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The Ethical, Social and Legal Issues with Expanding the Newborn Blood Spot Test

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The Ethical, Social and Legal Issues with Expanding the Newborn Blood Spot Test

Sian Taylor-Phillips, Senior Research Fellow¹

Felicity Boardman, Senior Research Fellow¹

Farah Seedat, Research Student¹

Alison Hipwell, Research Fellow in Patient and Public Involvement²

Nicola K Gale, Lecturer in the Sociology of Health Care³

Angus Clarke, Clinical Professor⁴

Anne Slowther, Associate Professor of Clinical Ethics¹

Morag Sime, Foundation Year 2 Doctor in Public Health¹

Sian Thomas, Consultant Systematic Review Researcher¹

Hugh Davis, Evidence and Policy Manager⁵

Aileen Clarke, Professor of Public Health and Health Services Research¹

1. *Warwick Medical School, The University of Warwick, Coventry, CV4 7AL, UK*
2. *Implementation Research Team, Warwick Business School, The University of Warwick, Coventry, CV4 7AL, UK*
3. *University of Birmingham, Health Services Management Centre, Park House, 40 Edgbaston Park Road, Birmingham, B15 2RT, UK*
4. *Cardiff University, Institute of Medical Genetics, University Hospital of Wales, Heath Park, Cardiff CF14 4XN, UK*
5. *UK National Screening Committee, Mint Wing, 3rd Floor, Centre Block G, South Wharf Road, London W2 1NY, UK*

Author Contributions

FS conducted the searches, AH and ST sifted the papers, AH and MS extracted the data. FB and STP synthesised the data and drafted the report. STP led the project. All authors contributed to study design and write up and approved the final version of the report.

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Abstract

Aim

To summarise the debate around the ethical, social and legal implications of extending the newborn blood spot test to other conditions.

Methods

We performed a rapid review of empirical research since the publication of the US panel in 2006 and of opinion pieces from the last 5 years, on the ethical, social or legal implications of expanding the number of conditions reported on in the newborn blood spot test. Systematic searching was followed by sifting conducted by one reviewer, with one in ten references checked by a second reviewer. Data extraction and synthesis were undertaken using narrative thematic analysis.

Results

The search identified 2312 unique articles, and after full text review 93 opinion and 71 empirical papers were included. There was a broad range of views with little consensus in the literature, with the UK and US characterised as opposite extremes in the debate. Key themes are whether screening should be implemented only when there is morbidity and mortality benefit for the child screened, and whether randomised controlled evidence is required before implementation. This is in the context of uncertainty about whether truly informed choice to participate, when sought, can ever be achieved in the few days after childbirth, and the increasing advocacy for genomic tests for which the public perception may not be a true representation of reality.

Conclusion

These complex ethical questions should be incorporated into decisions about whether to change blood spot screening programmes.

Executive Summary

Introduction

Currently in the UK the newborn blood spot screening programme screens infants 5-8 days after birth for phenylketonuria (PKU) congenital hypothyroidism (CH), sickle cell disease (Hb SS), cystic fibrosis (CF) and medium-chain acyl-CoA dehydrogenase deficiency (MCADD), with Northern Ireland also screening for homocystinuria (HCY) and tyrosinaemia (TYR1). Four additional conditions are currently being added: homocystinuria (HCY), maple syrup urine disease (MSUD), glutaric aciduria type 1 (GA1), and isovaleric acidaemia (IVA). In the US over 50 conditions are recommended on the core and secondary panels. The UK National screening Committee commissioned this report to investigate the ethical, social and legal implications of extending the newborn blood spot test to further conditions in the UK.

Methods

We conducted a rapid review of the literature. On 05 October 2013 we searched Embase, Medline, CINAHL, Social Science Citation Index, and Sociological Abstracts. Our search strategy combined search terms for “blood spot” and “newborn screening” with search terms for “social”, “personal”, “ethical”, and “legal” issues. We used both MeSH terms and free text terms in the title and abstract, limiting results to January 2006 and humans.

One author screened all titles and abstracts using the inclusion and exclusion criteria, another author independently screened a random sample of 10% of titles and abstracts. Eligible studies included peer-reviewed, English-language studies which considered social, personal, psychological, ethical, or legal implications of extending the newborn blood spot test as currently used in the UK to those conditions already included by the United States ACMG Recommended Uniform Screening Panel – see Table 2. (1)

The included articles were separated into opinion articles and empirical, and data were extracted from each on two separate data extraction forms. We used a thematic approach to synthesis (referred to as ‘narrative review’ by Mays et al.)(2, 3) Open (inductive) coding was applied to the empirical and opinion pieces separately, which involved applying descriptive labels to key content in the articles. An iterative process was undertaken with all authors to further refine and group these themes.

Results

The search identified 2312 unique articles and after scrutinising full texts we included 93 opinion papers and 71 empirical papers in the synthesis. See Figure 1 for the PRISMA flowchart detailing this. The synthesis resulted in 20 themes, grouped into three categories, contextual, population level and individual level issues. The contextual themes included local history, advocacy and lobbying, and the advent of increasing genomic testing. The population level themes included evidence requirements and the opportunity cost of screening programmes. The themes at the individual or familial level included the debate around the purpose of screening, and harms of screening including receiving false positive or indeterminate results, and being over diagnosed and over treated.

Context: History, advocacy and technological advances

The ethical implications of extending the newborn blood spot test to other conditions are reported as dependent upon the context in which the newborn blood spot is implemented. In

particular the local historical context and advocacy influences, and the advances in diagnostic test performance including genetic testing.

Regional history in particular related to race, eugenics and stigma is reported as an influence on the ethical implications of an extension to the newborn blood spot test. For example in the US there are reports of the historical context of racism against African Americans and mishandling of sickle cell screening resulting in mistrust and suspicion in screening, (4-6) with sickle cell screening described as viewed by some as a potential attempt at racial genocide or to reduce reproduction amongst African Americans. (6) Similarly in Germany the legacy of the Nazi era includes fear of the abuse of genetic information which is cited as influencing policy and law making today. (7)

Advocacy and lobbying in relation to screening may also be an important contextual factor in decision making. The introduction of the original blood spot test for PKU in the US has been described as influenced by lobbying from the National Association for Retarded Children, (5, 8, 9) the march of Dimes, (9) parents of children affected by the disease or disorder, (10) genetics specialists, (8) and the interest of the Kennedy family. (8) Such influence of lobbying has been described as ongoing, for example state level implementation decisions in the US, (9) influencing state level programs to be mandatory rather than using informed consent, (11) and reversing a decision in New Zealand to cease screening for CF. (12) Brosco et al. (13) describes a small number of passionate advocates as influential when compared to “abstract notions of opportunity cost and public health priorities”. These advocacy groups have been described as well intentioned, but often forming alliances with industry, (5) and so some advocacy may be influenced by commercial interests. (14) Politicians in the process have their own set of interests, with discussion of screening decisions being made based on ‘political expediency’ in New York (13) and screening having “provided politicians with an attractive opportunity to advocate for child health”. (8) Pollitt (15) describes the US and the UK as the extremes internationally, with the US public and political lobbying leading to a rapid expansion in the number of diseases screened for, and the UK “a more exacting scientific approach, with emphasis on universal criteria and quantitative data”. Therefore whilst such lobbying is present throughout the world, its influence varies between countries.

The cost of whole genome sequencing is decreasing (16) with some argument in the literature that it may eventually become cheaper than separate analysis of a set of mutations for a particular disorder. (5) Clayton argues against whole genome sequencing becoming a part of the newborn blood spot test, but describes it as a realistic possibility due to the “technological imperative” in the US. (11) Pollitt (17) describes difficulties in distinguishing between disease causing genetic variants with those with limited effects, alongside variants with only limited effects and truly disease-causing mutations. Additionally, the concept of genetic privacy and exaggerated beliefs in the predictive power of DNA analysis raise legal and ethical difficulties.” (17) In fact Wilcken (16, 18) argues that if the whole genome is sequenced then every person would be found to be above risk for at least one disorder, and genetic counselling would be required to understand that risk. In the context of concerns about the current levels of patient education and physician communication (5) this scale of counselling may be untenable. On this basis Wilcken (18) recommends that “newborn screeners would seem well advised to proceed with very great caution”.

Population Level: Evidence and Opportunity Cost

At the population level two key issues are identified as pertinent to the decision of whether to extend the newborn blood spot test to new conditions. The first is what type of evidence is acceptable to inform the decision, in particular whether Randomised Controlled Trial (RCT) evidence is necessary to estimate the mortality and morbidity benefits and harms of screening. The second is the opportunity cost of extending screening, the lost opportunity to spend the resources on another part of healthcare, which may produce greater morbidity or mortality benefits to the population at the same cost.

The argument advanced in favour of a requirement for RCT evidence is that it is the least biased estimate of the balance of benefits and harms of screening available in advance of commencing screening. It is argued that even though a slow evidence based approach may be distasteful to advocacy groups as children will continue to be affected by the diseases in question in the meantime, it may be preferable in terms of producing a screening programme with a high probability of success and low risk of harm. (19) The counter-argument revolves around decision making for rare diseases. The majority of diseases which could be considered for addition to the Newborn blood spot test are rare, and several papers (12, 18-21) describe the lack of evidence related to rare diseases, in particular associated with their natural history and their unsuitability for RCT testing. Wilckens (18) advocates that the huge sample sizes and long duration required for RCTs of rare diseases means alternative evidence sources should be found. Levy (22) describes how our knowledge and understanding of PKU, galactosemia, maple syrup urine disease, and homocystinuria has developed since the introduction of the newborn blood spot. Bailey (23) characterises it as the chicken and egg problem, arguing that screening is required to amass the information to make a decision about whether screening is required. In this search we did not find any proposals for alternative study designs in place of the RCT for estimating mortality and morbidity benefits and harms prior to commencing screening.

The decision to implement any screening programme will use resources which could be used elsewhere in healthcare, and therefore have an opportunity cost associated with it. Baily (24)(24)(24)(62) describes a reality in which “Every child is priceless; at the same time, we must recognize that how we deploy our scarce resources has an impact on who lives and who dies”. There is worldwide variation in the amount a country is willing to pay for one Quality Adjusted Life Year (QALY), (25) but this QALY approach of a single threshold is criticised in the literature. In particular it is suggested that it might be just to prioritise serious and urgent situations for a few people over smaller and broader population gains even if they have the same overall cost/QALY (12), and that a simple cost-effectiveness analysis often does not in itself produce equity, and thus equity must be considered separately and even balanced against cost effectiveness. (26) Whilst equity is an issue for all national screening programmes, Delatycki (27) makes a case that it is a greater issue in those programmes where there is a financial cost incurred if people wish to take the test. For example in Australia screening for cystic fibrosis carrier status and trisomy 21 screening incur a financial cost. As these tests are only available for those who are wealthy enough to be able to afford them the authors argue that this concerns the ethical principle of distributive justice. (27) Programmes which incur a cost because they do not meet the criteria of proven mortality or morbidity reduction for a nationally funded screening programme may still be in high demand by the general public, and will only be accessible to those who can afford it. However, some screening programmes in high demand have no mortality or morbidity benefit, and therefore committing resources to such programmes would take expenditure away from

more effective healthcare. When Mississippi expanded its newborn panels it is reported that the state concurrently saw a rise in infant mortality. There is no evidence of a causative link, but it has been used as an example of potential negative implications on overall mortality from the opportunity cost of implementing ineffective newborn screening. (24, 28)

Individual and Familial Level: Screening Benefits and Harms

There is considerable debate as to whether extra conditions should be added to the newborn screening test for reasons other than mortality or morbidity benefit to the child screened, including reducing the diagnostic odyssey, stimulating research, providing reproductive risk and carrier status information to either the parents or child. The counter argument is primarily associated with the harms of screening, including harms to healthy babies as a result of false positive results, indeterminate results and overtreatment, and the opportunity cost.

The diagnostic odyssey refers to a long journey of multiple medical tests over a prolonged time period before a correct diagnosis of the condition is achieved. An early diagnosis may reduce the cost to society of extensive medical testing (29) and the cost to the family of an extended period of uncertainty. However, in the case of diseases without an effective treatment this could simply replace the family's diagnostic odyssey journey with a 'treatment odyssey' instead, (23, 30) whilst simultaneously having a high cost to healthy infants and their families (14) who may receive false positive results or overtreatment or other unintended negative consequences of screening. Furthermore, Elliman (26) explains how reducing the diagnostic odyssey is primarily advantageous for the family or society more broadly, and not necessarily for the individual child. Harrell (30) goes further, arguing that the benefit in a reduced diagnostic odyssey may be an illusion, and there is harm to families in elimination of the "care-free" period of ignorance that the child is ill, in which the parents and child may bond.

Providing information about reproductive risk is described as an advantage as it can enable provision of timely genetic counselling and family planning (31) which may lead to a reduction in the overall burden of disease in the population for example as has been attributed to CF screening. (32) Whilst reproductive risk information is often considered a secondary aim of screening, some providers consider it a primary aim. (33) However, Bombard points out that newborn screening is often either mandatory or has far from perfect consent procedures, and so effectively requires parents to receive reproductive risk information, which they may not want. (34)

Further societal benefits may come from the research associated with implementing a screening programme and the associated knowledge it would produce (8, 14, 29, 35) and may have benefit for the child in detection through screening providing the opportunity to participate in research. (36)

Moving on from the debate about whether reducing the diagnostic odyssey, providing reproductive risk information, and research opportunities are benefits which are worthy of implementing a screening programme, there is a separate debate about whether such benefits are worth the harms of screening. Such harms include harms to healthy babies of false positive screening results, indeterminate results, and overdiagnosis and overtreatment. Balancing these has been described as a societal value judgement (5) dependent on clarifying the values at stake. (35)

Mandatory screening is described by Tarini and Goldenberg (5) in the US as on the basis of *parens patrie* power, which is applicable where failure to attend screening could harm the child. Therefore the debate about the purpose of screening is entwined with that about informed consent. Even in countries where the aim is informed choice for parents about whether to participate, there are some arguments that due to the timing of the test shortly after giving birth, (37) and the 'proceduralisation' from offering the test amongst other standard postnatal checks (38, 39) a truly informed choice may not be achieved. One study in the UK found that 41.7% of the 129 parents and future parents thought that the heel prick test was compulsory. (40) There are some suggestions that the informed choice should be moved to the last trimester of pregnancy. (37)

Discussion

We conducted a rapid review of the reported ethical social and legal issues associated with extending the Newborn Blood spot test to other conditions. We found 164 articles, representing a wide variety of views. The range of issues identified were underpinned by two critical points of disagreement between contributors: What is the aim of screening? What evidence do we need prior to implementation that screening will deliver the anticipated net benefit? There are some advocates for extending the aim of screening beyond mortality and morbidity benefit of the child screened, for example to providing information for reproductive choice or to reduce the diagnostic odyssey? Others counter that the diagnostic odyssey is simply replaced by a treatment odyssey, that there is not adequate informed choice if the objective is provision of reproductive risk information, and that these benefits are not sufficient to justify the known harms to healthy children from false positive and indeterminate test results and overtreatment. The evidence requirements debate revolves around the level of confidence in the net benefit of screening before commencement, on the one hand some advocate implementation on the basis of very poor evidence so that evidence can be amassed in the process of screening, for example for rare diseases where collection of evidence outside of screening has practical difficulties. The counter argument is that this approach uses scarce healthcare resources for screening programmes of no known benefit, and certain harms for healthy children.

This rapid review included a large number of papers and a broad range of opinions. There was no quality assessment, and so the results expressed here can only be interpreted as a summary of the range of opinions expressed on the topic.

Implications for policy practice and research

There are complex issues around expanding the newborn blood spot test, with multiple stakeholders, perspectives and values to consider. The simplest approach to screening is to only screen if there is randomised controlled trial evidence demonstrating mortality and morbidity reduction for the infant screened. However this presents an ethical dilemma in the case of rare diseases, where it is not feasible to produce such evidence. Expanding the definition of benefit to include reducing the diagnostic odyssey, providing information to parents, and increasing research about these rare diseases would ameliorate this ethical difficulty but create or exacerbate several more; namely that the child did not consent to the procedure, that parental consent is unlikely to be adequately informed, that there is a potential harm for the affected children, including those receiving false positive or indeterminate results, and that there is an opportunity cost to society of the money spent on screening.

There is advocacy and lobbying for the introduction of many screening programmes, particularly from parents of children affected by diseases detectable on the newborn blood spot test. Whilst such advocacy should be considered by policy makers, they must also consider the interests of children and parents who will be negatively affected by the introduction of screening, such as those receiving false positive results, indeterminate results or overtreatment. These people cannot advocate against screening because they are as yet unidentified.

This review has highlighted several areas for future research. Firstly that countries who do implement blood spot screening should take the opportunity to create and share screening outcomes databases, linked to follow up data for positive cases, which can be used to increase our knowledge of the rare diseases screened for, and determine whether screening is delivering the desired benefits. Secondly this review highlighted some potential legal issues around ownership and storage of samples, and implementing additional tests on the newborn blood spot without robust evidence of mortality or morbidity reduction, in the context of the complexities of informed consent in this area. Further focussed analysis of this topic would be of interest.

Acronyms

A full set of disorder specific acronyms are included in table 2, the following acronyms are used through the report:

ACCE	Analytic validity, Clinical validity, Clinical utility and Associated ethical, legal and social implications (Model process for evaluating genetic tests)
ACMG	American College of Medical Genetics and Genomics
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator-related
CH	Congenital Hypothyroidism
DNA	Deoxyribonucleic acid
GA1	Glutaric aciduria type 1
Hb SS	Sickle cell disease
HCY	Homocystinuria
HPLC	High performance liquid chromatography
IEF	Iso-electric focusing
IVA	Isovaleric acidaemia
MCADD	Medium-chain acyl-CoA dehydrogenase deficiency
MSUD	Maple syrup urine disease
NBS	Newborn Blood Spot
PKU	Phenylketonuria
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REA	Rapid Evidence Assessment approach
TMS	Tandem mass spectrometry (also known as MS-MS)
TYR1	Tyrosinaemia
UK NSC	UK National Screening Committee
WGS	Whole genome sequencing

Introduction

Developments in technology are posing questions for the future shape of newborn screening programmes. New technologies offer new opportunities for screening programmes. The advent of new testing methodologies allows many, many more conditions to be identified than was the case ten or twenty years ago.

Tandem mass spectrometry (TMS, also known as MS-MS) is able to measure in a single step many of the small molecules present in samples of serum or whole blood, while 'next generation' or 'massively parallel' DNA sequencing can identify variation in DNA sequence among individuals in many or all genes simultaneously at relatively low cost. The principal constraint on what we can detect in newborn screening is fast becoming what we choose to detect: rather than what is limited for us by technical feasibility or cost. (As an aside, both genetic and non-genetic tests need to be considered in this context of expanding blood spot testing because, for example, much the commonest disorder detected by newborn screening in most countries - congenital hypothyroidism - is so often not genetic in origin.)

The debate about what diseases to screen for in the newborn has some parallels with what information to release when one has generated more than is required for immediate medical management of a sick child. If newborn screening were ever to broaden to include whole genome sequencing (WGS), as is happening now in an NIH-funded study in USA, (41) then decisions will have to be made, as to whether information will be passed to each child's parents. Such information for example about carrier status for autosomal (and sex-linked) disorders or susceptibility to many late-onset disorders may not be relevant to the child for at least 15-20 years. There have been suggestions for example that it is useful to know one's genetic susceptibility to adult-onset degenerative diseases which can be influenced by lifestyle. However there is a lack of evidence that health-related behaviours are influenced helpfully by such knowledge. (42)

There have been some notable attempts to develop a professional consensus towards these questions, which is often described as the question of whether or when to disclose incidental findings. A strongly worded statement from the American College of Medical Genetics and Genomics (ACMG) (43) proposed that where likely pathogenic mutations in a set of genes are found in a child, this information 'should' be disclosed to the parents, whether these changes are found in a diagnostic or a research setting. This evoked a chorus of objections but has had the effect of moving professional opinion in a constructive direction. A subsequent revision of ACMG policy has added the rider that patients (or parents) should have the right to decide whether to be given these incidental findings and this brings ACMG policy into line with most other professional bodies. The ACMG proposal triggered a rapid, and salutary, maturation of the debate within the USA and internationally. The powerful point made by ACMG is that releasing incidental findings to a child's parents, when the family would otherwise be completely unaware of a strong genetic risk for which there is likely to be a useful medical intervention, is a very different setting from considering when is the best time to make genetic testing available to a child for a genetic disorder already known to be present in the family.

