

FIXING THE PRESENT

BUILDING FOR THE FUTURE

Newborn screening for rare conditions

ABOUT GENETIC ALLIANCE UK



Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 200 patient organisations. We undertake various initiatives to improve health service provision, research and support for families. These initiatives include:



Rare Disease UK, a multi – stakeholder coalition brought together to work with the government to effectively implement the UK Strategy for Rare Diseases.



SWAN UK (syndromes without a name), the only UK-wide network providing information and support to families of children without a diagnosis.

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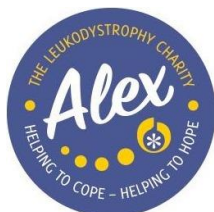
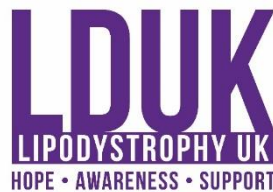
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- Sickle Cell Society
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- Dr Bobby Gaspar, UCL Great Ormond Street Institute of Child Health
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INTRODUCTION

Newborn screening in the UK comprises the heel prick blood spot test, a hearing test and physical examination to check the baby's eyes, heart, hips and (in boys) testes. The newborn blood spot screening programme, which is the focus of our work. A small sample of blood is taken from the newborn baby, with parental consent, by a midwife, nurse or health visitor within a few days of birth. Blood samples are collected on pre-printed 'Guthrie' cards which are sent to a laboratory for testing for a group of rare genetic conditions.

Residual newborn blood spots may be used for further testing should a clinical need arise, as well as for audit, training, improvement and development of laboratory methods. Residual newborn blood spots or screening data may be used for research, without seeking individual consent, if the identifiers have been removed. Laboratories are required to retain the blood spot cards for five years for quality assurance purposes after which time they should be destroyed by the laboratory within 12 months

A **rare disease** is defined by the European Union as one that affects less than 5 in 10,000 of the general population. There are between 6,000 and 8,000 known rare diseases. Collectively rare conditions are not rare. One in 17 people will be affected by a rare condition at some point in their lives. This equates to approximately 3.5 million people in the UK. Approximately 80% of rare diseases are believed to have a genetic component.

Often rare diseases are chronic and life-threatening. Rare diseases can be single gene, multifactorial, chromosomal or non-genetic. Those living with a rare condition can face significant challenges in getting a diagnosis, accessing treatment and receiving coordinated care, as well as challenges with employment, education, social life and mental health.

Genetic Alliance UK decided to do this work at the request of our membership. The family challenge of dealing with the devastating impact of a rare condition affecting a young child is tremendous. The condition may creep into a family's life gradually with missed milestones, unusual illnesses or symptoms slowly appearing, or they can arrive very suddenly with an emergency trip to a hospital to deal with a seizure, loss of consciousness or other crisis. The search for a diagnosis can be just as destabilising, and can last months or years. Life with a child with a rare condition can be complicated further by the struggle to keep up with the progression of the condition. Just as one adaptation is made to the home for a child to pull themselves up steps, adjustments might have to be made to allow for a wheelchair. The scale of unmet need combined with the sheer number of rare conditions mean that this experience is happening all over the UK in many different ways.

Newborn bloodspot screening could identify that a child will develop a rare disease before the impacts begin, bringing treatment and planning opportunities. For those that might have received this early warning had their child been born in a different country, the urgency to fix newborn bloodspot screening is acute.

This report describes the current landscape for newborn bloodspot screening, and delivers the views of people living with rare and genetic conditions on how we can fix our current system and build for the future.

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FIXING THE PRESENT

Newborn screening for rare conditions

In order to adapt decision making to fit rare diseases

Recommendation 1: The methodology for decision making on newborn screening should be adapted in recognition that the conditions being screened for are rare and thus present specific challenges

Recommendation 2: Decisions on newborn screening should be made by a body with specific and relevant expertise

Recommendation 3: Benefits to the patient, family and broader society other than preventative interventions should also be considered

In order to embrace the potential of screening as a rare disease identification system

Recommendation 4: Newborn screening should be recognised as a mechanism for earlier diagnosis as part of a broader care pathway, keeping step with progress in disease identification and diagnosis in symptomatic patients

In order to Take full advantage of developments in technology

Recommendation 5: The Newborn screening programme should be 'opportunity based' – based on categories of conditions it is possible to detect through screening, not condition by condition

Recommendation 6: Measures should be taken to address out of date infrastructure and technologies

BUILDING FOR THE FUTURE

Newborn screening for rare conditions

Recommendation 7: Having examined the evidence and the views of our workshop participants, Genetic Alliance UK has reached the view that a pilot of genome sequencing in newborn screening should be planned for delivery within the NHS as soon as possible.

