/1470594X13505412. Politics, philosophy and economics

39. Cornel M, Rigter T, Weinreich S, *et al.* Newborn screening in Europe. 2012. Available from: ec.europa.eu/chafea/documents/news/Expert_opinion_document_on_NBS_20120108_FINAL.pdf

40. Joly Y, Burton H, Knoppers B, *et al.* Life insurance: genomic stratification and risk classification. Eur J Hum Genet. 2014;22(5):575-9.

Appendix 1: Search terms

PubMed

1. Mass screening
2. Policy making or public policy or health policy
3. Guideline
4. Decision making
5. review
6. Health planning or health planning guidelines or health planning technical assistance or regional health planning
7. Decision making or decision making*Ti / Abs
8. national health programs or government programs
9. Screen* Ti / Abs
10. 1 or 9
11. Genetic* Ti / Abs
12. Genomic* Ti / Abs
13. 11 or 12
14. polic*OR guideline*OR program*OR strateg* OR process* OR procedure*OR review*OR plan*OR recommend*OR committee* Ti / Abs
15. government agencies
16. 2 or 3 or 4 or 5or 6or 7or 8 or 14 or 15
17. 10 and 13 and 16
18. Limit 18 to yr#1996-current

Embase

1. screening
2. policy
3. healthcare policy
4. hospital policy
5. practice guideline
6. health program
7. decision making
8. process design or process development or process optimization
9. procedures
10. "review"
11. hospital planning or patient care planning or planning or strategic planning or healthcare planning
12. program development
13. advisory committee
14. "screen*".ti,kw.
15. 1 or 14
16. (polic* or guideline* or program* or strateg* or decision making* or decision making* or process* or procedure* or review* or plan* or recommend* or committee*).ti,ab,kw.
17. consensus development
18. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 16 or 17
19. "genetic*".ti,ab,kw
20. "genomic*".ti,ab,kw.
21. 19 or 20
22. 15 and 18 and 21
23. limit 23 to yr="1996 -Current"

Social Science Citation Index (SSCI)

Title=(screen*) AND Title=(genetic* OR genomic*) AND Topic=(polic* or guideline* or program* or strateg* or decision making* or decision making* or process* or procedure* or review* or plan* or recommend* or committee*) Timespan=1996-2013. Databases=SCI-EXPANDED.

Applied Social Science Index and Abstracts (ASSIA)

screen* AND (genetic* OR genomic*) AND (polic* OR guideline* OR strategy* OR program* OR decision making OR decisionmaking OR process* OR procedure* OR review* OR plan* OR recommend* OR committee*)

Appendix 2: Data extraction form

Ref No.	Country / region	Author	Title	Year	Type of article	Purpose of article / report	General or specific area of genetic testing?	Source / Participants	Main findings / recommendation headings / criteria

Appendix 3: NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Ideally all the following criteria should be met before screening for a condition is initiated:

The condition

1. The condition should be an important health problem.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

7. The test should be acceptable to the population.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (*e.g.* Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment / intervention) is clinically, socially and ethically acceptable to health professionals and the public.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (*i.e.* value for money). Assessment against this criteria should have regard to evidence from cost benefit and / or cost effectiveness analyses and have regard to the effective use of available resource.

17. All other options for managing the condition should have been considered (*e.g.* improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

20. Evidence based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members.

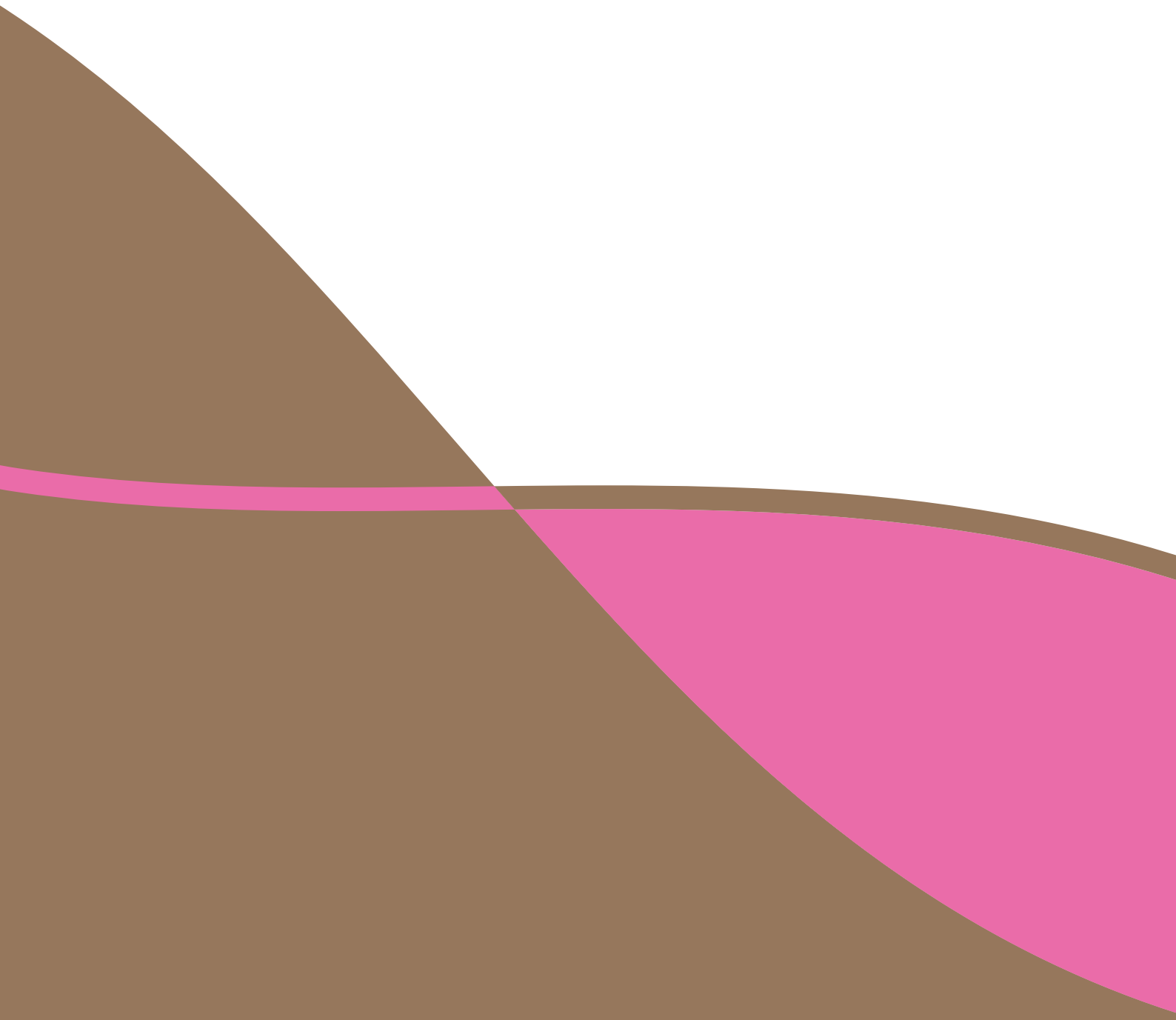
phg foundation

making science work for health

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.



CAMBRIDGE UNIVERSITY
Health Partners
Knowledge-based healthcare

PHG Foundation
2 Worts Causeway
Cambridge
CB1 8RN
T +44 (0) 1223 761 900

www.phgfoundation.org

phg
foundation
making science
work for health