Currently in the UK the newborn blood spot screening programme uses tandem mass spectrometry (TMS), alongside a variety of other techniques, to screen infants 5-8 days after birth for phenylketonuria (PKU) congenital hypothyroidism (CH), sickle cell disease (Hb SS), cystic fibrosis (CF) and medium-chain acyl-CoA dehydrogenase deficiency (MCADD), with Northern

Ireland also screening for homocystinuria (HCY) and tyrosinaemia (TYR1). Four additional conditions are currently being added: homocystinuria (HCY), maple syrup urine disease (MSUD), glutaric aciduria type 1 (GA1), and isovaleric acidaemia (IVA). In the US over 50 conditions are recommended on the core and secondary panels. The UK National screening Committee commissioned this report to investigate the ethical, social and legal implications of extending the newborn blood spot test to further conditions in the UK.

Methods

We adopted a rapid evidence assessment approach. (REA approach). This approach is systematic, but 'rapid' because it does not entail all the steps and quality assessments that are part of a systematic review.

Selection

We developed the eligibility criteria for study selection by referring to previous literature, (44) and consulting an information specialist and all authors using an iterative process. (see Table 1).

Eligible studies included peer-reviewed, English-language studies which considered social, personal, psychological, ethical, or legal implications of extending the newborn blood spot test as currently used in the UK to those conditions already included by the United States ACMG Recommended Uniform Screening Panel – see Table 2. (1) We considered primary research, systematic reviews and secondary research which provided empirically collected data, published from January 2006 (the year in which the US panel was published) to October 2013. We included articles which provided quantitative data on the financial cost-effectiveness of expanding the newborn blood spot test. Non-empirical (opinion) articles were included if they provided opinion or discussion around the specified issues associated with extending the newborn blood spot test to the other ACMG-listed conditions. This yielded an unmanageable number of results so opinion articles were restricted to publications within the last five years.

We excluded articles that were concerned with other newborn screening tests (such as hip dysplasia, jaundice, or hearing screening), grey literature, and those that considered screening for unrelated issues (such as domestic violence, pre-natal/conception testing, labour positions, retinopathy of prematurity). Articles not concerned with the implications of extending newborn blood spot screening, were also excluded. These exclusions were related to ACMG-listed conditions, but were focussed on treatment, data about numbers of babies tested, genes, diagnostic techniques, or the initial introduction of NBS. We excluded articles solely concerned with biobanking, or research methods.

Table 1: Study Inclusion and Exclusion Criteria

Inclusion:

1. Peer-reviewed journal publications of any research study inclusive of primary research and systematic reviews/secondary research.
2. Empirical: Provides empirically collected data on the social, personal/psychological, ethical, or legal issues associated with extending the newborn blood spot test to other conditions
3. Opinion: Provides opinion/discussion on the social, personal/psychological, ethical, or legal issues associated with extending the newborn blood spot test to other conditions
4. Published from 2006 (empirical papers)
5. Published within the last 5 years (opinion papers)
6. Financial cost-effectiveness articles

Exclusion

1. Not English: Article published in a language other than English
2. Not blood spot: Articles associated with other newborn tests such as the newborn hearing test (hip dysplasia/jaundice/domestic violence). Or unrelated e.g. pre-natal/conception testing, labour positions, retinopathy, language development. See Table 2 for the list of included conditions.
3. Biobanking issues: Articles exclusively concerned with the issues associated with biobanking blood spot data
4. Not implications of extension: Not concerned with the ethical, legal, or social issues associated with extending the newborn blood spot to other conditions
5. Research methods: Opinion/editorials solely concerned with research methods of studies
6. Grey literature, and anything published outside of academic journals
7. Papers relating to developing countries whose health systems differ significantly from the UK

Table 2: ACMG Recommended Uniform Screening Panel – United States (excluding hearing screening) (1)

Core Panel	Secondary Panel
1. Propionic academia (PROP)	1. Methylmalonic acidemia with homocystinuria
2. Methylmalonic acidemia (mutase deficiency)(MUT)	2. Malonic acidemia
3. Methylmalonic acidemia (Cbl A,B)	3. Isobutyrylglycinuria
4. Isovaleric acidemia (IVA)	4. 2-Methylbutyrylglycinuria
5. 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	5. 3-Methylglutaconic aciduria
6. 3-hydroxy 3-methyl glutaric aciduria (HMG)	6. 2-Methyl-3-hydroxybutyric aciduria
7. Multiple carboxylase deficiency (MCD)	7. Short-chain acyl-CoA dehydrogenase deficiency
8. β -Ketothiolase deficiency (β KT)	8. Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency
9. Glutaric aciduria type I (GA1)	9. Glutaric aciduria type II
10. Carnitine uptake defect (CUD)	10. Medium-chain ketoacyl-CoA thiolase deficiency
11. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	11. 2,4 Dienoyl-CoA reductase deficiency
12. Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	12. Carnitine palmitoyltransferase type I deficiency
13. Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	13. Carnitine palmitoyltransferase type II deficiency
14. Trifunctional protein deficiency (TFP)	14. Carnitine acylcarnitine translocase deficiency
15. Argininosuccinic acidemia (ASA)	15. Argininemia
16. Citrullinemia, type I (CIT)	16. Citrullinemia, type II
17. Maple syrup urine disease (MSUD)	17. Hypermethioninemia
18. Homocystinuria (HCY)	18. Benign hyperphenylalaninemia
19. Classic phenylketonuria (PKU)	19. Biopterin defect in cofactor biosynthesis
20. Tyrosinemia, type I (TYR1)	20. Biopterin defect in cofactor regeneration
21. Primary congenital hypothyroidism (CH)	21. Tyrosinemia, type II
22. Congenital adrenal hyperplasia (CAH)	22. Tyrosinemia, type III
23. Sickle cell anemia (Hb SS)	23. Various other hemoglobinopathies
24. Hb S/ β -thalassemia (Hb S/ β Th)	24. Galactoepimerase deficiency
25. Hb S/C disease (Hb S/C)	25. Galactokinase deficiency
26. Biotinidase deficiency (BIOT)	
27. Cystic fibrosis (CF)	
28. Classic galactosemia (GALT)	

Search

We conducted a search on 05 October 2013 in Embase, Medline, CINAHL, Social Science Citation Index, and Sociological Abstracts. We applied a search strategy that combined the search terms for “blood spot” and “newborn screening” with search terms for “social”, “personal”, “ethical”, and “legal” issues. We used both MeSH terms and free text terms in the title and abstract, limiting results to January 2006 and humans (see Appendix 1 for full strategies). Time constraints precluded the use of hand-searching reference lists and key journals. The expert panel were also consulted to identify additional references.

One author (AH) screened all titles and abstracts using the inclusion and exclusion criteria. To perform double sifting, another author (ST) independently screened a random sample of 10% of titles and abstracts, and a third author (AC) screened all the abstract-included articles to review the decision. In the case of disagreement, consensus was reached through a discussion between the three reviewers (AH, ST, AC) and where agreement was not possible a fourth author (STP) arbitrated. The abstract-included articles were separated into opinion articles and empirical articles. One author (AH) reviewed the full text of the empirical articles and another author (MS) reviewed the full text of the opinion articles.

Data extraction

As this was a rapid review, formal quality assessment was not undertaken. (45) However, we separated data extraction into opinion and empirical to make a distinction between types of evidence.

These were defined as follows:

Opinion - opinion or discussion around the specified issues associated with extending the newborn blood spot test to the other ACMG-listed conditions with no data collection

Empirical - empirically collected data derived from observation or experiment

Data extraction was performed separately on pre-defined data extraction forms – one for empirical articles and one for opinion articles (including author and country perspective, conflicts of interest, and themes). Both forms were developed by one author with input from the expert panel and piloted beforehand. One author (AH) extracted data for the empirical articles and another (MS) extracted data for the opinion articles. For all articles, this included the implications (social/ personal/ ethical/ legal/financial) considered by each article in addition to the authors' perspective and country, any conflicting interests, funding details and reviewer's comments and concerns. For empirical articles, the extracted data included the study's relationship to our research question, design and details of study group participants, its key findings of relevance, and key themes. For the Opinion articles, the extracted data included relevant sections of text copied from the papers and categorization of the ethical social or legal issues that these represented. These categories were developed by the reviewer during the extraction process.

Data synthesis

We used a thematic approach to synthesis (referred to as 'narrative review' by Mays et al.)(2, 3) Open (inductive) coding was applied to the empirical and opinion pieces separately (by AH and MS respectively), which involved applying descriptive labels to key content in the articles. These numerous codes were then grouped into broader themes (by STP, AH and MS) and discussed at a steering group meeting. After this discussion FB, AS and STP generated a single list of 13 themes (some with sub-themes) across both the empirical and opinion articles and these were arranged into three overarching meta-themes (context, population-level implications and process/individual Level Implications), which were checked by the steering group. Within each theme, the findings or opinions were compared and contrasted and an overview is presented in the results. We aimed to describe the full range of ethical, social and legal implications being explored in the public domain, and to generate 'questions' and points of discussion for consideration.

The whole team was involved in decision making regarding the collection, interpretation, and synthesising of the data in an iterative process. This was achieved through regular team meetings where the evolving thematic framework was discussed at length, and any disagreements regarding the extraction of the themes resolved. The range of disciplinary and professional backgrounds of the research team facilitated a thorough and nuanced analysis of the emerging data, and meetings continued throughout the analysis process until the final theoretical framework was agreed upon.

Results

The search identified 2312 unique articles and after scrutinising titles and abstracts we included 262 articles (155 Opinion, 107 Empirical). After reviewing full texts, we included 220 articles in the analysis - 71 empirical and 149 opinion articles. After restriction of eligible time periods for opinion articles to the last 5 years 93 opinion papers and 71 empirical papers remained and were included in the synthesis. See Figure 1 for the PRISMA flowchart detailing this.

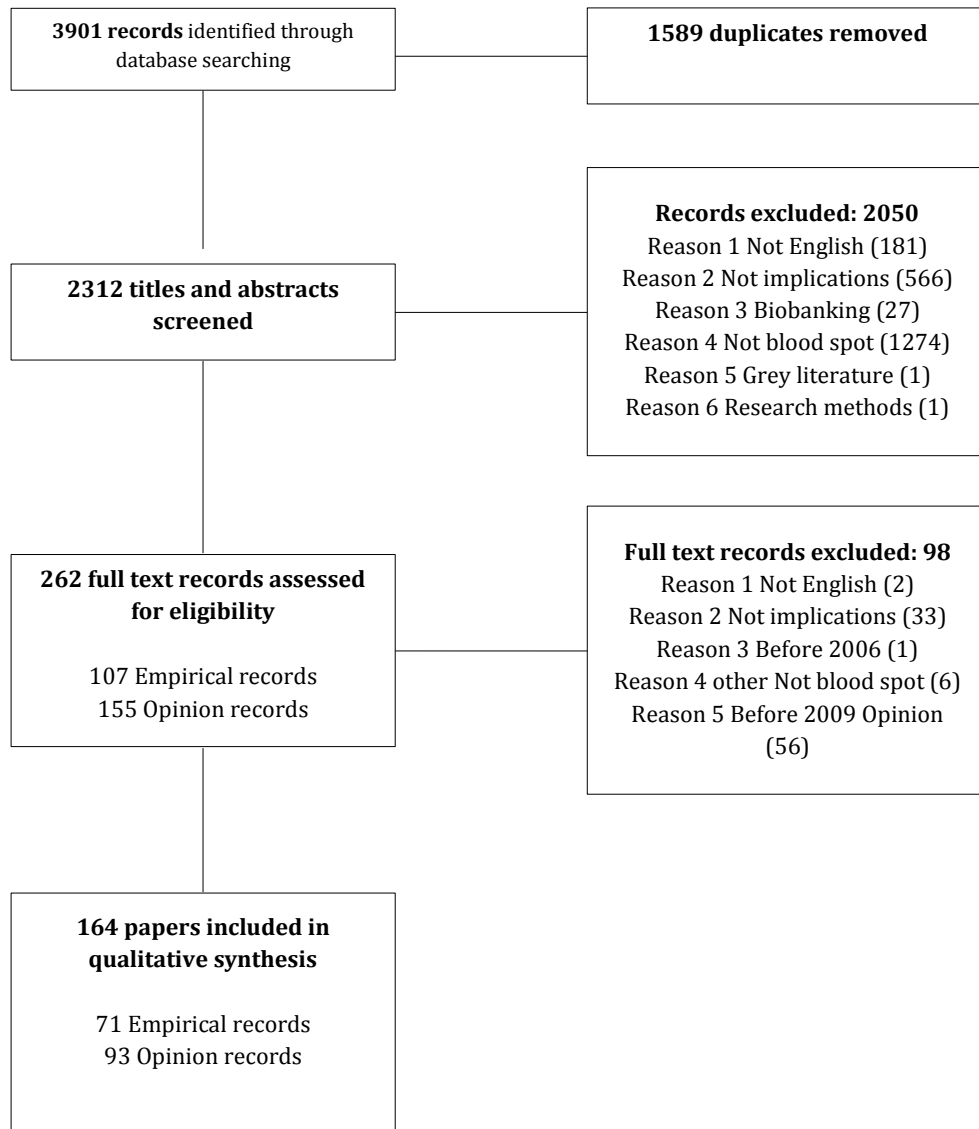


Figure 1. PRISMA flow chart of search

There were three overarching themes in the papers reviewed, the context in which extending the newborn blood spot test is being considered, implications of extension at the population level, and implications for the individual and family. There are several sub-themes within each of these. We present the results for each sub-theme as a summary of the publications which present an opinion, followed by a summary of the publications which describe empirical research related to the ethical, legal or social implications of extending the newborn blood spot test.

Context

The context in which extension of the newborn blood spot is being considered is pertinent to the ethical and legal and social implications. This section is in five parts describing the effect of the historical context, the legal framework determining ownership of screening data and the blood sample, the awareness and attitudes of the population, the influence of advocacy lobbying groups, and the technical developments driving a move towards genome sequencing.

History, Race and Eugenics

The national historical context in which a screening programme is implemented affects both practical and ethical issues with making changes to the programme. In particular concerns about eugenics, racial discrimination, and social stigmatisation are dependent on historical context and experience.

Opinion papers

Societal attitudes towards screening are influenced by the historical context. Ethnically targeted screening programmes using perceived ancestry as a selection criterion can raise concerns associated with discrimination, stigmatisation and labelling. (25, 46) The level of concern depends on the historical context. The opinion pieces about this discuss for example, the US historical context of racism against African Americans and mishandling of sickle cell screening resulting in mistrust and suspicion in screening. (4-6) Early mandatory screening programmes for sickle cell disease in the US were met with opposition as they were perceived as an attempt at racial genocide or to reduce reproduction amongst African Americans (6), in the context of a long history of interference with self-determination of African Americans. (4) There are many historical examples of racism, misinformation, and resultant discrimination for employment and insurance from within screening programme itself. (5) Such historical examples may leave a legacy for current screening programmes, and there is still an ongoing debate concerning sickle cell carrier status (4) with misunderstandings about the difference between a sickle cell carrier and someone with sickle cell disease, (5) confusion about the inheritance patterns (5) and controversy around testing recruits to the US armed forces and professional athletes. (4)

“Programs that require or encourage the receipt of sickle cell carrier results might create particular moral burdens given the frequency of these alleles in specific ethnic populations, the relevance of carrier information almost exclusively for reproductive decision making, and the legacy of mistrust created by earlier sickle cell–screening efforts. Conversely, to withhold carrier status results may be experienced as an ethnic specific denial of care.”(6)

Similarly in Germany the legacy of the Nazi era includes fear of the abuse of genetic information which influences policy and law making today (7)

“The legislation was intended to protect the population from the possible abuse of genetics, but instead presents an unreasonable threat to the health of individuals with treatable genetic disorders. One problem is that the law ranks patient confidentiality above a doctor’s responsibility to the health of that patient’s relatives. It rules, for example, that genetic data collected for diagnosis should be destroyed after ten years, even though the guidelines of the German Chamber of Physicians say that such data should be retained for at least 30 years to provide for the health of the next generation. The law also misunderstands details of science. To name but one instance, it redefines neonatal screening for genetic disease — used routinely for decades to identify 12 treatable genetic disorders by chemical, not DNA, analysis — as ‘genetic screening’... These problems have their roots in a cultural fear of sharing medical data — a legacy of the Nazi era.”(7)

The public may be cautious about genetic screening and storage of genetic information in the context of a fear of eugenics, and this is the context in which expansion of the newborn blood spot test is being considered:

“it should be recognized that genetic screening does not aim for the perfectibility of human beings. It is merely one among many other uses of medical knowledge to improve the adaptive state of genetically threatened persons and to prevent needless suffering and human and economic waste. Rigorous safeguards are required to prevent its perversion to selective discrimination for any other than generally accepted medical or scientific reasons or for such illusory goals as the betterment of human beings”(47)

Empirical studies

The social and attitudinal context in which genetic screening programmes are implemented has been identified by Potter et al. (48) as a key concern when evaluating genetic screening programmes such as the newborn blood spot screening programme.

Potter et al.,(48) in their identification of ‘key social, ethical and legal issues’ related to genetic screening, obtained through a process of knowledge synthesis, highlight two major concerns around the social milieu in which screening is carried out (p. 6). The first major concern relates to the potential of ‘eugenic’ motivations underpinning genetic screening practices, and in particular the use of newborn screening to manage reproductive decisions through the identification of carriers and those affected by genetic disease. In spite of this concern being identified by Potter et al., (48) however, the concept was not further explored within their paper, and indeed, within the rest of the empirical studies explored as part of this review.

In summary the implications of an extension to the newborn blood spot test are highly contextually dependent, affected by regional history in particular related to race and eugenics, however these concepts were generally under-explored within the empirical literature, with mentions of ‘eugenics’ often being subsumed within studies of social stigma (48-50). Whole genome and whole exome sequencing is becoming more affordable, but genetic tests may not be considered as equivalent to other tests in the complex social context.

Storage and legal ownership of genetic material

Biobanking was specifically an exclusion criterion of this review, however some related legal and ownership issues have been found, particularly associated with the legal ownership of the results of the blood spot test.

Opinion papers

The international situation concerning legal ownership of the physical card, the spot of blood and associated blood products, and the laboratory reports appears to remain unclear, and therefore who is able to use it, for what purposes, at which time point is even more difficult to determine. (51) In the US the debate is around combined interpretation of the Newborn Screening Act and the Genetic Information act, (52) although in 2011 genetic privacy bills were introduced in two US states proposing that genetic information and material are an individual's exclusive property. (53) Bowman (51) describes some of the complexities in Australia and the UK. This is a complex issue which would require a separate review, but these issues interact closely with the debate around the benefits of newborn screening, in particular in growing our collective knowledge around rare conditions.