This is primarily because of its potential to **vastly increase the number of rare conditions** that could be identified at birth. The opportunity for efficiencies within screening pathways and for a repository of genomic information to be created were considered secondary to this primary benefit.

The aims of this pilot should include:

- Delivering a clear message on the cost-benefit of such a programme by:
- Establishing the breadth of value to the rare disease community, to the NHS and to a rare disease treatment and care in the UK of such a programme.
- Establishing the predicted costs of the system, taking into account the efficiencies that may be delivered in other areas of the health service and more broadly.
- An examination of society's attitudes to the storage of genome sequence information collected at birth:
- To take advantage of the infrastructural legacies of the 100,000 genomes project.
- To address the challenges associated with genome sequencing in newborn screening, including:
 - Where does newborn screening using genome sequencing fit within the system?
 - Which conditions should be screened for? How should they be selected?
 - To what extent do ethical challenges raised in the delivery of a genomic medicine service apply to a genomic screening service, and whether these topics need to be revisited.

Such a pilot should:

- Be offered in parallel to existing biochemical screening to ensure that standards of turnaround times, accuracy and sensitivity can be met
- Be offered in a small number of specialist hospitals where the quality of information provision, consenting and genetic counselling can be carefully monitored, interventions can be evaluated and feedback from healthcare professionals and patients can be evaluated.
- Allow parents the opportunity to be informed of additional results by category based on actionability, age of onset and certainty
- Parents should be offered the opportunity to participate in additional research studies consented separately from screening
- Development and implementation of the pilot should be carried out transparently and with the full involvement of stakeholder groups, including the genetic and rare disease patient community

Any decisions about data storage and sharing in the pilot should be made on the basis of a full public conversation about appropriate safeguards, involving all relevant stakeholders including genetic and rare disease patient groups.

FIXING THE PRESENT

Newborn screening for rare conditions

WHAT IS THE VALUE OF BLOOD SPOT SCREENING TO IDENTIFY RARE CONDITIONS?

Screening programmes aim to detect signs that a disease might develop in people who otherwise feel or appear entirely well. The idea is that the disease can be prevented from progressing to a further stage when treatment is more invasive, risky or less likely to succeed, when damage may be permanent or symptoms distressing.

Timely treatment

Screening at birth to identify children born with rare condition allows the delivery of the appropriate care, support and treatment to begin as soon as necessary to minimise the impact of the condition. This means that treatments that stop the progress of a condition can be delivered before any morbidity, such as intellectual disability, reduction in growth or other damage can occur. More broadly, medical management of the condition can have the same mitigating effect.

Timely information

Screening at birth can provide information to parents of a child with a rare condition much earlier than they would otherwise receive it. The benefit of a diagnosis in rare disease is broad: it can include, but is not limited, to provision of insights into what the future might hold which can allow families to plan, to make adjustments to their lifestyle, home, location or career so that they can best manage the condition that will affect their family. In the absence of a diagnosis through screening, the families of children affected by a rare condition may consequently undertake a lengthy, agonising and frustrating diagnostic odyssey, that can take years and may involve unsafe misdiagnoses. During this diagnostic odyssey a child's health may deteriorate, or their condition may be sub-optimally or incorrectly treated.

Opportunity for choice and planning

In addition, a molecular diagnosis allows couples to exercise reproductive choices if they wish to, with information about the chance of their next child having an inherited condition. The timing of the delivery of information can be crucial in this context, as the onset of some childhood conditions can be in the third or fourth year of life, which can mean families have had further affected children who in turn may embark on their own diagnostic odyssey.