“The approach has been to treat tissue as a res nullius (a thing belonging to no one) until it was transformed by labour into a product (like an anatomical display specimen or a human hair wig). The property rights would go to whoever provided the skill and labour in creating the product, not to the human source of the tissue. However, the Court of Appeal of England and Wales recently held that there are situations in which the res nullius presumption will not apply. One view of this decision is that it dealt with an unusual situation; another view is that the courts are laying the groundwork for stronger proprietary rights in human tissue. For current purposes, the salient point is that, without legislative direction, it is unclear who Australian courts might favour today in a contest over blood removed from an NBS card.” (51)

The newborn blood spot test only requires a small amount of the dried blood, with the opportunity to use the residual dried blood for research, quality assurance of the screening programme, and even identification of missing children or in the case of unexpected death (54). Research is often cited as a key benefit of screening, but for this to be possible both legal and ethical issues with storage, access and use of the samples must be addressed. (11) Loeber (37) reviewed storage practices for newborn blood spots across Europe and found variability in storage between 3 months and 1000 years and even indefinitely. Beyond the cost issues associated with physically storing the cards, there are potential implications for uptake if there is parental concern about reuse or misuse of genetic material, (55) with Clayton describing a “largely unspoken concern about creating a national forensic DNA database through the back door” (11) Clayton suggests a staged access approach would be appropriate, (11) but this would hold risks for the reputation of the programme if security is breached. Storage and use of residual dried blood spots without consent has already resulted in legal challenges in the UK, US, and Australia (54). As medicine moves towards genetic testing these issues may increase:

“The potential value of the blood spot from a newborn screening extends beyond the initial testing for inherited diseases conducted shortly after birth. Because blood spot collections contain the DNA of all state residents born each year and often span many years, they represent an important source of population-representative genetic samples

that could be used for population-based genomic studies. Moreover, given the recent calls for better translational research both within and outside of newborn screening, there has been a heightened interest in utilizing these residual newborn screening blood spots for research purposes. As programs begin to consider expanding to include complex genomic technologies such as whole-exome and whole-genome sequencing, there may be an increased call for genomic studies utilizing these residual samples for testing new methodologies. However, like expanded screening, the use of these specimens for research purposes raises a number of ethical, legal, and social challenges that involve public trust, privacy, and consent as well as broader questions about the public health ethic that justifies and sustains the practice of mandatory newborn screening.” (5)

Empirical Studies

The empirical studies on attitudes towards, and understandings of, policy relating to the storage and usage of genetic material showed a high amount of trust of, and support for, storage of Newborn blood spot specimens, with 80% of the 200 mothers surveyed in Quinlivan & Suriadi's (2006) (50) study supporting the (hypothetical) creation of a 'DNA library' where their newborn's blood spot would be stored. However, 87% of mothers in the same study also stated that informed consent should be sought before storage, and that parents should have the right to decline storage of their child's blood spot specimen. Moreover, over 80% stated that when their child is older, they should be permitted to withdraw the sample from the database if they so chose.

Support for storage of genetic material was also reflected in Muchamore et al.'s (56) discussion group' study with 40 participants in Victoria, Australia. The study comprised of parents of children who had recently undergone blood spot screening, parents of older children whose blood spot specimen was currently being stored and young adults whose blood spot specimen had recently been destroyed. The authors note that this support for storage of genetic material was often predicated on the 'mistaken' belief that such storage may potentially offer a range future benefits to the individual, whereas in reality, the direct benefits to the family of new born blood spot storage usually only relate to prenatal testing and forensic investigation.

Notwithstanding the high level of trust reported by Muchamore et al., (56) it was noteworthy that prior to participation in the study, none of their 40 participants had been aware that that their blood spot card, or their child's blood spot card, had been stored. Privacy and security concerns were raised about the storage, and in particular concerns about the practicalities of blood spot specimen storage (in terms of the physical space required), as well as the impossibility of offering parents (whose baby's blood spot is to be stored) a guarantee against potential abuses of the system. Indeed, fears reported by the participants around the improper use of the specimens included fear of identity theft, the possibility of human cloning and the specimens being used in unauthorised medical research. In spite of the fact that none of the participants had seen that their own, or their child's, blood spot card had been stored prior to participating in the study, they nevertheless did not claim ownership of the specimens, although they did assert that they had some rights over how they should be used.

In summary there are complex legal issues associated with ownership of the screening data and residual blood spot and card, and this in itself is worthy of a separate focussed review. This has implications for who can use the data and samples, for example whether it is appropriate to re-use them for research within the bounds of the current consent process. However, the empirical studies do show broad support for storage and use of genetic material.

(For further information on ownership of genetic material, see: Communication- withholding information and Personal Implications- wider family and paternity issues)

Awareness and attitudes of the population

Linked to the complex ethical issues surrounding autonomy in newborn screening, one of the emerging themes from the literature explored the levels of understanding in both parents and health professionals of the purpose of screening and the nature of included conditions

Opinion papers

The opinion literature suggests that education of parents of those children who are being screened is important because parents have the right to know what tests are being conducted on their children and so that they take appropriate actions after receiving the test results. (57) In the US parents have been described as “woefully undereducated” about newborn screening either not remembering the reason for testing or not remembering the test at all. (5) This is important when considering extending the newborn blood spot test as it increases the amount of information for parents if disease specific information is provided, and increases the probability of positive test results where education and understanding are key.

“despite the years of experience with carrier screening, physician communication and management as well as patient education need to improve. This does not bode well for newborn screening programs’ ability to communicate with patients about future results from genetic testing for complex common conditions or genetic risk variants”(5)

Parents in the US have a preference for more information and for this to be delivered prenatally, when parents are eager to learn about their child. (57) Education provided during or soon after childbirth may be ineffective in the context of tired parents caring for a newborn child. (57)

“Childbirth is a busy, confusing, and exhausting time that does not lend itself to education about topics that are not immediately relevant to the care of the baby.” (57)

Simopoulos (47) takes this one step further to advocate education much earlier:

“It is essential to begin the study of human biology, including genetics and probability, in primary school continuing with a more health-related curriculum in secondary school because: (a) In the absence of sufficient public knowledge of human biology and genetics, the difficulties of arousing concern over genetic diseases cannot be overcome, since even longstanding attempts to educate the public regarding traditional preventive health measures have had variable success. (b) In the short run, the educational aspects of genetic screening must consist of special campaigns devoted to each program. Sufficient knowledge of genetics, probability, and medicine leading to appropriate perceptions of susceptibility to and seriousness of genetic disease and of carrier status cannot be acquired as a consequence of incidental, accidental, or haphazard learning.”(47)

Empirical Studies

Empirical studies exploring awareness of, and interest in, newborn screening for a range of different conditions have focused on the attitudes and knowledge of health professionals (58-62) as well as the general public (56, 63) together with that of ‘interested parties’, such as parents

and prospective parents, (46, 64, 65) people in 'high risk' populations, (66) parents of children diagnosed with a screened-for condition (49, 67, 68) and parents whose newborn had recently undergone screening. (38, 50, 69, 70)

The range of health professionals involved in empirical studies included genetic counsellors (58), paediatricians, (60, 71) medical directors (61) and general practitioners. (62) The studies revealed a high degree of support for newborn screening amongst health professionals- particularly for Sickle Cell Disease and Cystic Fibrosis, with 99.5% of the 391 paediatricians in Stark et al.'s (60) study supporting screening for Sickle Cell Disease, and 98% supporting screening for Cystic Fibrosis. Lower levels of support were reported for newborn screening amongst genetic counsellors surveyed for Hiraki et al.'s (58) study (n= 227) for conditions reported to challenge the Wilson and Jungner Criteria (such as Type 1 Diabetes, Fragile X and Duchenne Muscular Dystrophy), however two thirds of respondents nevertheless supported testing for high risk infants for these conditions. (58)

Whilst levels of support and acceptance of newborn screening was reported in the empirical literature in relation to health professionals, there were nevertheless reported gaps in knowledge and training that were of concern. Indeed, the 139 GPs surveyed in Vansenne et al.'s study (62) reported that they had a lack of clinical experience and knowledge of the conditions that are screened for, and 37% of the 391 paediatricians in Stark et al.'s study were unaware that infants with the sickle cell trait (as well as those with disease) could be identified through newborn screening, highlighting issues around knowledge and training amongst health care professionals.

The general public were similarly supportive of newborn screening, with 69% of the 648 people in Etchegary et al.'s survey (63) supporting newborn screening for conditions irrespective of whether there was an effective treatment for that condition. Facilitating reproductive choice was cited as the most important reason for the inclusion of un-treatable conditions in newborn screening programmes. Similar support for screening for un-treatable conditions was reported amongst the 1372 prospective parents surveyed as part of Plass et al.'s study, (64) with 72% approving of the inclusion of un-treatable conditions in newborn screening programmes. There appeared to be more support of screening for the purposes of the reduction of disease severity, however, than for family planning and reproductive choice purposes. (50)

Whilst there was clear support for newborn screening amongst the general public and other lay stake holders, there was also an evident lack of knowledge about the purpose of screening, (67) the nature of the screened for conditions and their mode of inheritance, (49, 70) as well as concerns about the timing and content of information given about screening and screening results. (38, 46, 69)

In summary, whilst there appears to be general agreement in the included literature that parents should understand the purpose of testing, both empirical studies and opinion pieces suggest that there are significant gaps in knowledge in both parents and health practitioners. Clearly adding extra conditions to the newborn blood spot test would exacerbate this problem. Suggested solutions are all in the theme of education at an earlier stage, although there is disagreement about exactly what stage that should be.

Extension to whole genome sequencing

The costs of whole exome and whole genome sequencing are rapidly declining and so may eventually offer the potential for inclusion in newborn testing. (5) This has the potential to exacerbate existing ethical issues and create new dilemmas.

Opinion papers

The cost of whole genome sequencing is decreasing (16) to such an extent that it may eventually become cheaper than separate analysis of a set of mutations for a particular disorder. (5) The current tandem mass spectrometry employed to analyse the newborn blood spot test can detect many more abnormalities than are currently reported in the UK, and whole genome sequencing as it becomes more cost effective may present similar ethical and practical issues but on a much wider scale. Clayton argues against whole genome sequencing becoming a part of the newborn blood spot test, but describes it as a realistic possibility due to the “technological imperative” in the US. (11) Interpretation of results may become increasingly difficult in an expanded blood spot test, and in whole genome sequencing. Pollitt (17) describes the potential and the difficulties in characterising illnesses:

“In theory, it would be possible to employ gene scanning to screen for almost any inherited disorder, but there are practical limitations in that most disorders (the sickle cell diseases being the main exceptions) are extremely heterogeneous at the DNA level and until the genome has been better characterized, there will often be difficulties in distinguishing between variants with only limited effects and truly disease-causing mutations. Additionally, the concept of genetic privacy and exaggerated beliefs in the predictive power of DNA analysis raise legal and ethical difficulties.” (17)

Whole genome sequencing produces an excess of information, which links into many of the existing concerns about storage linking to privacy and eugenics, with Clayton (11) discussing “concern about creating a national forensic DNA database through the back door”, and Goldenberg and Sharp (72) expanding on how concerns about this could undermine public confidence and threaten the ‘political tenability’ of the newborn blood spot test. The general public’s ability to discriminate between the directed search for or exclusion of a specific disease and an undirected multiparameter exploration of the whole genome has been questioned, and such misunderstandings may lower uptake. (73) Conversely there may be a strong consumer demand for genetic testing, in which case Burke, Laberge and Press consider the “appropriate role of consumer preference when medical outcomes are uncertain”. (35) There are also related issues associated with informed consent for the testing, with Goldenberg and Sharp (72) discussing a tiered consent system in the US with some tests mandatory and some with informed consent. There may be an increased need for genetic counselling associated with extension to whole genome sequencing, (18, 74) and a large increase in the number of carriers identified (26). In fact Wilcken (16, 18) argues that if the whole genome is sequenced then every person would be found to be above risk for at least one disorder, and genetic counselling would be required to understand that risk. In the context of concerns about the current levels of patient education and physician communication (5) this scale of counselling may be untenable. The implications of extensions towards whole genome sequencing appear similar to those of adding extra conditions to the current blood spot test, but on a larger scale. There are similar but greater concerns about the effect on public confidence, political goodwill, and uptake of the existing tests, if they become associated with a DNA database, examples of poor communication, education and harm from

screening from a much wider range of diseases. On this basis Wilcken (18) recommends that “newborn screeners would seem well advised to proceed with very great caution”. Tarini and Goldenberg (5) recommend that extensive public consultation and engagement in decision making could reduce the level of risk, and Simopolous (47) suggests responsibility for the organization and control of genetic screening programs should be with an organisation including a combination of the public and health professions .

There were no empirical studies on the extension to whole genome sequencing.

In summary, whilst the costs are decreasing for whole exome and whole genome sequencing, several opinion pieces advise caution in the implementation of these tests because of concerns regarding creating DNA databases, a perception of low public understanding of the poor predictive value of most genetic susceptibilities, and a potential for increases in overdiagnosis to the extent of every person could be classified as high risk for at least one disorder, for which the duty of providing genetic counselling could not possibly be achieved.

Advocacy/lobbying

The role of advocacy and lobbying by patients, relatives, clinicians, policy makers and politicians was highlighted as a potential ethical concern, as although it gives a voice to families who may have benefitted from extension of screening, it is imbalanced in not representing people who may be harmed if screening were to be extended, as they are yet to be identified.

Opinion papers

Lobby and advocacy is widely cited as playing a role in making policy decisions about the introduction of newborn screening programmes. (5, 8-15, 24, 57)

The introduction of the original blood spot test for PKU in the US has been described as influenced by lobbying from the National Association for Retarded Children, (5, 8, 9) the march of Dimes (9) parents of children affected by the disease or disorder (10) genetics specialists, (8) and the interest of the Kennedy family (8). Burke et al. (8), summarising the literature, go on to describe the evidence at the time of the introduction:

“The groundswell of advocacy was sufficient to overcome cautions expressed by many in the medical community that the evidence for benefits from newborn screening was weak. These cautions were not unreasonable: one historian has estimated that newborn screening for phenylketonuria was promoted on the basis of experience with diet therapy in fewer than 20 infants with the disease . In addition, although phenylketonuria screening is considered highly successful, a full understanding of the implications of screening emerged only over time.” (8)

Lobbying doesn't only influence policy decisions regarding the introduction of screening, but also state level implementation decisions in the US, (9) influencing state level programs to be mandatory rather than using informed consent, (11) and reversing a decision in New Zealand to cease screening for CF. (12) Brosco et al. (13) describes a small number of passionate advocates as influential when compared to “abstract notions of opportunity cost and public health priorities”. Such advocacy groups have been described as well intentioned:

“Although the fundamental mission of advocacy groups—to bring attention to causes and issues that might otherwise be overlooked by the general public—is a laudable one,

the groups are often motivated by the “rule of rescue,” the impetus to save lives with less attention focused on the attendant costs” (5)

However such advocacy groups often form alliances with industry (5) and some advocacy can be influenced by commercial interests (14)

“The argument for newborn screening in the developing world is suggested as a matter of justice- that it is unfair to withhold the benefits of first world medicine from infants in under privileged communities. Ultimately, however, developments in NBS are propelled by a range of more prosaic interests: private firms seeking commercial opportunity from the sale of screening tests, specialist professionals determined to advance the technological and clinical sophistication of their fields in their respective jurisdictions, and parents and consumer advocacy groups with powerful-often deeply personal- attachments to the clinical potential of early detection”. (14)

Politicians in the process have their own set of interests, with discussion of screening decisions being made based on ‘political expediency’ in New York (13) and screening having “provided politicians with an attractive opportunity to advocate for child health”. (8) Pollitt (15) describes the US and the UK as the extremes internationally, with the US public and political lobbying leading to a rapid expansion in the number of diseases screened for, and the UK “a more exacting scientific approach, with emphasis on universal criteria and quantitative data”. Therefore whilst such lobbying is present throughout the world, its influence varies dramatically between countries.

There were no empirical research papers associated with advocacy or lobbying in the search results.

In summary there are examples of screening programmes which were introduced largely based on effective lobbying, which many people in the medical and scientific communities now consider clinically and cost effective. Lobbying also gives a voice to families who would have benefitted from an expanded newborn blood spot test were it in place. However, lobbying by well-intentioned individuals may also be exploited in a complex picture involving commercial and political interests. Furthermore there is no voice in the debate for families who would be adversely affected by screening.

Population Level Implications

There were two population level implications of extending the newborn blood spot test identified from the literature. Firstly the opportunity cost of investing financial and human resources into screening rather than alternative health investments. Secondly that if only randomised controlled trial evidence of mortality or morbidity benefit of screening is acceptable to influence extension of the newborn blood spot test, then rare diseases are by definition excluded as it would be impossible to conduct screening trials for these diseases.

Opportunity cost

The opportunity cost of extending the newborn blood spot test is an ethical issue related to equality and equity. The resources spent on expanding the number of conditions on the blood spot test could be spent on other parts of healthcare from prevention to treatment.

Opinion papers

Baily (24)(24)(24)(62)(61)[60] describes a reality in which “Every child is priceless; at the same time, we must recognize that how we deploy our scarce resources has an impact on who lives and who dies”. The decision to implement any screening programme will use resources which could be used elsewhere in healthcare, and therefore have an opportunity cost associated with it. Grosse (25) describes worldwide variation in the amount a country is willing to pay for one Quality Adjusted Life Year (QALY), but this approach of a single threshold is criticised in the literature. In particular it is suggested that it might be just to prioritise serious and urgent situations for a few people over smaller and broader population gains even if they have the same overall cost/QALY (12), and that a simple cost-effectiveness analysis often does not in itself produce equity, and thus equity must be considered separately and even balanced against cost effectiveness. (26)

“The ethical issue behind some criticisms of newborn screening pivots around the ‘Justice Principle’ (Bailey and Murray 2008; Rawls 1971, 2001), which emphasizes the distribution of risks and benefits across populations in an equitable fashion. Here, the argument is that better health gains might be obtained by investing financial resources in other parts of the health system, and is implicated in the ninth criteria outlined by Wilson and Jungner (1968). Namely, the costs of diagnosis and treatment for specific conditions should be financially weighed against potential medical expenditure, as a whole. Whilst the wise use of resources is an important political and ethical consideration, it can be applied in such an overly simplistic way that important medical interventions and programmes are excluded as funding priorities. The counterbalancing argument within the Justice Principle is that cases with serious impact and severe outcomes also need special consideration. Treating like cases alike can be rephrased as treating unequal cases unequally. That is, different criteria might apply, or different weighting given within criteria, for unusual situations that do not fit typical scenarios. This may lead to prioritization for the most serious and urgent situations, rather than to the widest spread of health gains across a population.” (12)

“The use of QALYs (Quality Adjusted Life Years) allows one to compare different interventions, but even this has limitations. Rigid adherence to principles based on cost may mean that some sections of society are neglected. Broader considerations, such as equity of outcome must also be considered.”(26)

Whilst equity is an issue for all national screening programmes, Delatycki (27) makes a case that it is a greater issue in those programmes where there is a financial cost incurred if people wish to take the test. For example in Australia screening for cystic fibrosis carrier status and trisomy 21 screening incur a financial cost. As these tests are only available for those who are wealthy enough to be able to afford them the authors argue that this concerns the ethical principle of distributive justice. (27) Programmes which incur a cost because they do not meet the criteria of proven mortality or morbidity reduction for a nationally funded screening programme may still be in high demand by the general public, and will only be accessible to those who can afford them. However, some screening programmes in high demand have no mortality or morbidity benefit, and therefore committing resources to such programmes would take expenditure away from more effective healthcare. When Mississippi expanded its newborn panels it is reported that the state concurrently saw a rise in infant mortality. There is no evidence of a causative link, but it has

been used as an example of potential negative implications on overall mortality from the opportunity cost of implementing ineffective newborn screening. (30)

Empirical Studies

The majority of the empirical literature on the financial aspects of screening comprised of cost effectiveness analyses- using different methods of economic modelling to project the anticipated cost/benefit outcomes of hypothetical newborn screening programmes for various different conditions, or using different technologies. Medium-chain acyl-coenzyme A dehydrogenase deficiency (MCADD) was one such condition that was studied by Hamers et al. (75) in France, Prosser et al. (76) in the US, van der Hilst et al. (77) in the Netherlands and Pandor et al. (78) in the UK. Each of these studies concluded that mass newborn screening for MCADD would be cost effective by calculating the QALYs gained through screening. For example, Hamers et al. (75) by using a decision model and applying it to a French birth cohort using one-way sensitivity analyses and worst-case scenario simulation, estimated that MCADD newborn screening in France could prevent five deaths each year and the occurrence of neurological sequelae in two children under five years, resulting in an overall gain of 128 life years, or 138 quality-adjusted life years (QALYs). Hamers et al.'s (75) recommendation that screening for MCADD be introduced was taken up by the French Ministry of Health, and was further reinforced by an Australian study by Haas et al. in 2007, (79) who also explored the cost-effectiveness of newborn screening for MCADD. However, this research team approached the topic by analysing the cost of hospital services used by children with MCADD by comparing those who had been diagnosed through a newborn screen for MCADD, and those who were diagnosed at a later stage (between 1 and 9 years of age). Haas et al. (79) found that in the first 4 years of life, children who had been identified as having MCADD through newborn screening cost an average of \$A1676 (US\$1297) per year for inpatient, emergency department and outpatient visits, compared with \$A1796 (US\$1390) for children in whom a later-stage clinical diagnosis was made. Forty-two percent of the children who were diagnosed through newborn screening were admitted to the hospital, compared with 71% of children who did not undergo screening. By highlighting the costs of ongoing clinical care, this research team made a case for the cost-effectiveness of screening for MCADD in the Australian context.