Wider benefits

The existence of a screening programme for a given rare disease has wider benefits too. In the absence of an existing treatment, screening can build a platform to deliver new treatments. Comprehensive registries can be supported with the high diagnostic rates that screening delivers.

These can be leveraged for natural history studies and clinical trial recruitment. There are clinical trials currently recruiting overseas that would be impossible to deliver in the UK, as no screening means there is no means to recruit patients into the studies. Similarly new medicines are receiving regulatory approval which require early or even pre-symptomatic administration which would be significantly less effective or potentially impossible to use, with patients diagnosed after symptoms have begun to take effect.

A platform for a strategic approach

The UK Strategy for Rare Diseases (2013), contained the commitment that England, Wales, Scotland and Northern Ireland would 'continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes'. This commitment acknowledges the potential role that screening can play as a foundation for a strategic approach to rare diseases in the UK. Despite this, the only major change in newborn screening for rare diseases in the UK since publication of the 2013 UK Rare Disease Strategy has been the adoption of a set of four metabolic conditions to the national programme in 2014, an addition resultant of a pilot that started in 2012.

The value of newborn screening in rare diseases - the ability to identify that a child will develop a condition before the child becomes ill - is broad and multifaceted, delivering benefit to babies, families and more broadly, our ability as a society to plan for and deliver treatments for rare diseases.

WHERE DOES THE UK STAND IN COMPARISON TO OTHER COUNTRIES?

The UK currently screens for between five (in Northern Ireland) and nine conditions (in the rest of the UK) as part of the newborn blood spot screening programme. The system (existing processes and technologies) has the potential to test for many more conditions, potentially delivering earlier diagnosis to many more UK families.

The UK screening programme compares unfavourably to those of the majority of comparable high income countries, for example USA (59 conditions), Italy (43), Hungary (26). Table 1 shows the slow rate of addition of new conditions to the UK's programme. Only eight conditions have been added to the UK programme since 1965 when blood spot screening began.

Table 1: Current newborn bloodspot screening programmes in the four UK nations and their start year

Condition Recommended by the UK NSC	England	Scotland	Wales	Northern Ireland
Phenylketonuria	1969	1969	1969	1969
Congenital hypothyroidism	1981	1981	1981	1981
Sickle cell disease	2006	2006	2006	2006
Cystic fibrosis	2007	2003	1997	1983
Medium chain acyl coA dehydrogenase deficiency	2009	2009	2009	2009
Maple syrup urine disease	2015	2017	2015	No
Isovaleric acidaemia	2015	2017	2015	No
Glutaric aciduria type 1	2015	2017	2015	No
Homocystinuria	2015	2017	2015	No

Comparison with other countries

The UK tests for relatively few conditions in its newborn bloodspot screening programme compared to similar high income countries. Within the group of 29 comparable countries we have examined, shown in Figure 1, the mean and median number of conditions screened for is 22, twice as many as is screened for in England, Wales and Scotland.