Cost-effectiveness analyses have also been conducted in relation to Cystic Fibrosis newborn screening in the UK by Sims et al. (80) (by using a prevalence strategy to undertake a cost of illness retrospective snapshot cohort study), Farrell et al. (81) in Ireland and Marle et al. (82) in the Netherlands. However, other studies have explored the financial implications of using different technologies for screening e.g. tandem mass spectrometry (83, 84) as well as the expansion of existing screening programmes for metabolic disorders, taking into account parental tolerance of false positive results. (85, 86)

In summary, the opportunity cost is described in terms of cost per Quality Adjusted Life Year, providing a platform to compare expanding the newborn blood spot test to other health interventions. Whilst the QALY is a well-accepted tool to implement equality, considerations of equity and justice provide a more complex context.

Randomised Controlled Trials and rare diseases

It is impossible to obtain randomised controlled trial evidence of mortality or morbidity benefit for screening for very rare diseases due to large sample sizes that would be required. There is

considerable debate of the ethical implications of this, and the evidence requirements for expanding the newborn blood spot test.

Opinion papers

The majority of diseases which could be considered for addition to the Newborn blood spot test are rare, and several papers (12, 18-21) describe the lack of evidence related to rare diseases, in particular associated with their natural history and their unsuitability for Randomised Controlled Trial (RCT) testing. Wilckens (18) advocates that the huge sample sizes required and long duration required for RCTs of rare diseases means alternative evidence sources should be found, with Pollitt extending the argument for expansion on the basis that “any case that provokes the reaction if only we had known earlier should raise the question of whether newborn screening would have been practicable”, (15) and Grosse (25) describing the argument that RCT evidence is the only way to address the questions as ‘tryanny’. However, Petros (19) considers that even though a slow evidence based approach may be distasteful to advocacy groups as children will continue to be affected by the diseases in question in the meantime, it may be preferable in terms of producing a screening programme with a high probability of success and low risk of harm.

International efforts have been proposed to increase the evidence base for rare diseases. Barrera proposes drug approval for rare diseases requires clinical trials for to recruit from all over the world, (21) and Dhont (87) advocates harmonising policy across international borders.

“how does one explain to the parents of a child with brain damage caused by one of the screenable diseases that, if the child had been born in an adjoining country, he or she would have been screened and treated for the disorder and would be developing normally?” (87)

Increasing the evidence base about natural history of disease through international collaboration appears possible, but RCT for screening must draw participants from the healthy population and so remain infeasible for rare diseases, knowledge about asymptomatic versions of rare diseases cannot be ascertained until screening is introduced, and treatment is less likely to be available. There are several proposals for frameworks to fill the gap here. Petros (19) proposes a set of 11 criteria in addition to Wilson and Jungner to use in consideration of adding extra tests to the newborn blood spot. These include “the diagnostic odyssey for the patient/family may be reduced or eliminated”, “adverse outcomes are rare with a false positive test”, and “if carriers are identified, genetic counselling is provided” but does not appear to address or provide a method of assessing the implications for patients receiving indeterminate or ‘sub-clinical’ test results. This is related to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children in the US six key questions to decide whether to add conditions to the Newborn Blood Spot, based on around benefits for the child and family, the natural history of the condition, analytic validity (technical accuracy), clinical validity (ability to detect disorder), clinical utility (balance of benefits and harms upon implementation), and cost effectiveness. (19, 88) This is based partly on the ACCE framework (89) there are three questions regarding ethical legal and social implications: “What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues? Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements? What safeguards have been described and are these safeguards in place and effective?”

A population level extension of the definition of benefit of screening, (see definition of benefit section) beyond reducing mortality and morbidity for the child and wider benefits for the family, is the knowledge gained by society from the screening results. This encompasses knowledge about the natural history of the condition gained by systematically identifying patients earlier, and the pool of potential participants for clinical trials of new treatments that becomes available (32) Levy (22) describes how our knowledge and understanding of PKU, galactosemia, maple syrup urine disease, and homocystinuria has developed since the introduction of the newborn blood spot. Bailey (23) characterises it as the chicken and egg problem, screening is required to amass the information to make a decision about whether screening is required.

There were no empirical research papers associated with evidence levels, RCTs and rare diseases in the search results.

In summary, for rare diseases for which no RCT evidence can be produced there are deeply divided views about how to proceed. Some argue that the criteria for screening should be changed and the level of evidence reduced, on the basis that for some rare conditions screening is likely to be beneficial for some individuals, and there are ethical implications of not acting when there may be potential to assist children affected by these diseases. The counter-argument is that implementing such programmes would be taking a chance, with the balance of benefits and harms not known. Slow and deliberate expansion based on evidence of mortality or morbidity benefit maximises the probability of benefit and minimises the probability of harm, particularly in the context of the opportunity cost of such programmes. There does appear to be broad consensus that there should be international collaboration to research rare diseases, and the particular importance where screening for rare diseases is implemented it should be quality assured and have excellent screening databases with follow-up data to inform about the balance of benefit and harm post-implementation.

Familial and Individual Level Implications

Expanding the number of conditions screened for on the newborn blood spot test has implications for the infants screened, and their families. These can be split into implications of screening for any purpose beyond mortality or morbidity benefit to the infant screened, implications of a range of potential test results, and implications in terms of effective communication in consent for the test and results of the test.

Definition of Benefit

Extending the definition of benefit beyond mortality or morbidity benefit to the infant screened is a key issue in search results.

Opinion papers

The opinion papers describe a debate regarding whether the benefits of screening considered in the decision of whether to implement a programme should be limited to clinical benefit to the child, or broadened. Tarini and Goldenberg (5) describe the debate as:

“a growing clamor for expansion of the notion of “benefit” in newborn screening, from one focused on individual medical benefit to one that includes psychosocial and research benefits to other recipients, such as family members and society as a whole . In the end, such a mission shift remains a societal value judgment; newborn screening programs can choose to shift their mission to include screening for conditions to promote a notion of

benefit that is broader than just direct benefit to the infant's health. However, this reconceptualization of benefit does not justify mandatory screening that can override parental authority. Thus, transforming the mission of newborn screening through a broader definition of benefit becomes ethically and socially problematic within this existing child welfare/child benefit framework that justifies mandatory screening "(5)

The issues related to mandatory screening or parental informed consent apply directly to countries with mandatory newborn screening (such as the US) but also partially to countries where informed consent (or informed choice) is made at a time where competing priorities and the routinisation of testing cast doubts over the validity of such consent – see informed consent section.

These other definitions of benefit are associated with either assisting with reproductive choice for the family, reducing the “diagnostic odyssey”, increasing medical knowledge of the natural history of diseases in particular those rare diseases which are not well understood, or simply a benefit to the parents in knowing.

The diagnostic odyssey refers to a long journey of multiple medical tests over a prolonged time period before a correct diagnosis of the condition is achieved. An early diagnosis would reduce the cost to society of extensive medical testing (29) and the cost to the family of an extended period of uncertainty. However, in the case of diseases without an effective treatment this could simply replace the family's diagnostic odyssey journey with a ‘treatment odyssey’ instead, (23, 30) whilst simultaneously having a high cost to healthy infants and their families (14) who may receive false positive results or overtreatment or other unintended negative consequences of screening. Elliman (26) explains how reducing the diagnostic odyssey is primarily advantageous for the family or society more broadly, but not the individual child.

“It has been argued that screening should be considered if it reduced the "diagnostic odyssey" or allows planning for future pregnancies ie the diagnosis of Duchenne muscular dystrophy in one child may change a family's plans for future children. In the absence of any treatment, this would be of benefit to the family with little, if any advantages for the child. This is highly contentious. Where there is early treatment, this may reduce net costs to society.”(26)

Harrell (30) goes further, arguing that the benefit in a reduced diagnostic odyssey may be an illusion, and there is harm to families in elimination of the “care-free” period of ignorance that the child is ill, in which the parents and child may bond. This is especially acute if early diagnosis does not have any known benefits.

Providing information about reproductive risk can enable provision of timely genetic counselling and family planning (31) which may lead to a reduction in the overall burden of disease in the population for example as has been attributed to CF screening. (32) However Bombard points out that newborn screening is often either mandatory or has far from perfect consent procedures, and so effectively requires parents to receive reproductive risk information, which they may not want. (34) Whilst reproductive risk information is often considered a secondary aim of screening, some providers consider it a primary aim (33)

“providers do indeed perceive the incidental generation of reproductive risk information through NBS [Newborn Blood Spot] as one of its primary benefits. This assertion derives

from their dominant rationale that identification of reproductive risk through NBS is an inherent – inextricably linked – consequence of NBS and, in turn, the disclosure of reproductive risk information facilitates disease prevention, one of the main goals of NBS” (33)

In the absence of an effective treatment, early detection may provide some benefit in the provision of supportive or palliative care (8) which may increase quality of life. (90) Furthermore, Coman and Bhattacharya in an article aimed at updating paediatricians asserts that although treatment is ineffective for methylmalonic aciduria and propionic aciduria, testing may provide an earlier diagnosis and therefore defines this as benefit in itself. (31) Other familial and societal benefits of testing when there is no treatment benefit include giving parents a realistic expectation of their child’s prognosis (90) helping the family to prepare for the expected health outcome of the child (54) and increased confidence in the medical profession. (32) Whilst there is no treatment for X-linked retinitis pigmentosa the information that the child will probably go blind may be useful for social benefit such as educational and career planning rather than clinical benefit (35) Furthermore parents often express a preference for knowing even if there is no treatment available. (32) The ethical issues at the individual (infant) family and societal level may be complex and intertwined. Forman argues that familial and infant benefits may effectively overlap:

“If benefits and harms are applied as though to an adult, one outcome may result; another outcome may emerge from these principles as applied to a newborn baby if the interests of this young child are seen as intertwined and perhaps inseparable at that stage of life from the close interests of parents and family. Benefits to a family might be an indirect but still significant benefit to the newborn”(12)

Further societal benefits may come from the research associated with implementing a screening programme and the associated knowledge it would produce (8, 14, 29, 35) and may have benefit for the child in detection through screening providing the opportunity to participate in research. (36)

Extension of the goals of screening beyond reduction of mortality and morbidity in affected children may have unintended consequences, for example increasing the number of false positive and indeterminate test results, increasing overdiagnosis, and affecting trust in screening and the health system as described by Van der Burg (91)

“Trust may also deteriorate if newborn screening turns out to serve goals other than those initially explained to the parents. If the goal of screening is to benefit the health of the infant, for example, parental expectations may be upset if screening turns out to reveal the child’s carrier status for sickle-cell disease and thalassemia. Carriers are not ill, and information about carrier status is not relevant to the health of the infant. Moreover, knowledge about carrier status may have negative effects on the child’s well-being, for children sometimes experience psychological disadvantages (such as low self-esteem or stigmatization) because of it Having information about carrier status, on the other hand, may be worthwhile to parents If a child is a carrier, then one of the parents must be as well— and possibly even both parents. If both parents are carriers of sickle-cell disease, then they have a 25 percent chance that their next child will have the

disease. Informing parents about this risk enables them to take it into account in their future procreation ” (91)

The UK NSC criterion number 13 determines that it should be “effective in reducing mortality or morbidity” but also goes on to say “Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (eg. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk.” (92) This is adapted from the Wilson and Jungner criteria. In practice it can be difficult to know how to apply these criteria, and what the threshold is for meeting each criterion. (93) The idea of changing the definition of benefit from mortality and morbidity reduction for the person screened takes emphasis off the criteria associated with having an effective treatment, and place more reliance simply on test performance. (35) Fingerhut (73) believes that screening programmes are driven by two different goals, to spare patients the burden of the disease weighed against saving money and resources. In practice the picture is often more complex, with some screening programmes saving money through reduced treatment and care costs, but presenting with a range of harms and ethical issues. The Presidents Council on Bioethics in the US in their analysis of the changing moral focus on newborn screening recommend mandating only those programmes that are of direct benefit to the child, and pilot programmes for other conditions with informed consent from parents. (29) Forman in support of extending the definition of benefit recommends extra criteria for determining which programmes to implement:

“Screening in the absence of an accepted treatment may be appropriate when it will provide information of benefit to the child or the family.

Benefit or harm to the family should be considered a benefit or harm to the child.

Decisions about screening should include community values, rights and duties alongside any cost-effectiveness assessment.

Action in the face of uncertainty may be justified in exceptional circumstances” (12)

However, Harrell argues against such an extension of the definition of benefit, linking to the informed consent debate, as the rationale for expanded newborn screening is based on personal ethics, and therefore the principle of autonomy in medical ethics should be central: (30)

“When the rationale for adopting mandatory tests is based on intimate beliefs, not public health reasoning, it is sensible to question the extent of government involvement in such private decisions.”(30)

Such divergent opinions may have their origins in the different values and approaches of different stakeholders and Burke et al. (35) call for clarification of the values behind screening decision making.

“Clarification of different stakeholders whose interests are at stake, and their preferences and values, will also be important. ... Stakeholders for these decisions include not only clinicians, patients and health care funders, but also test developers, regulatory agencies and lawmakers. In these latter cases, endless debate without resolution can occur – and clarifying the values that are at stake and how different stakeholders prioritize them may be the only way to move discussion forward to a resolution.” (35)

Some of the values that Burke et al. (35) consider important in the debate include what is appropriate for a publically funded screening programme, issues surrounding effective pre-test informed consent, and harms from false positive test results and unproven treatments. So the debate encompasses the evidence requirements for assessing both benefits and harms, and the values that inform the decision making process: (35)

“the debate centers on what concerns or risks justify providing unsought information to parents of healthy infants. The newborn screening example thus illustrates that some contributors to clinical utility – including acceptability of testing from societal and patient perspectives, financial trade-offs, and the balance of positive and negative consequences of testing (table 1) – cannot be assessed without also considering whose views matter and how they should be weighed and incorporated in decision-making”
(35)

There were no empirical research papers related to the definition of benefit of screening.

In summary, advocates for extending screening beyond conditions for which there is mortality or morbidity benefit for the child screened describe benefits such as reducing the diagnostic odyssey, providing reproductive risk information, providing palliative care for children where there is no treatment, and the screening stimulating research and providing information to benefit to society. The majority of these benefits are not direct benefits to the child screened. There are likely to also be harms to the children screened associated with the additional cases of overtreatment and indeterminate results from the extra conditions included in the test. The issues associated with screening for benefit beyond mortality or morbidity benefit for the child screened are closely intertwined with the randomised controlled trial evidence, opportunity cost, informed consent and autonomy debates. In particular autonomy and informed consent may be more important if there is no evidence of mortality or morbidity benefit, and the same potential harms.

Test Results

The extension of the newborn blood spot test in relation to the potential negative outcomes of screening are discussed here, including overdiagnosis and overtreatment, false positive results, and indeterminate results. Then the implications of these results are covered, including the psychological impact, social stigma, wider family and paternity issues, and the autonomy of the child in relation to carrier status and late onset diseases.

Overdiagnosis and overtreatment

Overtreatment is an unintended consequence of almost all screening programmes, and is discussed in relation to expanding the newborn blood spot test.

Opinion papers

Overdiagnosis and overtreatment are key themes in the literature, with discussion of overtreatment for milder forms of PKU (22), galactosemia (22), congenital hypothyroidism (17), and MCADD, (31) where often the introduction of screening programmes has revealed asymptomatic variants of disease which were previously unknown. The existence of seemingly similar screening programmes may be persuasive to some to add new screening programmes, Brosco (13) describes overtreatment in histidenemia:

“The curious case of NBS for histidinemia highlights another potential pitfall of justifying NBS on the basis of the availability of treatment. A disorder of amino acid metabolism that initially seemed to be similar to phenylketonuria, histidinemia was first identified as a potential cause of intellectual disability in the early 1960s, and reports of dietary restriction normalizing patients’ biochemical profiles soon followed. Many early published reports, however, noted typical cognitive development without treatment, and by 1974 Levy et al argued that histidinemia was likely to be a normal metabolic variant. By the early 1980s, apparent consensus emerged that treatment and screening were unnecessary, and no author ever unequivocally recommended NBS. Nonetheless, from the early 1970s through the 1990s, at least 3.5 million children were screened for histidinemia as part of state NBS programs in Massachusetts and New York, and dozens of children were treated with low-histidine diets. Although there have been no reports of physical harm to any of these children, they and their families endured the burdens of a restricted diet, repeated blood draws, and uncertainty about the future. There were financial and opportunity costs to the families and society and reports of psychological stress for families of children with false positive results.”(13)

Pollitt (17) argues that in the presence of overdiagnosis, the problem is finding the balance between preparing parents in how to take appropriate precautions and respond to emergencies and overly medicalising the child’s life. Overmedicalisation may have an associated “impoverishment risk” where the costs associated with unnecessary treatment for an infant can put the whole family at risk of poverty. (14) Finding the balance between appropriate precautions and over-medicalisation is very challenging as the penetrance (likelihood of developing clinical symptoms) is often incomplete for these rare disorders, (8) with the likelihood of the evidence base remaining incomplete for decades. Fingerhut (73) takes this further suggesting that once identified it is very difficult for a doctor to suggest no treatment without compelling scientific evidence, and of course this is most often not present for the rare disease which can be found in the newborn blood spot test. Even in the presence of decades of outcomes data post implementation of screening, Coman and Bhattacharya (31) suggest that because environmental triggers interact with genetic predispositions we cannot fully predict which infants with the milder variants will eventually develop symptoms. Furthermore, for metabolic conditions identified on the blood spot test the symptoms can be common and non-specific, and not apparent until the child is seriously ill. (9) With such a difficult balance to make clinical expertise in making recommendations to parents of these children is necessary. Pollitt (17) describes treatment for the longest standing condition on the newborn blood spot test, PKU, as variable both between and within countries with some infants treated unnecessarily, and others put at risk through lack of intervention. Pollitt (17) goes on to suggest that policy makers may not add any extra tests until clinical services are optimised. Van der Burg and Verweij (91) suggest that overdiagnosis may also occur from other tests pursued in the follow up diagnostic process, and this may threaten trust in the screening programme.

There were no empirical research papers associated with overdiagnosis in the search results.

In summary, it is clear that the prevalence and complexities of overdiagnosis and overtreatment are difficult to predict. Many of the conditions which may be considered for addition to the newborn blood spot test are rare diseases for which there is little evidence about the natural history. Whilst those in favour of screening argue that there is a problem with the burden of RCT

evidence for rare disease, there are a variety of problems clinicians and parents face after the introduction of a screening programme with limited evidence about the natural history of disease. In such situations it is impossible to consider the balance of benefit and harm, when the harms through overdiagnosis are as yet unknown. Information from screening programmes in other countries could form part of the solution, as could an extensive international collaboration for collecting data on rare diseases. (17)

False positives

False positive screening results refers to infants who screen positive for disease, but do not have the disease and this is revealed on the follow up tests.

Opinion papers

The harm to families from false positive results can include parental stress, depression, anxiety, altered perceptions and worry about the child's health, persistent worry about the child's future, increased use of health care services by parents for the child, an impaired parent-child relationship, (57) unnecessary hospitalisations, (94) leading to unnecessary and possibly harmful treatments and tests, leading to misunderstanding of genetic risk information which can influence life planning decisions in unintended ways. (25) These negative consequences may be related to a parents understanding of the newborn test results. (8, 54, 95) Interpretation of disease risk is open to cultural interpretation (14) making communication of tests results challenging. After a false positive screening result parents may not withdraw from screening altogether, but their trust in the newborn blood spot screening programme may be eroded. (91) In the context of expansion of the newborn blood spot screening programme the potential consequences in terms of absolute numbers of families in the UK with false positive or indeterminate results would expand, and this may have consequences for trust in the existing screening programmes. Harrell (30) describes her experience of positive screening results in the US:

“when we were told my son had a positive newborn screen, the general sentiment of medical professionals was the result was a false positive. Despite this conclusion, there was not a full consent process or indication that we, as parents, could refuse the first or even second round of follow-up tests. My husband and I were concerned that declining follow-up testing could be considered neglectful of our son. In addition, would it be considered neglect to allow my son to sleep more than four hours, when we were told to wake and feed him, even if we believed the test result was a false positive and felt it was more important for our child's development to sleep until he naturally wakes...it is not inconceivable that some parents, weighing both information and values, would have a rational and thoughtful preference not to screen for certain rare genetic conditions.”(30)

Empirical Studies

The evidence surrounding the impact and perception of false positive test results on parents' experiences of, and attitude towards, newborn screening, appears mixed. Indeed, Dixon et al.'s (2012) study, (96) which used the contingent valuation method in order to assess the attitudes of 160 parents of children under 16 years of age towards false positive screening results by asking them about the maximum amount they would pay for an extension of the screening programme, and then ascertained how far the possibility of false positive results diminished their valuations. The parents surveyed were provided with a description of the current screening programme, a description of an extended screening programme and a description of an extended screening

programme that would yield no false positive results. 92.5% of the parents said that they would accept the extended screening programme, and 95% said that they would accept the extended screening programme that would yield no false positive results. The parents reported that the maximum they would be willing to pay for the extended screening programme would be £178, compared with £219 for the extended screening programme with no false positive results. The authors conclude from these results that there is a high acceptance of an extended screening programme and that the possibility of false positive results has little impact on this acceptance.

The six studies that directly explored parents' experiences of having a false positive screening result, however, reveal a slightly different picture of the perception of, and experience with, false positive results. (97-102) All six of these studies reported that parents who receive false positive results experience high levels of stress and anxiety at the point of receiving the false positive screening result and undergoing genetic testing, with 96.5% of the 86 families in Beucher et al.'s (97) French study reporting these high levels of anxiety, and 10% of the 31 parents in Morrison & Clayton's (98) US study reporting 'clinically significant' levels of stress at this time. Moreover, Lang et al.'s (102) telephone survey study of 90 parents who had received a false positive result for their child in relation to Cystic Fibrosis, and had undergone genetic counselling, highlighted that anxiety and 'residual risk' may persist for these parents, even after genetic counselling has been undertaken. Specifically, as Gurian et al. (99) have noted, false positive results affect the parent-child relationship; by asking parents of 173 infants with a false positive result to complete the 'parenting stress index' and then comparing their results with those completed by parents of infants with normal screening results. Gurian et al. (99) found that parents of infants who received false positive screening results scored more highly on the parenting stress index, and that they also scored particularly highly for the parent-child dysfunction subscale and the difficult child subscale .

Gluczek et al. (2011), (100) in their US study, found that the 87 parents they interviewed who had received false positive screening results in relation to newborn Cystic Fibrosis screening reported a range of impacts, of which stress and worry about the child's health and future was one. However, they also identified some potentially positive impacts of the false screening result retrospectively; parents reported that they experienced strengthened familial relationships as a direct consequence of facing a potentially traumatic and life-threatening diagnosis in their infant, as well as empathy towards parents whose infants received a 'true' positive result and an identification with the Cystic Fibrosis community. Gluczek et al. (100) also discovered that parents experienced renewed support for newborn screening as a consequence of their experience.

Only one of the studies exploring the impact of false positive results on parents' experiences of newborn screening followed parents up at 3, 12 and 24 months after screening, (97) and this study found that 86% of the 86 families surveyed felt 'entirely reassured' at just 3 months after the false positive screening result and diagnostic test. All parents stated that they would opt to have another infant undergo newborn screening. This finding somewhat contradicts a US study by Schmidt (101) who conducted focus groups and qualitative interviews with 27 participants who had received a false positive screening result (children now aged between 6 months and 16 years). Whilst Schmidt did not identify major long-term negative implications of a false positive result, she did note that many parents nevertheless experienced 'residual worry' about their child's health that persisted despite reassurances that their child's result had been a false positive.

The need for better communication between care providers and parents receiving the screening results was noted as a major conclusion by three out of the five studies that explored parents' experiences. (98, 99, 101) Indeed, only a third of the parents in Gurian et al.'s (99) study reported knowing the 'real' reason why their infant was being called back for further testing. Those parents who had better information experienced less stress than those who were misinformed, and consequently high quality communication between care providers and parents was highlighted as a key strategy for reducing the stress of false positive results.

In summary, false positive results result in high levels of stress and anxiety for parents at the point of receiving the positive results, with mixed evidence about whether there is persistent anxiety and perception of residual risk in the months and years after the blood spot test. There were also some positive consequences of false positive results including reports of strengthened familial relationships, and increased support for newborn screening. The consistent conclusion is that communication is key to reduce the negative effects of false positive results, which in the context of an expanded newborn screening programme would mean investment in training in the additional conditions for health professionals communicating results.

Indeterminate results (patients in waiting)

Patients-in-waiting is a term used interchangeably to describe indeterminate results and late onset conditions. Here we discuss indeterminate results, and late onset conditions are discussed in the section on autonomy of the child.

Opinion Papers

The most frequently discussed example of indeterminate results is Cystic Fibrosis Transmembrane Conductance Regulator-related (CFTR) metabolic syndrome occurring as a result of screening for CF. (8, 103) Buchbinder and Timmermans (9) describe the issue:

"Newborn screening creates ambiguous forms of biogenetic abnormality, foreshadowing a life of incipient disorder for children, families, and healthcare providers. In doing so, it destabilizes parents' desires, hopes, and anxieties about having a healthy child" (9)

Technical improvements far from improving the situation, tend to produce more markers of uncertain relevance, so increasing the number of indeterminate results. (104) Massie (103) advocates taking decisions in line with the ethical principles of beneficence, non-maleficence, and justice, arguing that there is harm for people with indeterminate results in the form of medication side effects, genetic counselling based on flawed information and psychosocial risks for the child taking on a sick role when there is no illness. They go on to discuss the principle of justice, and using healthcare resources for treating people with no illness.

Empirical Studies

There were only two studies in the empirical literature exploring the phenomena of indeterminate results, or 'patients-in-waiting', and these two studies showed quite a different picture of the experiences of families receiving these results.

Timmermans and Buchbinder (105) in their observational study of a Californian genetics clinic that follows up children with indeterminate results in relation to newborn screening for metabolic disorders, found that the 55 families they observed occupied a 'liminal' space between health and disease, the boundary of which is policed by medical professionals, who waited for either

symptoms of a metabolic disease or genetic markers to emerge, or else the passage of a 'sufficient' amount of time for the newborn to be declared 'symptom free'. During this time, Timmermans and Buchbinder note, '...the newborn screening results oscillate between a biochemical artefact and a life threatening disease' (p. 412). The effects of these indeterminate results on the families who receive them were reported to be profound. Indeed, for some families, even after the presence of a disease had been dismissed, 'residual risk' did not necessarily dissipate, as the authors note:

"...the majority of parents tend to obsess about the lingering dangers and downplay the qualified reassurances. Parents continue to watch their child carefully and incorporate the worst possible outcome as a contingency in their lives. For them, the child is the same as before [before reassurance that there is no disease] and without a critical time period defined in advance, it is difficult to accept that their child is now out of danger"

(Timmermans and Buchbinder, 2010; p. 416)(105)

Perobelli et al.'s (106) Italian questionnaire study of parents who received an ambiguous diagnosis in relation to their infant following newborn Cystic Fibrosis screening, however, revealed a different picture of the experience of receiving, and responding to, indeterminate screening results. Like the families in Timmerman and Buchbinder's (105)(2010) study, the parents in Perobelli's study faced a long period of diagnostic uncertainty following the reception of their baby's indeterminate results. The parents were informed that some infants with indeterminate results may, in time, develop Cystic Fibrosis, whilst others will develop no symptoms at all (and it is impossible to discern between these two groups). All infants who receive an ambiguous diagnosis are offered a follow up appointment in the clinic.

In their comparison of 11 parents who received an ambiguous diagnosis for their newborn, 11 parents who received a Cystic Fibrosis diagnosis, and 11 parents whose babies had a normal screening results, Perobelli et al. (106) through the use of a questionnaire, concluded that levels of anxiety were lower amongst the parents who had received an ambiguous diagnosis than amongst the parents who had received a Cystic Fibrosis diagnosis. Moreover, the parents of children with an ambiguous diagnosis were also reported to show no more concern about their child's health than the parents of children with normal newborn screening results. These results appear to contradict the findings of Timmerman and Buchbinder's (105) study, which highlighted the tensions in parents' experiences of living on the uncertain boundary between health and disease, and indeed, the difficulty of resolving this tension even after the presence of a metabolic disease had largely been discounted.

In summary, parents of children with indeterminate results endure significant time periods of months or years with uncertainty as to whether their child is completely healthy or has a life threatening disease, interspersed with follow up tests and observation. The evidence about the effects of this is mixed, but there is some evidence of a persistent feeling in parents that the child retains a residual risk.

Psychological Impact

The psychological impact of receiving a range of test results was touched upon in a range of the opinion papers, but was a focus of many of the empirical studies.

Opinion papers

The psychological impacts of false positive and indeterminate test results, discovery of carrier status or late onset disease are widely discussed. To mitigate these negative consequences Bailey (23) asserts that there will be a much greater role for psychologists in future screening programmes as part of a four pronged approach covering accurate and understandable information, formal and informal support; participation in active surveillance, the opportunity to participate in research on general and targeted interventions, (and providing access to these interventions as they become available). They go on to suggest that the methods of support to families should be developed and tested with effective research methods as well as the screening programmes.

Empirical Studies

The empirical literature on the psychological impact of newborn screening is varied, with studies focusing on the implications associated with false positive screening results, (97-101, 107) indeterminate results or ambiguous diagnoses, (105, 106) carrier status (67, 108-110) and the psychological implications of the diagnosis of disease through newborn screening. (100, 111) These different areas of the empirical literature will be addressed in turn.

1) The psychological impact of false positive results

The literature on the psychological implications of false positive screening results has been discussed in an earlier section on false positives. However, in summary, the six studies (97-101, 107) (102) that directly explored parents' experiences of having a false positive screening results, revealed that they experienced high levels of stress and anxiety at the point of receiving the false positive screening result and undergoing genetic testing, with 96.5% of the 86 families in Beucher et al.'s (97) French study reporting these high levels of anxiety, and 10% of the 31 parents in Morrison & Clayton's (2011) US study reporting 'clinically significant' levels of stress at this time. Moreover, Lang et al.'s (102) telephone survey study of 90 parents who had received a false positive result for their child in relation to Cystic Fibrosis, and had undergone genetic counselling, highlighted that anxiety and 'residual risk' may persist for these parents, even after genetic counselling has been undertaken. Specifically, as Gurian et al. (99) have noted, false positive results appear to affect the parent-child relationship; by asking parents of 173 infants with a false positive result to complete the 'parenting stress index' and then comparing their results with those completed by parents of infants with normal screening results. Gurian et al. (99) found that parents of infants who received false positive screening results scored more highly on the parenting stress index, and that they also scored particularly highly for the parent-child dysfunction subscale and the difficult child subscale.

Gluczek et al. (100) in their US study, found that the 87 parents they interviewed who had received false positive screening results in relation to newborn Cystic Fibrosis screening reported a range of impacts, of which stress and worry about the child's health and future was one. However, they also identified some potentially positive impacts of the false screening result retrospectively, including strengthened familial relationships, as well as empathy towards parents whose infants received a 'true' positive result and an identification with the Cystic Fibrosis community.

Only one of the studies exploring the impact of false positive results on parents' experiences of newborn screening followed parents up at 3, 12 and 24 months after screening, (97) and this study found that 86% of the 86 families surveyed felt 'entirely reassured' at just 3 months after the false positive screening result and diagnostic test. This finding somewhat contradicts a US

study by Schmidt (101) who, through focus groups and qualitative interviews with 27 participants who had received a false positive screening result (children now aged between 6 months and 16 years), did not identify major long-term negative implications of a false positive result. Schmidt did note, however, that many parents nevertheless experienced 'residual worry' about their child's health that persisted despite reassurances that their child's result had been a false positive.

2) The psychological impact of indeterminate results and ambiguous diagnoses

Timmermans and Buchbinder (105) in their observational study of a Californian genetics clinic that follows up children with indeterminate results in relation to newborn screening for metabolic disorders, found that the 55 families they observed occupied a 'liminal' space between health and disease, the boundary of which is policed by medical professionals, who waited for either symptoms of a metabolic disease or genetic markers to emerge, or else the passage of a 'sufficient' amount of time for the newborn to be declared 'symptom free'. During this time, Timmermans and Buchbinder note, '...the newborn screening results oscillate between a biochemical artefact and a life threatening disease' (p. 412). For Timmermans and Buchbinder, (105) the psychological implications of these indeterminate results were profound.

Perobelli et al.'s (106) Italian questionnaire study of parents who received an ambiguous diagnosis in relation to their infant following newborn Cystic Fibrosis screening, however, revealed a different picture of the experience of receiving, and responding to, indeterminate screening results. Like the families in Timmerman and Buchbinder's (105) study, the parents in Perobelli's study faced a long period of diagnostic uncertainty following the reception of their baby's indeterminate results. The parents were informed that some infants with indeterminate results may, in time, develop Cystic Fibrosis, whilst others will develop no symptoms at all (and it is impossible to discern between these two groups). All infants who receive an ambiguous diagnosis are offered a follow up appointment in the clinic.

In their comparison of 11 parents who received an ambiguous diagnosis for their newborn, 11 parents who received a Cystic Fibrosis diagnosis, and 11 parents whose babies had a normal screening results, Perobelli et al., (106) through the use of a questionnaire, concluded that levels of anxiety were lower amongst the parents who had received an ambiguous diagnosis than amongst the parents who had received a Cystic Fibrosis diagnosis. Moreover, the parents of children with an ambiguous diagnosis were also reported to show no more concern about their child's health than the parents of children with normal newborn screening results.

3) The psychological impact of carrier status

An exploration of the psychological impact of carrier status was undertaken by Kladny et al. (67) and Miller et al. (108) and was also considered in studies by Lewis et al. (109) and Ulph et al. (110) The research studies were conducted in the USA, Canada, Australia and the UK respectively. Despite carrier status results being generally considered medically 'benign' information, (108, 110) the empirical literature has highlighted the often significant emotional and psychological implications this information can nevertheless have. Indeed, out of the 114 participants in Kladny's (67) US survey study of parents whose children had been identified as being a carrier of Sickle Cell Disease, 19% reported feeling guilty or upset when learning of their child's genetic status and 4% believed that their partner blamed them for it. Moreover, Miller et al.'s (108) qualitative Canadian study of the experience of Sickle Cell carrier status through interviews and focus groups with health care providers, community-based Sickle Cell Disease activists and parents of children identified as carrying the trait, highlighted anxiety and uncertainty within families about the true clinical significance of carrier status for Sickle Cell Disease. Indeed, many of the parents expressed concerns about the health of their carrier child and interpreted diverse symptoms as being linked to the trait, as one mother commented:

"You know lately she's been saying her leg always hurts like anything, she does, 'My leg hurts.' So I'm thinking, 'Is she just saying that or does it hurt because of the trait?' So I have to take her in for that but other than that she seems okay."

(Mother of carrier child, herself
affected with Sickle Cell Disease, p. 306) (108)

Enduring concerns about the health of their child following their identification as a carrier through newborn screening was also identified by Lewis et al. (109) in their Australian postal questionnaire study of parents of children identified as carriers of Cystic Fibrosis at two time points (1996-1997 and 2001). Indeed, 28% of the parents from the 1996-7 cohort had 'residual anxiety' about the current health status of their child, and 18% of the 2001 cohort reported similar concerns. Moreover, these parents also expressed worries about the implications of carrier status for their child's future reproductive decision-making, as well as the appropriate time and manner to disclose that information to their child.

4) The psychological impact of the diagnosis of disease

The final area of the literature which addresses psychological impact is in cases where disease is detected and diagnosed through newborn screening. Grob's (111) US study, which involved 35 semi-structured interviews with parents of children who were diagnosed with Cystic Fibrosis either through newborn screening (n=16), prenatally (n=4), or after the development of symptoms (n=11), noted some of the difficulties of parents of coming to terms with an unsought diagnosis so early in a child's life. Indeed, she highlighted the possibility of the diagnosis interfering with the process of parents 'falling in love' with their newborn baby as it forces parents to consider their child in a new light- as seriously ill- and to reconcile the apparent contradiction of being faced with a potentially life-limiting condition, but also holding an apparently thriving infant in their arms, as one mother of a baby diagnosed with Cystic Fibrosis through newborn screening commented:

"The hardest part about that whole time.... it's just knowing that this is something that could potentially take her life. Having been a mom already, the hard part was that at times I felt like I was scared to fall in love with her because I didn't know how long I'd have her and so that was the hardest part, because I mean those, those [weeks and months] that we were waiting for the information back, um, I have to say I did look at her a lot and think about it... and it's hard not to look at her and go 'well nothing's wrong with her cause she's beautiful and she's, you know, just the epitome of healthy..' [When she was a newborn I wondered] you know, 'Okay, who are you?' [...].....I'm trying, now's the time when I'm supposed to be falling in love with you, but I'm scared to."

(Mother of child diagnosed with CF through NBS, p.1060).(111)

Parents also experience sustained periods of uncertainty when their child has received a diagnosis and yet remains asymptomatic. For these parents, not knowing whether or not to treat their child as 'sick' or 'healthy' could be both distressing and confusing, for both themselves, and the child, as one mother of a child diagnosed with Cystic Fibrosis through newborn screening- but who was still asymptomatic years later- commented,

"It's hard to tell Tess that she can't go play with Chris. I say, 'Well you can't.' 'Why?' she says. I'm like, 'You're sick.' She says, 'Well, I don't feel sick. I'm not sick' I say, 'Honey, but you're always kind-of sick, you just don't realize it.'"

(Mother of young child

diagnosed with cystic fibrosis through newborn screening, p.
1056)(111)

This finding was echoed in Tluczek et al.'s (100, 112) study of factors associated with parental perceptions of child vulnerability at 12 months after a diagnosis of either congenital hypothyroidism (n=36) or Cystic Fibrosis (n=23) as compared with carriers of Cystic Fibrosis (n= 40) and healthy controls (n= 37). Using mixed logit structural equation modelling, and after controlling for infant and parental characteristics, the study found that parental perceptions of child vulnerability were linked with parental sex female, illness frequency and Cystic Fibrosis diagnosis. Moreover, that parental perception of child vulnerability was also positively associated with maternal parenting stress, highlighting that gender may play a part in the psychological implications of a diagnosis derived through newborn screening.

Whilst reactions of guilt and blame have been noted in the wider literature as a common reaction to a diagnosis of genetic disease in the family- and indeed, have been observed in relation to the identification of carrier status through newborn screening, as described above- it is noteworthy that these concepts were not explored in the literature specific to newborn screening and genetic diagnosis.

In summary, there is empirical research exploring the psychological consequences of receiving false positive, indeterminate, carrier and true positive screening results. False positive results can cause stress, anxiety, damage to the parent-child relationship, and perceptions of residual risk even after subsequent negative tests and genetic counselling. The longer term consequences are unclear. Indeterminate results can cause parents' uncertainty, where they may swing between believing their child is healthy, and believing their child has a life threatening illness. For children shown to be disease carriers there may be enduring concerns about the health of the child. Even the parents of those children for whom screening is designed to help, those with true positive results there may be negative psychological consequences of testing. Coming to terms with an unsought diagnosis so early in the life of a child who appears healthy poses difficulties for parents. There may be an increased role of psychologists in the future of newborn screening, with suggestions that research on the effectiveness of the psychological support should be considered alongside evidence of clinical effectiveness of screening when deciding whether to implement or expand screening programmes.

Autonomy of the child

Consent to participate in newborn screening cannot be given by the child tested due to their age, which creates a range of issues associated with the autonomy of the child tested.

Opinion papers

The autonomy of the child is highlighted as a key ethical issue (12, 27) in particular with regard to late onset conditions, (55, 113, 114) and revealing the child's carrier status. (26, 32, 54) Bunnik et al. (113) describe this as particularly acute when considering genetics and informed consent:

"[Questions] arise when late-onset diseases are concerned or when test results are retained and accessed later on in the child's life. Testing for late-onset diseases has traditionally been considered morally unjustified in view of children's right not to know, because it would deprive them of their right to decide (when competent to do so) whether to be tested for these conditions. 17 Other questions relate to who has access to the information and when, and for how long it should be stored. If we take seriously the possibility of newborn profiling, the accompanying informed consent procedure should address these issues." (113)

Disease carrier status and late onset conditions cannot be neatly segregated into a separate category, some late onset conditions are variants of other conditions and so separating them for individual consideration is not always straightforward. In practice parents may be told about the child's carrier status, the issue of whether the parents should then pass the information to the children and at what stage has ethical implications (26) Ross (114) discusses the example of early onset Pompe Disease (PD) which is offered in Taiwan. The arguments for screening include treatment of infants with early onset variants, potential treatment of late onset variants, and cascade testing of relatives at risk of late onset forms. The arguments against were summarised as the testing does not benefit the minor as a child, violates their right to privacy and autonomy, and may change how the children are treated.