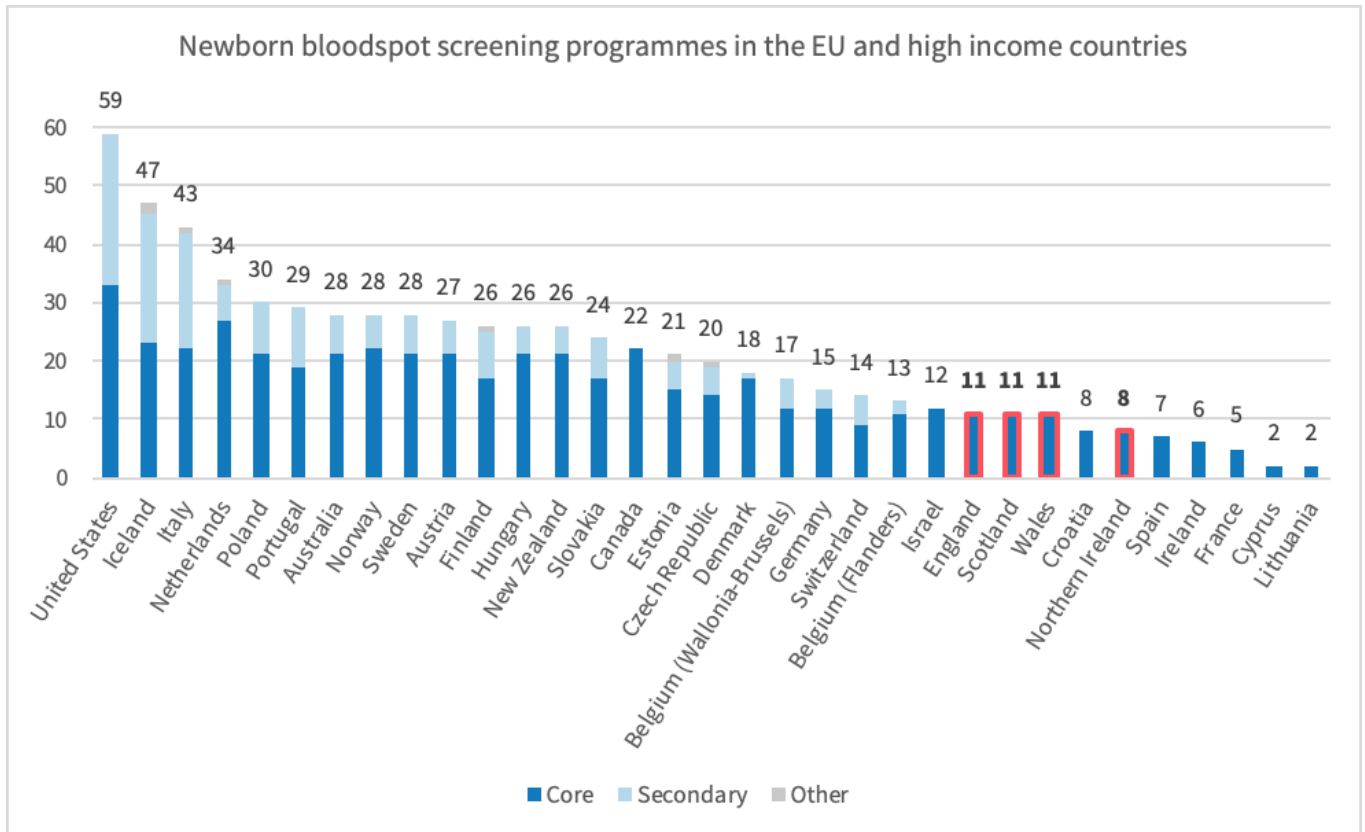


Figure 1: Current newborn bloodspot screening programmes internationally,

Note: to allow comparison the nomenclature used in the US Recommended Uniform Screening Panel (RUSP) has been applied. This lists sickle cell disease as three separate conditions: S,S disease (sickle cell anaemia), β -thalassaemia and S,C disease (a milder form of sickle cell anaemia). This means these are counted separately for the UK on this figure, increasing the totals for UK countries by two.

Secondary conditions are those which are detected in the course of testing for a primary condition. These have been included where they would be reported to the baby’s parents or clinicians.

Other conditions are those which are only screened for by one country, often because of local priorities. These are difficult to categorise as core or secondary.

The UK has not followed the majority of high income countries in embracing the broad value of newborn screening. Very few high income countries screen for as few conditions as the UK.

HOW DOES THE NEWBORN SCREENING SYSTEM WORK AND WHERE DO THE OPPORTUNITIES LIE?

Individuals who are picked up through screening will undergo further diagnostic testing in order to definitively determine whether they have the condition being screened for. If so, the individual can then be assigned to a clinical pathway which will allow the risk of developing the condition to be managed optimally with appropriate intervention at the appropriate time.

The newborn bloodspot screening programme is a complex programme delivered by a range of organisations working together. In England, this includes NHS England, Clinical Commissioning Groups and local authorities. Also known as the heel prick test, it involves a midwife, nurse or health visitor taking a small sample of the blood by pricking the baby's heel and squeezing out a few drops of blood onto an absorbent pre-printed paper card (also known as a Guthrie card). In the UK, the bloodspot is taken when babies are five days old. Parents must give verbal consent to the test. Each year, more than 600,000 babies are tested in this way, accounting for the majority of live births in the UK.

After the sample of blood is taken from each newborn baby, the Guthrie card is sent off for testing to one of the 13 newborn screening laboratories in England or the laboratories in Northern Ireland, Scotland, and Wales.

There are two primary biochemical approaches currently used in UK laboratories as part of the newborn bloodspot screening programme: tests which require one assay to be carried out per analyte, to detect a single condition, and multiplex testing using tandem mass spectrometry.

Single analyte assays

Fluoroimmunoassay is a laboratory technique that identifies and quantifies a protein associated with a disease, based on its ability to act as an antigen or antibody in a chemical reaction. The proteins are tagged with fluorescent markers and the light emitted is used to measure the amount of protein present. Fluoroimmunoassay methods are used for **congenital hypothyroidism** and part of the process used to screen for **cystic fibrosis**. Some UK laboratories use these methods to screen for **sickle cell disease** too.

Tandem mass spectrometry

Tandem mass spectrometry (or MS/MS) is a technique to analyse proteins by breaking them down into their component parts (ions) and measuring the mass-to-charge ratio of those ions. This allows the laboratory to identify and quantify molecules in simple and complex mixtures.

Tandem mass spectrometry has significant advantages over the technologies previously used for blood spot analysis due to its ability to detect levels of metabolites suggestive of a large number of diseases in a single assay both reliably and accurately.

Tandem mass spectrometry is currently used in UK screening laboratories for detection of the inherited metabolic disorders that are included in the current newborn screening programme. These are **phenylketonuria**, **medium-chain acyl-CoA dehydrogenase deficiency (MCADD)**, **maple syrup**

urine disease (MSUD), isovaleric acidemia (IVA), glutaric aciduria type 1 (GA1), and homocystinuria (HCU). Some laboratories also use tandem mass spectrometry to screen for **sickle cell disease**.

Missed opportunities based on what labs are already looking for

Table 2 shows the analytes that tandem mass spectrometry detects according to our current list of approved conditions in the UK and the other rare conditions that can be detected based on the same analyte. There are 13 conditions that could be detected from the analytes UK labs are already examining.

The numbers in brackets shown next to the conditions show how many other nations in our sample of 29 are screening for the conditions. The four conditions in bold are mentioned in Public Health England’s laboratory guide for newborn blood spot screening for inherited metabolic conditions (2017) as potential causes of ‘false positives’ ie reasons why the test might indicate a positive result that is not accurate. These are four conditions, screened for elsewhere that could be detected with systems used in the UK, that are not being reported back to families. The condition short/branched chain acyl-CoA dehydrogenase deficiency (SBCAD) is listed in the Public Health England laboratory handbook as ‘probably harmless’. This is a grossly simplified description of the condition, which is asymptomatic in most patients, but can cause serious developmental delay and neurological problems in a small portion of patients. [ref = <https://www.omim.org/entry/610006>]

Table 2: Opportunities for screening based on analytes already tested for

Condition Recommended by the UK NSC	Analyte	Other conditions potentially identified
phenylketonuria (PKU)	phenylalanine (Phe)	Hyperphenylalanemia (10), disorders of bipterin metabolism[N1] (6), galactosaemia (13), tyrosinaemia type 1 (19)
medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	C8 acylcarnitine	glutaric aciduria type 2 (15) , short-chain acyl-CoA dehydrogenase deficiency (7), medium-chain ketoacyl-CoA thiolase deficiency (2)
maple syrup urine disease (MSUD)	leucine (Leu)	
isovaleric acidemia (IVA)	C5 acylcarnitine	2-Methylbutyrylglycinuria (3), glutaric aciduria type 2 (15), short/branched chain acyl-CoA dehydrogenase deficiency (7)
glutaric aciduria type 1 (GA1)	C5-DC acylcarnitine	glutaric aciduria type 2 (15)
homocystinuria (HCU)	methionine (Met)	Hypermethioninemia (6), MTHFR deficiency (2), defects [N2] of vitamin B12 metabolism (19)

Missed opportunities based on what tandem mass spectrometry technology could detect

Because the technology is able to detect so many different metabolites associated with many conditions in a single run, laboratories in the UK run their machines in a selective mode. This mode is an active choice to prevent the machines from providing all possible information on conditions that could affect the babies being screened. UK labs only look at the subset of compounds that are associated with those conditions that are being targeted in the screening programme.