Screening newborns for late onset conditions raises particular concerns as it is not known at the time of screening what treatment will be available for that condition when the child has grown up, (115) it is not possible to predict future changes to medical practice. Patients in waiting is a term applied to both indeterminate results and late onset diseases, including some lysosomal storage disorders, (116) Krabbe disease (117) and late onset Pompe disease. (114) Alongside the obvious difficulties for a child and his or her parents with the knowledge that they may develop a serious condition in adulthood, and the violation of the autonomy of the child in producing this knowledge without their consent, there are also some practical issues with how the family may behave in light of this knowledge. There may be no eventual benefit of the knowledge as there is some evidence that they may fail to disclose it to healthcare providers at the point in time where it would be of benefit. (114) Furthermore Bleicher (117) asserts that having been worried by newborn screening results parents may pursue risky tests and unproven treatments as a result of their worry about the child, or avoid routine tests to avoid the risk of bad news.

Empirical Studies

The major concerns in the empirical literature which reference the autonomy of the child relate to whether or not genetic results obtained through newborn screening which reveal carrier status, (34) non-treatable and/or late-onset conditions (46) or other incidental findings (118) should be reported to the parents of the screened infant. Indeed, it appeared that whilst the overwhelming majority of the 1615 health care providers surveyed and interviewed in Bombard et al.'s (34) Canadian study agreed that the management of (future) reproductive risks was an acceptable goal of newborn screening (through the identification of carrier newborns), some participants queried whether this practice violated the child's rights, and asserted that informing parents of a child's carrier status challenges the individual's choice to learn of their own reproductive risks.

Similar arguments were put forward within this same study population in Miller's (118) analysis of attitudes towards the disclosure of incidental findings which may emerge through newborn screening practices. Whilst the vast majority of the 1615 health care providers who participated in the study supported the reporting of incidental findings to parents, and indeed, raised concerns about the legal implications of not doing so (e.g. future 'wrongful birth' lawsuits etc.) (p. 629), a slim majority of genetics professionals (51.9%) nevertheless agreed that a reason to avoid disclosure of incidental findings was the importance of letting the child decide.

Disclosure of late-onset conditions appeared to be the most controversial issue relating to the autonomy of the child. Indeed, all of the 114 women (all of whom were mothers to children

under ten years of age) who took part in focus groups (across four US States) as part of Hasegawa et al.'s (46) study supported the use of newborn screening to identify conditions for which no known effective treatment exists, however opinions were much more divided when this untreatable condition was late-onset. Whilst two of the participants argued that the health status of the child should be regarded as the property of the child's parents (and as such those parents have a right to be informed about any conditions affecting the child) (p.302), 50.9% of the participants stated that they nevertheless would not want their newborn to be screened for a late-onset condition which could not be treated/prevented, such as Alzheimer's Disease or Duchenne Muscular Dystrophy. Their reasoning for not wanting this screening mostly included concerns around the psychological impact of that information- its 'emotionally taxing' nature as well as the fear that they might view their healthy child as disabled, or even that the information could lead to abuse.

In summary, informing parents about a child's carrier status, reproductive risk, or late onset disease may violate the child's autonomy, and right not to know. In particular, such information could change how the parents treat their children, and it is not known if and when the parent will pass the information on to their child.

Carrier status

Revealing that a child is a carrier of a disease can occur as an incidental finding when screening for disease, or can be screened for in itself

Opinion papers

The debate about carrier status focuses on whether to reveal the information to the parents about the child's carrier status, which encompasses issues of withholding information, autonomy and informed consent covered in other sections. Miller (6) brings together some of the literature:

"Empirical evidence about the benefits and harms of disclosing carrier status information is both limited in quantity and equivocal in the policy guidance it provides. The primary benefit is that parents and future adults may be made aware of the reproductive risks that they face. Some also suggest that individuals may benefit from "ownership" of genetic information. The primary harms include misunderstanding the meaning of carrier status, leading to overmedicalization, vulnerable child syndrome, stigmatization, and discrimination and the detection of misattributed paternity,..... An apparent consensus governs the management of carrier status information generated incidentally through newborn screening: results cannot be withheld from parents. This normative stance encodes the focus on autonomy and distaste for paternalism that characterize the principles of clinical bioethics. However, newborn screening is a classic public health intervention in which paternalism may trump autonomy and through which parents are—in effect—required to receive carrier information. In truth, the disposition of carrier results generates competing moral infringements: to withhold information or require its possession"(6)

The ethical issues extend beyond the child's status, to that of the parents and wider family

"If parents opt out of receiving carrier status information (assuming they are given that opportunity), then they might infer that they will not learn anything about carrier status from newborn screening. But this is not the case. All diseases but one in the Dutch

newborn screening program are genetic disorders that are inherited in an autosomal recessive pattern. For those diseases, if a child receives a true positive result from screening, then the parents are carriers of the disease. In short, for seventeen of the eighteen diseases in the program, a positive screening result will provide information not only about the child but also about the parents. It will give the parents “reproductive knowledge” that is irrelevant to the health of the infant. This also exceeds the declared goals of newborn screening. “ (91)

Revealing carrier status is often not the intended purpose of screening, but rather forms an incidental finding, or is an element of mission creep:

“The expansion of newborn screening led inexorably to “mission creep” and unintended consequences. Hemoglobinopathy screening, introduced in the mid 1980s to permit life-saving penicillin prophylaxis for children with sickle cell disease, also detected children who were sickle cell carriers. States and clinicians varied widely in whether and how they would provide the so-called “reproductive benefit” of knowing that the child and at least one of the parents were carriers.⁴ Cystic fibrosis screening raises similar issues in those states that use protocols that test a panel of CF mutations after screening reveals an elevated level of IRT.⁵ While some people may value this information, other parents who specifically chose not to have carrier screening for themselves may be less pleased when they involuntarily learn their carrier status from their child’s newborn screen. “ (11)

There is significant debate about whether to reveal carrier status once it is known, with international variation in approach, see also the withholding information section of this report.

“The Health Council of the Netherlands argues that the interest of the family should serve as the ethical ground for disclosure of carrier status as an incidental finding [2, 84] . In the United States, newborn screening programs routinely disclose carrier information to either physicians or families but without consistency in the reporting of information or the provision of genetic counseling. Not surprisingly, the implications of carrier status are often not adequately communicated or understood by families [93–95] . Furthermore, it is uncertain how often the information is retained for future use or whether the child ever receives genetic counseling. Programs in other countries sometimes choose not to disclose carrier status on the grounds of lack of immediate medical relevance and the view that testing violates the rights of privacy, confidentiality, and autonomous decision-making of the individual ”(25)

There are some empirical studies on the effects of revealing carrier status in the section on psychological implications.

In summary, revealing a child’s carrier status is often an incidental finding rather than an aim of screening, and there are variable views as to whether it is appropriate to inform the parents of a child’s carrier status, feeding into the debates about autonomy, informed consent, and withholding information. There is some empirical evidence (see psychological implications section) that revealing a child’s carrier status to parents can lead to enduring concerns about the child’s health. When a child screens positive for disease this also provides incidental findings of carrier status in the parents. There is not a clear consensus on the appropriate levels of genetic

counselling following a positive test for carrier status, or indeed whether this offer should be made to the parents, the wider family, or the child later in life.

Wider Family and Paternity issues

Whilst the results of newborn screening tests pertain to the child tested, they may have implications for the child's family.

Opinion papers

There may be benefits to the family from newborn screening, but there are also potential harms with respect to family relationships, including revealing misattributed paternity, use of donor gametes or adoption. (119) Such information is often an incidental finding of genetic testing, and it has been recommended that plans about disclosure of nondisclosure be in place before testing. (119) This is one in a range of culturally specific harms (14) and therefore any plans to mitigate risks should assess the full range of cultural contexts in which the test may be applied.

Empirical Studies

Two studies focused on the implications of newborn screening for the wider family. Tluczek et al. (100) in a US qualitative study with 87 parents of 44 infants who were falsely identified as having Cystic Fibrosis through newborn screening, but after a sweat test, were confirmed as carriers of the condition, developed a relational understanding of the family unit in order to describe the ways in which parents responded to their child's genetic status. Knowledge of their infants' carrier status had implications for both the 'spousal subsystem' (p. 9) and the wider family unit. For some couples, the information was described as prompting emotional closeness following the 'traumatic' experience of first believing their child had a life-threatening illness, and then experiencing the relief that they were in fact, a carrier instead;

"I think it almost brings you closer just going through that experience because you're kind of scared and the people that it's going to affect are the family. So you kind of come together and stay pretty close." (Parent, p.9)

For one participant however, knowledge of his child's carrier status, together with a misconception about the inheritance of Cystic Fibrosis, caused him to question his paternity of his child, highlighting the 'profound' impact that genetic information can have on family groups.

Tluczek et al. (100) also note the 'moral responsibility' that family members felt, once a Cystic Fibrosis carrier has been identified within the family, to alert extended family members to this information, and particularly to those of child-bearing age, or those who had experienced symptoms which came to be seen as potentially being linked to the Cystic Fibrosis gene within the family. Whether or not this moral responsibility was experienced as an 'opportunity' or a 'burden' was largely dictated by the quality of the relationships in the family (p.10), and it was observed that it was not uncommon for searches to commence within families for the 'origin' of the gene and 'finger-pointing' as to who was to 'blame' for the mutation. Guilt and blame have been described in the literature as a common reaction to the discovery of a genetic condition within the family, and Tluczek et al.'s (100) research has demonstrated the way in which this potential blame and guilt extends beyond the infant's nuclear family to include 'proximal and distal' family subsystems (p. 10). Parents who felt that they had poor relationships with their wider families

particularly struggled with how and when to initiate conversations about their child's genetic status.

Ulph et al.'s (110) UK-based study of the way in which individuals belonging to ethnic minorities process information about carrier status (derived either from newborn or antenatal screening- or both), however, revealed a different picture regarding the operation of family dynamics and its influence on the way in which genetic information is received and managed within families. Through semi-structured interviews with 37 participants (14 people who identified as being of African-/African-Caribbean origin, 10 from the Indian sub-continent, 4 who identified as Middle Eastern, 2 from South East Asia and China, 6 of white European origin and one of 'mixed' origin), the interviews revealed that families not only influenced the way in which individuals acted on genetic status information, but also framed the way in which they understood inheritance:

"We thought in our family a lot of people are carriers and nothing ever happened so we didn't think it would happen to us"

(#47 mother, knew both were carriers of thalassemia, parents declined prenatal diagnosis and child has Thalassemia major) (p. 365)

As Ulph et al. (110) note, as well as influencing how parents understood genetic information, families were also actively involved in decision making about how to use genetic information. This influence was not always welcome, sometimes being perceived as control, which might also explain why some participants selectively, rather than universally, disclosed genetic information to family members. Indeed, the fact that information about carrier status was not disclosed to all family members highlights the great emotional significance attached to what otherwise might be considered 'benign' medical information.

Whilst these studies have explored the impact of newborn screening and carrier status on wider family, no studies focused on the impact on the family where an infant is diagnosed with a genetic condition.

In summary, results of the newborn screening test have implications not only for the infant screened but beyond to the parents and wider family. These implications may include revealing carrier status and misattributed paternity. In the case of revealing carrier status parents may feel a moral responsibility to inform the extended family, and there may be attribution of blame for the actual or perceived source of the genetic inheritance.

Stigma

There may be culturally specific stigma associated with newborn screening results.

Opinion papers

There are fears of discrimination for employment, (5, 17, 55, 95, 120) education, (120) loans (17) or insurance, (17, 55, 95, 120) particularly for those who test positive as carriers, so screening programmes must ensure the confidentiality of data. (21) There is the associated fear of social stigmatisation in light of genetic test results, alongside potential psychological distress, regret, and worry associated with the disease in question, and this can extend beyond the person tested to their families who share some of the same genetic information and may be exposed to similar environmental triggers. (120) These concerns were recently debated in relation to testing of professional athletes in the US:

“Recent case reports of football players who had SCT and suffered exercise related deaths led the National Collegiate Athletic Association to require that collegiate athletes be tested to confirm their SCT status if it was not already known. Although the intent of this testing is good, privacy concerns and possibly discrimination based on carrier status have yet to be addressed. Discrimination based on genetic difference is not new, but in the past it was largely limited to conditions that were phenotypically evident, such as Down syndrome. Since the Human Genome Project was completed, it is now possible to test for minute genetic differences that may never have any significant effect on a person’s health but that, if made public, could lead to discrimination in insurance applications, employment and other opportunities.” (55)

This has led to the Genetic Information Nondiscrimination Act with regard to health insurance and employment in the US, (95) and in Australia the Investment and Financial Services Association Ltd whose policies require that genetic testing cannot be required from insurance applicants, however, results of tests that have already been taken must be disclosed. (16) This has the potential to deter people from having tests which may be beneficial to their clinical management for reasons related to insurance. (16)

Empirical Studies

The evidence regarding personal experiences of stigma appeared to be mixed. Acharya et al. (49) for example, found low perceptions of stigma amongst the 53 participants in their Chicago based study. All participants either had Sickle Cell Disease or were carriers for the condition. Indeed, all respondents disagreed or strongly disagreed with the statement ‘I worry about people discriminating against me’ although 2 of the 27 carriers reported being denied health insurance, or having insurance offered at a prohibitive rate because they or their child had SCT. (49) This study is in contrast to Quinlivan and Suriadi’s (50) Australian oral questionnaire study of 200 women who had recently (within the past 24 hours) undergone newborn blood screening with their baby. Indeed, 60.5% of this cohort reported that their child would more likely face discrimination if he or she had a genetic disease, and one third felt that even being a carrier of a known disease could cause difficulty in obtaining personal health insurance and impact upon employment. Lang and Ross (121), citing Woolridge and Murray (1984) have suggested that differences in perceptions of stigma may reflect the finding that non-carriers have more negative attitudes about carriers than carriers have themselves (p. 1070). This might explain the differences in findings between Quinlivan & Suriadi’s (50) and Acharya et al.’s (49) studies. However, the studies were also conducted in different social, economic and cultural contexts that may have influenced the perceptions of stigma within American and Australian society respectively.

Indeed, there was some evidence in the empirical evidence that carriers themselves do perceive stigma around their identities. Ulph et al. (110) through a UK-based cross-sectional qualitative study interviewed both carriers and non-carriers from different ethnic minority groups who had received their genetic status results through either newborn or antenatal screening. Fourteen participants identified themselves as being of African-/African-Caribbean origin, 10 as from the Indian sub-continent, 4 Middle Eastern, 2 from South East Asia and China, 6 white European and one mixed. By exploring the ways in which carrier status information is disclosed (or otherwise) within proximal and extended family groups, Ulph et al.(110) highlighted the presence of stigma

in perceptions of carrier status and the fear of being tarnished by genetic information, as one participant described disclosing her carrier status to her sister,

“She said ‘what is this?’ I was crying. I didn’t want anyone to know. I didn’t want anyone to pity me, I didn’t want anyone to say oh, to pity the baby [...] I explained to her everything I knew. That it’s just a 1 in 4 chance of her being a carrier you know, but I cried because I didn’t want anyone to know. I mean I wanted everyone to rejoice with me that I have a baby and I didn’t want anyone to say ‘oh that baby could be a carrier.’”

(Ulph et al., 2011; p. 367)(110)

Lang and Ross’ (121) Canadian based study of 100 black African-American mothers of infants determined to be carriers of Sickle Cell Disease following newborn screening found similar evidence of selective disclosure amongst family members. They speculate that this might be explained through reference to personal feelings of stigma, however this was not directly explored within their questionnaire.

Overall, the evidence on the personal implications of stigma appears contradictory. The studies described were conducted in the UK, Canada, America and Australia, which may make comparisons difficult given the different cultural contexts of the studies.

In summary, fear of stigma with regard to insurance, employment, education and loans is widely reported, but there is mixed evidence about whether this stigmatisation materialises. This will be dependent on the societal, cultural and legal context.

Communication

There are three themes within communication, informed consent before testing, and after testing safe and effective communication of results, and the implications of withholding information.

Informed Consent

Approaches to informed consent are varied internationally, with some countries mandating newborn screening and others striving for informed consent

Opinion papers

The level of consent required may vary dependent on the definition of the purported benefit in screening, with the notion that those programmes providing direct mortality benefit to the child having less stringent requirements for consent. Tarini and Goldenberg (5) explain this in the US context:

“The mandatory nature of newborn screening has been justified based on the individualized child welfare/child benefit model, which supports the addition of tests to mandatory screening panels under the argument that information gathered from newborns is used to directly benefit children. States support mandatory screening on the basis of parens patriae power, which gives them inherent authority to act to promote the welfare of children . If a state is concerned that forgoing screening could result in harm to a child, parens patriae permits the state to override the parents’ autonomy. Yet the use of the term mandatory to describe newborn screening is slightly misleading. Although formal parental permission is generally not required for testing, the mandatory nature of testing does not mean that parents are prohibited from refusing or opting out

of screening. In fact, many states allow parents to refuse newborn screening for religious or other reasons, and such refusal does not usually engender civil or criminal penalty. One exception is Nebraska, where a case in which parents refused newborn screening for their child was considered neglect and led the state to temporarily remove the child from the home (48).” (5)

This requirement for informed consent is described by Buchbinder and Timmermans (9) as applying differentially to pre and post-natal testing. However many of the proposed extensions to the newborn blood spot test take it at least partially into the territory of pre-natal test, relating to reproductive choices with regard to having siblings, or for the child being tested once they are an adult.

“Juxtaposing prenatal testing with postnatal screening reveals similar technologies with different social logics: one aims for knowledge production in the context of reproductive decisions and the other raises alarm for a baby already born. Prenatal testing is couched as a deeply personal choice for information while postnatal screening is state-mandated and typically does not require informed consent. Prenatal testing may lead to difficult decisions about whether to continue a pregnancy; newborn screening announces the presence of an invisible burden that warrants a relatively passive response.” (9)

If we presume informed consent to be a positive element there is a question of how and when this can best be achieved. Any extensions to the newborn blood spot test would likely increase the amount of information necessary for informed consent, and the timing of the test may be suboptimal in terms of the parents’ capacity to absorb information and make informed choices:

“The optimal period to provide information seems to be during the last trimester of pregnancy, separated from all information on prenatal screening. It is obvious that the postpartum period should be avoided because the magnitude of events and emotions new parents have to face. Before delivery prospective parents have more time to read and understand the information, at least if that information is available to them. In order to provide such information it is imperative that the professionals concerned have themselves access to such information” (37)

Nicholls (39) takes this argument further, postulating that the newborn blood spot has been ‘proceduralised’ and therefore informed consent cannot occur under such circumstances. If this is the case the argument about not extending the test beyond conditions with morbidity or mortality benefit to the child is more pertinent:

“For most parents the offer of the heel prick was experienced as a routine procedure or what I refer to as ‘proceduralisation’ in order to emphasise that the process was almost automatic. It is in this sense that some parents recalled being told that midwives were coming to conduct the heel prick and so, as reported in other studies, screening was seen as a fait accompli.23 Indeed, several parents prefaced their interviews by saying that they had not considered screening a choice. The implication of this is that rather than providing an informed choice parents may simply be complying. This was often facilitated by its inclusion with other postnatal checks that were being conducted by the midwife, both for the child and for the mother. Parents talked about how their midwife visited them once they had returned home and discussed other things such as breast

feeding or wound healing, and that the heel prick was then raised while these checks were being conducted. The fact that the other checks were readily accepted led some to the conclusion that the process was an automatic part of the routine postnatal procedure.” (39)

Whilst there is considerable heterogeneity worldwide with regard to the approach to consent for the newborn blood spot screening, uptake is uniformly very high regardless of procedure. Grosse et al. (25) describe the French programme:

“In France, bioethics legislation requires written consent before a specimen is collected for DNA analysis, and when IRT (immunoreactive trypsinogen)/DNA screening for CF was introduced in 2002, a new written consent protocol had to be introduced [73] . When asked to consent on behalf of their child’s best interests, most parents do; by the end of the first year of screening for CF in France, 99.8% of parents gave written consent!” (25)

The expansion of the blood spot and the extension towards genetic testing produces novel biomarkers and indicators and increased challenges for informed consent.

“the notion of informed consent itself may need revision in light of the new genetics. ... not everyone will want to know their genetic risk for diseases for which there are no treatment or preventive options,³⁹ or for psychiatric diseases.⁴⁰ In the DTC context, such information may come as a terrible surprise for consumers who have purchased a very broad personal genome test without much thought as to its precise contents, without having given informed consent, and thus without (mental) preparation for the receiving of such test results.⁴¹ Differentiation of the testing offer and adequate procedures for informed consent will be indispensable protective shields against the potential harms of expanding genetic testing and screening offers, whether offered within (public) healthcare or outside.” (113)

Empirical Studies

The empirical literature on informed consent in relation to newborn screening highlighted the gaps in current information provision. Indeed, whilst 85% of the 114 parents being followed up in a genetic counselling clinic for hemoglobinopathies in Klady et al.’s (67) US study were aware that newborn screening had been performed on their child, only 55% of respondents reported being aware of the purpose of the screening. Moreover, 41.7% of the 129 parents and future parents who took part in Moody and Choudhry’s (40) UK study thought that the heel prick test was compulsory, as one participant commented:

“No- thought it was compulsory, didn’t realise I had a choice and therefore a decision to make” (SQ30, P72, p. 244)(40)

This confusion may be related to the timing of the information on newborn screening. Indeed, the importance of giving would-be parents information on newborn screening prior to delivery was highlighted by several studies. (40, 46, 69) The chaotic time period immediately after delivery of the baby was considered a difficult time to process information related to newborn screening and to make a truly informed decision, as a focus group participant in Moody and Choudhry’s (40) study commented;

“...after you have had a kid you have got so much on your mind that you don’t want to look through hundreds and tons of leaflets” (P3 A121-22, p. 244) (40)

Between 30 and 38 weeks of pregnancy was considered an appropriate time to give the information about newborn screening to prospective parents in order for them to fully consider the information. Parsons et al. (38) in their study of newborn screening in Wales, also raise the concern about the routinisation of newborn screening, indeed, many of the 18 mothers they interviewed who had recently had a child and had been offered newborn screening reported that they considered screening something that they ‘had’ to do. Being offered screening by a trusted health care professional was identified as a factor that could compound women’s sense of undergoing screening as a ‘responsible’ part of motherhood rather than something they had active control over.

In spite of these concerns, parents both in the UK and USA did not appear to want dramatic changes to the processes of taking informed consent for newborn screening. Indeed, the ‘informed dissent’ approach used in the US was adequate (46) and 71.2% of Moody and Choudhry’s (40) web-survey participants regarded an ‘opt out’ approach to consent for newborn screening to be adequate. Indeed, a formal signature to acknowledge that the information regarding screening had been imparted and understood was deemed unnecessary. (40)

Few studies appeared within our empirical literature search that explored health care professionals’ perceptions of informed consent procedures for newborn screening. However, an online survey of genetic counselling professionals conducted in the US by Hiraki et al. (58) revealed that participants generally preferred voluntary to mandatory newborn screening, except in the case of Cystic Fibrosis, where 56% of the 267 participants favoured compulsory newborn screening. However the information given to participants about each condition may have heavily influenced this outcome.

In summary, informed consent may not currently be achieved in newborn screening due in part to the timing and routinisation of the test, with many parents thinking that it is mandatory. There is some evidence that this does not concern many new parents. These contextual difficulties in obtaining informed consent may be pertinent to the debate about the evidence requirements to introduce screening programmes, in particular whether conditions without trial evidence of mortality or morbidity reduction are included in the test.

Safe and Effective Communication of Results and follow up care

Any expansion of the newborn blood spot test may have implications for the safe and effective communication of results, and follow up care.

Opinion papers

The need for effective communication of results is often cited in the literature with an expanding newborn blood spot requiring an extension of the expertise of genetic counsellors and screening health professionals. Bailey et al. (23) describes some of the information needs:

“For families the need for information about how to foster their child’s health and development and how to access support services is paramount (Bailey & Powell, 2005). With expanded newborn screening, both families’ and professionals’ need for information will intensify. Newborn screening’s disclosure that a child has a genetic or

chromosomal abnormality will initiate for many families a long-term search for information. They will want to learn more about (a) the genetics of the diagnosis, its associated symptoms, and prognosis for their child's health and development; (b) reproductive risks for themselves, their children, and relatives; (c) potential treatments and interventions; (d) how to find professionals who are knowledgeable about the disorder; and (e) how to locate and communicate with other families who have children with the same diagnosis. Helping families gain access to accurate and understandable information on these dimensions is an important component of support" (23)

Fay (74) extends this to consider liability when communication of results is sub-optimal:

"An interesting question that arises is whether healthcare providers owe a duty of care to parents who suffer psychiatric harm when the genetic counselling process breaks down... One of the risks of genetic testing and the subsequent communication of a person's future health is that learning about dispositions to particular diseases may cause psychiatric injury to the proband—the individual undergoing the test. If the proband's genetic information is disclosed to third parties—namely, his or her relatives—it is possible that these individuals might also experience psychical injury upon learning about their shared genetic heritage. Where the proband is a neonate, their genetic information is inevitably going to be communicated to their parents, who, in turn, may suffer psychiatric harm consequent to learning about the negative aspects of their offspring's genetic heritage."(74)

In practice in the US some issues have been identified with communicating results of a blood spot test for many more conditions than in the UK, including timeliness of results when lab teams have multiple complex results to analyse (122) and expertise to communicate results. (39)

"The communication of positive newborn screening results presents another challenge. Many of the disorders screened are rare, and primary care physicians have expressed a lack of comfort with explaining them to parents (32). Scenario-based studies about physician patient newborn screening communication have supported these concerns, showing that resident physicians' conversations did not contain a significant amount of content judged necessary for parental understanding and sometimes contained misleading content" (5)

Empirical Studies

Studies of the communication of newborn screening results highlight the importance of safe and effective communication as being key to mitigating parental stress and anxiety in the immediate aftermath of receiving the results. The primary areas reported in the literature that facilitated safe and effective communication of the results included:

- 1) Avoidance of jargon (123-126)
- 2) Appropriate timing of results delivery, with parents wanting to be prepared beforehand that the results were coming (102)
- 3) Appropriate pacing, ordering and flow of information provided (107, 124)

4) Appropriate method for communicating the results. Parents varied in their preference for how they wanted the results to be communicated to them, with parents of Cystic Fibrosis carrier infants in Salm's (124) US study preferring face-to-face communication of results and the parents of infants with abnormal hypothyroidism results preferring telephone communication, however contact with a professional at the point of results disclosure was generally considered more appropriate than more impersonal methods, e.g. receiving a letter. Receiving the news via voicemail was considered particularly inappropriate. (126)

5) Demeanour and knowledge of the health care professional delivering the results. Whether the health care provider was considered to be calm, a good listener, empathetic, knowledgeable and responsive were also considered key to parents having a positive experience of results delivery (107, 124, 126) Lang et al., 2011; (100) Indeed, the role of the person delivering the information was considered crucial. Whilst Parker et al.'s (123) UK study revealed a lack of clarity about which professional is best placed to deliver this information, parents were clear that previously-known health care professionals and ones with sufficient knowledge to answer their immediate questions and allay anxieties was crucial, as one father in Buchbinder and Timmermans' (107) study commented after a medical secretary rang to give his infant's screening result, "I'm actually kind of upset with them and I spoke to my doctor about it because who called wasn't even a nurse" (pg. 741). Offering parents hope and personalising the information was also considered important. (127) Whilst communication was key, however, studies with health care providers and co-ordinators have revealed that there are training needs around the communication of newborn screening results, (125) and particularly in relation to offering social support to parents. (128)

Only one study explored post-screening follow up care. La Pean et al. (129) in a telephone interview study with 195 parents of infants who had either been identified as a carrier of Sickle Cell Disease (n= 130) or Cystic Fibrosis (n= 30) were contacted 3-5 months after new born screening to explore their feelings about being followed up with a telephone call. All parents were asked the questions: 'what is your response to me phoning you today?' and 'what do you think of the state NBS having follow-up people calling parents like you?'. Most parents gave favourable opinions on being followed up with a telephone call following receiving their child's screening result, stating that it helped them to clarify the meaning of their child's screening result and/or provided them with another resource to talk about the screening result, as one mother of a child, identified as a carrier of Sickle Cell Disease commented,

"I'm happy because that was something that I actually wish that I could've talked to somebody about because I felt like, you know, I know that there's other parents going through this too and it would have been really nice to have more information especially right up front"

(Mother, CF carrier infant, p. 211). (129)

Only two participants mentioned negative reactions to being called by the research team and the reasons cited for this were that the call made them feel scared, anxious or worried, however these two participants also commented that these feelings were resolved during the course of the call.

Whilst this study is useful in highlighting parents' need for support and information in the months following newborn screening, the methodology could have led to some biases in the results; for example, the question 'what is your response to me phoning you today?' may have made it difficult for participants to offer negative reactions directly to the interviewer who was calling (and only two participants did so). Moreover, 17 of the participants (9% of the sample, all of whom had been identified as Sickle Cell Disease Carriers) reported that they were unaware of the screening results prior to the 'follow-up phone call' which may have altered their perceptions of the usefulness of the communication. Even so, these participants were not excluded from the final sample. Further evidence would be needed to explore the demand for, and most effective way of delivering follow up care after newborn screening reveals carrier results.

In summary, the safe and effective communication of results is an important element of a screening programme. Key elements of this may include avoidance of jargon, preparing parents beforehand that the results were coming, appropriate pacing, ordering and flow of information provided, appropriate method for communicating the results (not letter or voicemail), and the demeanour and knowledge of the health care professional delivering the results. This last criterion is pertinent to expansion of the newborn blood spot test, as this would necessitate the health care professional becoming knowledgeable in a wider range of conditions, which may or may not be practically achievable depending upon the extent of expansion and time and resources devoted to increased training.

Withholding information

Whether to withhold results is an ethical issue in the design of most screening programmes, but particularly complex in the context of newborn screening where there are consent and autonomy issues.

Opinion papers

Southern (130) proposes that "having undertaken a programme of screening and having identified a positive result (including carrier status) there is a moral duty on the health service to report that result to the family, even if the long-term consequences are not clear. However he also refers to the "burden of medicalisation" for genetic screening, which relates to the discussions on indeterminate results, patients in waiting and the autonomy of the child.

"Even if it can be presumed that parents want carrier status information about their infant, the infant's interests may differ. Indeed, an extensive policy and scholarly literature suggests that generating genetic information in childhood is inappropriate unless it is required to address health needs that emerge in childhood.^{12,33} The provision of carrier or predictive genetic testing is seen to infringe on the child's autonomy and right to confidentiality because it forecloses on the child's right to decide whether to seek this information and to whom it should be disclosed. ³⁴ In a recent systematic review, Borry et al. identified 2 guidance statements that addressed the incidental generation of carrier screening results in minors outside the context of newborn screening³⁴; these statements suggest that such information should be stored and withheld until the child reaches a state of maturity.³⁵ "(6)

The information withheld may be dependent on the screening technology used, with some technologies such as tandem mass spectrometry able to suppress information from the clinician, which shifts the ethical debate.

“One approach that state NBS programs may pursue in the short-term is to use next-generation sequence technologies to evaluate only those variants currently assessed using conventional screening methods, such as tandem mass spectrometry. As noted by Greeley et al, this approach would require that state programs destroy or suppress large amounts of data produced by genomic sequencing. If state programs pursue this course, they will need to be mindful that the suppression of genomic data raises difficult ethical and legal questions regarding the rights of patients to their genetic data (or data about their children). In our opinion, placing limits on parental access to genomic data is ethically problematic and withholding such data within the context of a public health department may lead to higher levels of mistrust by parents. These issues are complicated by the questions raised by Dondorp et al, who ask whether children should be able to decide for themselves when and how they learn about their risks of adult-onset diseases. The NBS programs have not had to address these concerns in the past given their traditional focus on serious early-onset conditions and the relatively limited amount of data generated through screening.” (131)

Empirical Studies

Only one empirical study explicitly explored the topic of health care providers withholding information derived from the process of newborn genetic screening. Miller et al., (118) through a survey with 1615 health care providers, and semi-structured interviews with a further 42 health care providers (including family physicians/ genetic professionals/ haematologists/midwives/ maternal and newborn nurses/ obstetrician/ paediatricians), explored attitudes towards the withholding of incidental findings derived from newborn genetic screening in order to inform policy discussions on the topic.

The study revealed that the majority of health care providers preferred disclosure of incidental results to their non-disclosure, and the most common reason for supporting this disclosure was supporting the parents’ rights to information about their child. Whilst some clinicians raised concerns about the implications this has for the child’s right to make their own decisions about their health information (and this view was most supported by genetics professionals- 51.9% of whom approved non-disclosure for this reason), others suggested that from a ‘consumers’ point of view, that parents had a right to know, as the information derived from screening was their property that the clinician had no right to withhold, as one obstetrician commented;

“you don’t do a test and not reveal the information...[...]it’s their knowledge”

(Obstetrician 11, page 629)

Indeed, some health care providers expressed concerns that withholding incidental screening results was akin to ‘keeping secrets’ (p. 629), which lead to a fear of legal liability if the clinician’s previous non-disclosure later comes to light in a situation where the information may, retrospectively have been beneficial.

The respondents in Miller et al.’s (118) also raised queries about with whom the responsibility primarily lies for disclosure of incidental findings. For the majority of respondents, the duty was

considered incumbent on the clinician who received the results report, however, others said that the responsibility was at a 'system level' and beyond the individual health care providers within it.

For those health care providers who did not approve of disclosure in all circumstances, a distinction was drawn between screening results and testing results, which might suggest a different disclosure policy depending on clinical benefits, as one clinical geneticist commented:

"You've got two medical models. One would say that you should disclose what you know about an individual's status. The other would say that newborn screening disclosure is about disclosure of a disease status for which an intervention is both available and effective."

(Clinical geneticist I 37, p. 631)

Whilst Miller et al.'s (118) study provides us with an insight into the views of health care providers regarding the withholding of incidental results from newborn screening practices, no studies had explored this issue from perspective of patients and the general population, which represents a serious omission in our understanding of this topic.

In summary, the majority of opinion pieces and research from health care providers show the balance of opinion against withholding results, we did not find any research exploring the views of the general public or patients, and so few conclusions can be reached about the topic. In an expanded newborn blood spot test the ethical issues would be the same, but the number of patients for whom results could potentially be withheld significantly greater.

The Treatment

Opinion papers

Much of the debate about the treatment offered after screening hails from the US (5, 23, 132) where a much broader spectrum of disorders is included in the newborn blood spot test, and there may be geographical heterogeneity in the treatment available post screening:

"It is crucial to remember that newborn screening is a system, not a test. Some have cautioned that the addition of new tests to screening panels is taking place without the funding or infrastructure needed to provide adequate follow-up care and clinical services to newborns and their families (9). Any expansion of newborn screening does not absolve a program of its duties to provide access to necessary testing and treatment resources... However, studies have shown that the coverage of medical formulas (e.g., formulas created to meet a disorder's specific metabolic requirements) and foods for disorders that require dietary treatment is a patchwork across states. In any mandatory screening program, failure to provide affordable treatment raises ethical concerns."(5)

In the UK the NSC criteria mandate "evidence of early treatment leading to better outcomes than late treatment", and "agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered" alongside optimisation of clinical

management and patient outcomes in all health care providers prior to screening. The wider the panel of diseases on the newborn blood spot test, the greater the requirement for clinical expertise:

“The range and variability of disorders that can now be detected by newborn screening place a special burden on clinical services. Whereas a biochemical diagnosis on a symptomatic patient can be a great help, a biochemical ‘diagnosis’ on an apparently healthy baby raises difficult questions as to prognosis and the most appropriate management. For many of the classical disorders, there is not much doubt as to the need for treatment despite a degree of biochemical heterogeneity. With maple syrup urine disease, for example, the adequacy of treatment can be monitored biochemically and serious loss of control is reflected immediately in the patient’s clinical condition. In diseases with more insidious, cumulative effects, there are difficulties in drawing boundaries, as seen with milder variants of phenylketonuria and congenital hypothyroidism. For risk disorders such as MCAD deficiency or 3-methylcrotonyl-CoA carboxylase deficiency, the problem is how to advise parents on warning signs and emergency measures without raising undue alarm or medicalizing the child’s life by burdensome regimes. Policy-makers may refuse to sanction screening for additional disorders unless clinical services are strengthened, with specialist regional centres to deal with the disorders concerned. In many countries, such centres already exist for CF and for the treatment of phenylketonuria, but there are relatively few specialist facilities for the wider range of inherited metabolic diseases.” (17)

Even with sufficient resources, deciding whom to treat with what poses significant challenges due to the complexity of many diseases with multiple sub-types for which there is often insufficient evidence to understand whether treatment is beneficial and if so which treatment

“Some of the emerging screening programmes for lysosomal storage diseases face a different dilemma; treatment is required in the presymptomatic phase if it is to be effective, but there is a range of variants with age of onset from early infancy to late adult life and only limited ability to predict phenotypes from biochemical or genetic analysis.”(17)

If screening is implemented then there are potential issues with separation of the screening programme from treatment and follow-up, as the latter is essential in informing the former. For example in a complex condition with several genetic variants decisions about which variants to report in screening are made within the screening programme, and this can be an evolving process, but the data to inform such decisions will come largely from long term follow up data of those screened, which is not always collected.

“Historically, newborn screening programs have focused on assuring that newborns are appropriately screened and that those children with an abnormal screening result are either rescreened or have diagnostic follow-up (i.e., short-term follow-up). The benefit of newborn screening, however, comes from the long-term treatment of those identified with a condition. The SACHDNC has defined the components of long-term follow-up as high quality chronic disease management with condition specific treatment and age-appropriate preventive care over the lifespan (Hinton et al., 2011; Kemper et al., 2008). In recent years, state-based and voluntary national registries have developed in the

United States for tracking and research of rare diseases. Gaps in long-term follow-up include shortages of specialists and lack of public awareness of the benefits of screening (Centers for Disease Control and Prevention, 2012). European screening systems provide expert short-term care, but long-term follow-up is organized locally without centralized longterm monitoring of patients (Burgard et al., 2012). Longterm follow-up is crucial for understanding the natural history of rare disorders and innovating and improving treatment. Raising public awareness through advocacy and the development of regulatory guidelines for followup may help close the gap in long-term service provision. Continuous quality assurance projects can help to identify areas for improvement in services to keep pace with rapid changes in newborn screening (Burgard et al., 2012; Hinton et al., 2011).”(54)

There were no empirical studies about the treatment

In summary, whilst consideration of having an effective treatment is often standard in the decision of whether to implement or extend a screening programme, where the screening programme involves rare diseases with limited knowledge about the natural progression or the most effective treatment there is a strong case to link treatment and follow up into the screening programme at least in terms of a comprehensive database. This would enable robust programme appraisal, particularly in the context of less evidence upon commencement of screening. Furthermore it would allow society to learn from the implementation of screening, not least to learn the balance of benefits and harms from screening and whether it is appropriate to continue.

Results Summary

This review covers a broad range of issues associated with the ethical, legal and social implications of extending the newborn blood spot test. Some of the key issues and how they map onto the screening pathway are shown in figure 2 and 3, alongside how they relate to the current NSC criteria, and some suggestions for additional areas for discussion. An overall summary of the results is included in the next section – Discussion.

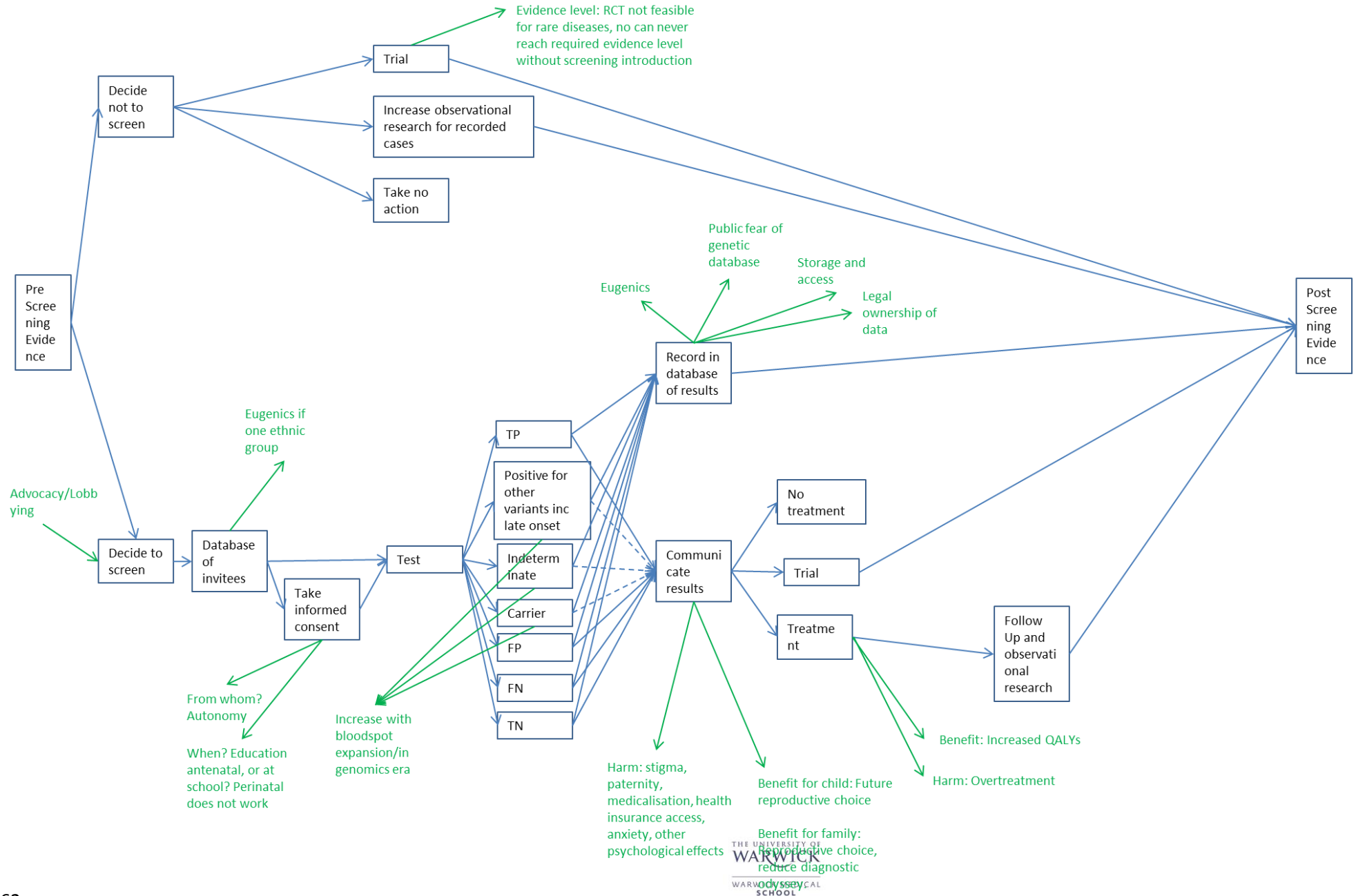


Figure 2. The screening pathway with ethical issues identified in this literature review highlighted in green.

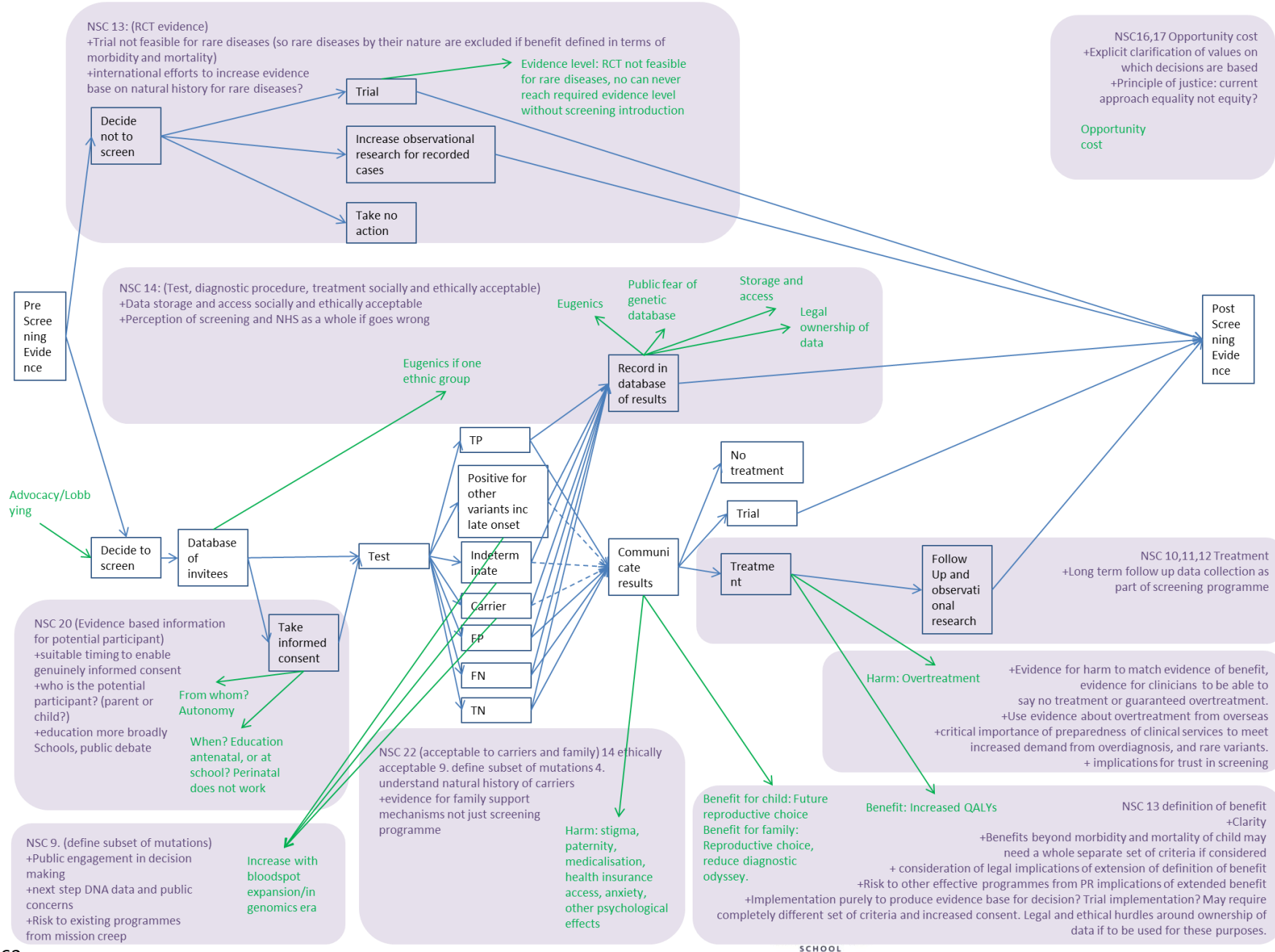


Figure 3. The screening pathway with ethical issues identified in this literature review highlighted in green, and the relevant NSC criteria in purple. Items after a + sign are suggestions made in the literature for amendments to either the criteria or the screening programme in light of the ethical issues highlighted. There has been no assessment of the quality of these recommendations.

Discussion

The UK National Screening Committee commissioned this review with the aim of bringing together the range of opinions and empirical research about the ethical, social and legal implications of further extensions of the newborn blood spot test.

We conducted a rapid review of the literature of empirical research since the publication of the US panel in 2006 and of opinion pieces from the last 5 years on the ethical social or legal implications of expanding the number of conditions reported on in the newborn blood spot test. Systematic searches, and data synthesis were undertaken using a narrative thematic approach. The search identified 2312 unique articles, and after full text review 93 opinion and 71 empirical papers were included.

We identified three overarching themes in the results including Context, Population level implications and Family level /Individual implications.

Context

In terms of context at the national/international level it is clear that the implications of an extension to the newborn blood spot test are highly contextually dependent and are affected by concerns about race, eugenics and stigma. There are complex legal issues associated with ownership of screening data and this is in itself worthy of a separate focussed review. There are significant gaps in professionals' and parents' knowledge about blood spot testing and implications for findings. Whilst costs are decreasing for whole exome and whole genome sequencing, there are concerns regarding creating DNA databases, e.g. due to the potential for increases in overdiagnosis. Lobbying has yielded identifiable benefits in terms of introduction of appropriate screening tests but lobbying by however well-intentioned individuals may also be exploited, and may over-represent one side of the debate.

Population level

At the population decision-making level, the QALY is a well-accepted tool for decision making but wider considerations of equity and justice are also seen to be important. Clearly we lack knowledge about the diseases under consideration, for example in terms of natural history so that the expected benefits or harms of expansion of newborn blood spot testing are difficult to predict. For rare diseases for which no RCT evidence can be produced, there are deeply divided views about how to proceed. Some argue that screening is likely to be beneficial for some individuals, whilst others argue that without an RCT the balance of benefits and harms is not known. Slow and deliberate expansion based on evidence of mortality or morbidity is thought to maximise the probability of benefit and minimise the probability of harm, particularly in the context of good quality assurance and follow-up to allow accrual of information and evidence on the balance of harm and benefit.

Family and individual level

There have been calls to extend the definition of benefit from screening beyond mortality or morbidity of the child screened, with proposed benefits for the family described as reducing the diagnostic odyssey, providing reproductive risk information, providing palliative care for children where there is no treatment, and stimulating research. However the majority of these benefits are not directly of benefit to the child screened. There may also be harms associated with overtreatment or indeterminate results. In the context of no clear evidence of mortality or morbidity benefit, autonomy and informed consent may become more important. Perhaps more importantly, where there is limited evidence about the natural history of disease, clinicians and parents face problems as to how or whether to intervene.

In addition to these problems associated with true positive results, there are also problems associated with false positive and indeterminate results. False positive results result in high levels of stress and anxiety for parents and potentially in damage to the parent-child relationship, although there is mixed evidence about how persistent these effects are. Parents of children with indeterminate results endure significant time with uncertainty as to whether their child is completely healthy or has a life threatening disease. There is some evidence of a persistent feeling by parents that the child retains a residual risk. Clearly, coming to terms with an unsought diagnosis so early in the life of a child who appears healthy (whether that unsought diagnosis is true or false positive) poses difficulties for parents.

A child's carrier status may often be revealed as an incidental finding rather than as an aim. Approaches vary as to whether it is appropriate to inform parents of a child's carrier status. There is no clear consensus on the appropriate levels of genetic counselling following a positive test for carrier status, or indeed whether this offer should be made to the parents, the wider family, or to the child later in life.

Of course results of the newborn screening test may raise wider family and paternity implications beyond the infant screened to the parents and wider family. These issues include misattributed paternity, or a new discovery of parental carrier status. The extent of disclosure to the extended family is an issue and there may be attribution of blame for the actual or perceived source of the genetic inheritance.

In this context, fear of stigma with regard to insurance, employment, education and loans is important and this is widely reported, although there is mixed evidence about whether and how this stigma manifests itself. This will be dependent on the societal, cultural and legal context.

Appropriate communication with informed consent may not currently be achieved in newborn screening due in part to the timing and routinisation of the test, with many parents thinking that it is mandatory. However from our sources there appears to be some evidence that this does not concern many new parents. Key elements for safe and effective communication are described in the literature. The consistent conclusion in the case of false positive results is that communication is key to reduce negative effects.

Certainly expansion of the newborn blood spot test would necessitate a concomitant expansion in knowledge and in communication training for health care professionals about a much wider range of conditions. This may have implications for time and resources devoted to screening.

Obviously one option is to withhold certain types of results, however the balance of opinion is against withholding results, although there was no research reported in this area. If a decision were taken to withhold results, an expanded newborn blood spot test would increase the number of patients/parents for whom results could potentially have to be withheld.

One of the major overarching concerns expressed was that since we have limited knowledge about the natural history, progression or the most effective treatment for most of the rarer diseases covered in expanded blood spot testing programme, the beneficial outcomes of expansion may be limited. If expansion were to occur then the literature we reviewed strongly suggested that linking treatment and follow up should be undertaken alongside a comprehensive database to allow us to learn more about the balance of benefits and harms from screening.

Strengths and Limitations

This rapid review included a large number of papers and a broad range of opinions. A decision not to limit the search to UK-based studies was made early on in the analysis process. Whilst including international studies potentially introduces concerns about the transferability of findings to the social and cultural context of the UK, as the aim of the review was to set out the range of possible social and ethical issues associated with expanding newborn blood spot screening, it was decided that the literature search should be extended beyond UK literature.

Material was collected and assessed systematically. We did not include grey literature however we consider that saturation was reached in our review of the opinion papers. This was a rapid review rather than a formal systematic review so we did not undertake duplicate inclusion and exclusion or quality assessment of included studies, rather we aimed to describe the range of opinion and qualitative empirical research in this area. The second reviewer checked one out of ten papers in the inclusion criteria, and we cross checked themes which were extracted by one reviewer and checked by another (and by a third reviewer in the case of disagreement). All the work was checked and considered by the wider group. As is usual for a qualitative review, the whole team was involved in decision making regarding the collection, interpretation, and synthesising of the data. This was achieved through regular team meetings wherein the search strategies for the collection of the papers and the evolving thematic framework were discussed at length, and any disagreements regarding the extraction of the themes resolved. The range of disciplinary and professional backgrounds of the research team facilitated a thorough and nuanced analysis of the emerging data, and meetings continued throughout the analysis process allowing an iterative development of the final theoretical framework.

Implications for policy practice and research

Decisions on expansion of the blood spot alongside advocacy of the analysis of the newborn's genome as a lifetime resource for lifestyle decisions and health care interventions appear to us to be premature. The technical flaws in this concept are powerful considerations. There are concerns such as privacy, the self-determination of the child (and the individual as a future adult), the need to decide how to handle the changes in interpretation of genome sequence data that are likely to occur frequently over the next decade or more, the likely deferral of most benefits from the information until well into adult life coupled with the possibility of causing harm in

terms of both over and under diagnosis and identification of both false positives and false negatives.

There are complex issues around expanding the newborn blood spot test, with multiple stakeholders, perspectives and values to consider. The simplest approach to screening is to only screen if there is randomised controlled trial evidence demonstrating mortality and morbidity reduction for the infant screened. However this presents an ethical dilemma in the case of rare diseases, where it is not feasible to produce such evidence.

Expanding the definition of benefit to include reducing the diagnostic odyssey, providing information to parents, and increasing research about these rare diseases would ameliorate this ethical difficulty but create or exacerbate several more; namely that the child did not consent to the procedure, that parental consent is unlikely to be adequately informed, that there is a potential harm for the affected children, including those receiving false positive or indeterminate results, and that there is an opportunity cost to society of the money spent on screening.

There is advocacy and lobbying for the introduction of many screening programmes, particularly from parents of children affected by diseases detectable on the newborn blood spot test. Whilst such advocacy should be considered by policy makers, they must also consider the interests of children and parents who will be negatively affected by the introduction of screening, such as those receiving false positive results, indeterminate results or overtreatment. These people cannot advocate against screening because they are as yet unidentified. Whilst policy makers' primary considerations are often the balance of benefit and harm at the population level, clarity about how individual benefits, harms, autonomy, and interests are considered and weighted in the decision making process is an important ethical requirement. In particular the approach taken to genetic screening and the storage and use of data and samples should involve public conversation and consultation prior to implementation.

This review has highlighted several areas for future research. Firstly that countries who do implement blood spot screening should take the opportunity to create and share screening outcomes databases, linked to follow up data for positive cases, which can be used to increase our knowledge of the rare diseases screened for, and determine whether screening is delivering the desired benefits. Secondly this review highlighted some potential legal issues around ownership and storage of samples, and implementing additional tests on the newborn blood spot without robust evidence of mortality or morbidity reduction, in the context of the complexities of informed consent in this area. Further focussed analysis of this topic would be of interest.

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Appendix 1. Final Search Strategy

(5/10/2013)

Ovid Embase/ Medline

Searches	Results
1	"bloodspot*".ab,ti.
2	"guthrie test*".ti,ab.
3	"blood spot*".ti,ab.
4	"pku test*".ti,ab.
5	"heel prick*".ti,ab.
6	(neonat* adj2 screen*).ti,ab.
7	(newborn* adj2 screen*).ti,ab.
8	(new-born* adj2 screen*).ti,ab.
9	exp newborn screening/
10	exp dried blood spot testing/
11	exp neonatal screening/
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	exp ethics/
14	psychological well being/
15	exp social aspect/
16	exp personal experience/
17	exp experience/
18	"psycholog*".ti,ab.
19	social.ti,ab.
20	"ethic*".ti,ab.
21	personal.ti,ab.
22	"experienc*".ti,ab.
23	"view*".ti,ab.
24	"belie*".ti,ab.
25	exp wellbeing/
26	wellbeing.ti,ab.
27	well-being.ti,ab.
28	well being.ti,ab.
29	exp attitude/
30	"attitude*".ti,ab.

31	"opinion*".ti,ab.
32	exp public opinion/
33	"perspective*".ti,ab.
34	exp legal aspect/
35	"legal*".ti,ab.
36	exp health belief/
37	exp Health Knowledge, Attitudes, Practice/
38	exp "Patient Acceptance of Health Care"/
39	"accept*".ab,ti.
40	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	12 and 40
42	limit 41 to (humans and yr="2006 -Current")

Social Science index

Topic=(blood spot* OR bloodspot* OR pku test* OR guthrie test* OR heel prick* OR newborn* screen* OR new-born* screen* OR neonat* screen*)

AND

Topic=(wellbeing OR well-being OR well being OR attitude* OR opinion* OR perspective* OR legal* OR accept* OR ethic* OR psycholog* OR social OR personal OR experienc* OR view* OR belie*)

Timespan=2006-2013. Databases=SSCI.

Sociological abstracts

ab(blood spot* OR bloodspot* OR pku test* OR guthrie test* OR heel prick* OR newborn* screen* OR new-born* screen* OR neonat* screen*)

AND

ab(wellbeing OR well-being OR well being OR attitude* OR opinion* OR perspective* OR legal* OR accept* OR ethic* OR psycholog* OR social OR personal OR experienc* OR view* OR belie*)

On or after 01 January 2006

Ebscohost CINAHL

#	Query	Limiters/Expanders
S34	S33	Limiters - Published Date: 20060101-20131131; Human Search modes - Find all my search terms
S33	S22 AND S32	Search modes - Find all my search terms
S32	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR	Search modes - Find all my search terms

	S29 OR S30 OR S31	
S31	AB new-born* screen*	Search modes - Find all my search terms
S30	AB newborn* screen*	Search modes - Find all my search terms
S29	AB heel prick*	Search modes - Find all my search terms
S28	AB guthrie test*	Search modes - Find all my search terms
S27	AB blood spot*	Search modes - Find all my search terms
S26	AB bloodspot*	Search modes - Find all my search terms
S25	AB pku test*	Search modes - Find all my search terms
S24	AB neonat* screen*	Search modes - Find all my search terms
S23	(MH "Neonatal Assessment+")	Search modes - Find all my search terms
S22	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	Search modes - Find all my search terms
S21	AB legal*	Search modes - Find all my search terms
S20	AB accept*	Search modes - Find all my search terms
S19	AB wellbeing	Search modes - Find all my search terms
S18	AB well being	Search modes - Find all my search terms
S17	AB well-being	Search modes - Find all my search terms
S16	AB perspective*	Search modes - Find all my search terms
S15	AB opinion*	Search modes - Find all my search terms
S14	AB attitude*	Search modes - Find all my search terms
S13	(MH "Health Beliefs")	Search modes - Find all my search terms
S12	(MH "Public Opinion")	Search modes - Find all my search terms
S11	(MH "Attitude of Health Personnel+")	Search modes - Find all my search terms
S10	(MH "Attitude+")	Search modes - Find all my search terms
S9	AB belie*	Search modes - Find all my search terms
S8	AB view*	Search modes - Find all my search terms
S7	AB experienc*	Search modes - Find all my search terms
S6	(MH "Life Experiences+")	Search modes - Find all my search terms
S5	AB personal	Search modes - Find all my search terms
S4	AB ethic*	Search modes - Find all my search terms

S3	(MH "Ethics+")	Search modes - Find all my search terms
S2	AB social	Search modes - Find all my search terms
S1	AB psycholog*	Search modes - Find all my search terms