However, while high or low levels of a particular metabolite can be considered suggestive of a specific condition, no single metabolite will entirely provide the information needed to diagnose or screen for a metabolic condition. **Confirmatory tests using other methods are always necessary to provide adequate information for a diagnosis.**

One of the major differences in strategy for countries that are screening for more conditions is the adoption of the opportunity provided by secondary screening methods. For conditions that would be secondary to those that we already screen for, there are five conditions that ten or more countries have decided are worth screening for. To adopt these conditions would take very little change in screening laboratory procedures, and would just require new pathways for treatment and case management.

Table 3: Newborn bloodspot screening conditions in the UK

Condition	UK incidence	PPV%	Without early treatment, the condition can result in
Phenylketonuria	1 in 10,000	80 to 90%	permanent brain damage and serious learning disabilities
Congenital hypothyroidism	1 in 2,000	70%	permanent, serious physical problems and learning disabilities
Sickle cell disease	1 in 2,800	95%	severe pain, life threatening infections and anaemia (symptoms can be present even with treatment)
Cystic fibrosis	1 in 2,500	70%	poor weight gain, frequent chest infections and reduced life expectancy (symptoms can be present even with treatment)
Medium chain Acyl CoA dehydrogenase deficiency	1 in 10,000	80 to 90%	serious illness, coma and possible death
Maple syrup urine disease	1 in 150,000	50%	coma, permanent brain damage and possible death
Isovaleric acidemia	1 in 150,000	50%	coma, permanent brain damage and possible death
Glutaric aciduria type 1	1 in 300,000	50%	coma and brain damage which affects muscle movement
Homocystinuria	1 in 300,000	50%	learning difficulties, eye problems, osteoporosis, blood clots or strokes

Note: The positive predictive value (PPV) is the likelihood that a baby with a screen positive result will have the condition. This varies with each condition. The uncertainty is dealt with through follow up testing, to ensure that those babies affected by the condition being screened for are identified, and unaffected babies can be released from follow up.

WHO MAKES DECISIONS ON NEWBORN SCREENING IN THE UK?

The UK National Screening Committee

While health services and public health are devolved, policy recommendations on screening programmes are made on a UK-wide level by the UK National Screening Committee (UK NSC). The UK NSC was established in 1996 to provide national coordination of population screening and move screening policy away from a localised, piecemeal approach (Science and Technology Select Committee, 2014).

In practice, the devolved nations tend to largely follow the advice of the UK NSC, at least on newborn screening, though there can be some delays to implementation of recommendation of screening programmes in Scotland, Wales and Northern Ireland. In England, under the NHS Constitution for England, the NHS has committed ‘to provide screening programmes as recommended by the UK National Screening Committee’.

The terms of reference state that the UK NSC ‘is an independent committee that:

- advises Ministers and the NHS in the four UK countries about all aspects of screening including the case for introducing new population screening programmes and for continuing, modifying or withdrawing existing population programmes against a set of internationally recognised criteria
- supports implementation of screening programmes in the four countries including the development of high level standards and maintains oversight of the evidence relating to the balance of good and harm as well as the overall cost effectiveness of existing programmes
- works with partners to ensure it keeps abreast of scientific developments in screening, including screening trials, screening policy in other countries and emerging technologies
- is accountable to the four chief medical officers (CMOs), who agree work plans for the UK NSC on an annual basis

Public Health England determines whether a test or programme is considered screening (as opposed to diagnostic or other testing) and thus within the remit of the UK NSC on a case by case basis using the following characteristics as a guide:

- The target population to be screened should be large (sufficiently large to enable safe, clinically and cost effective screening)
- The cohort to be offered screening would regard themselves as not necessarily having symptoms of the disease or to be at risk of the disease (the business of the committee should be apparently healthy people)
- There should be an effective means of identifying and contacting the whole cohort to be offered screening
- The population should be proactively approached (by written invitation, verbal invitation at the time of the contact with the health service, encouraging attendance for screening) to ensure that those offered screening would be properly informed of the potential benefits and risks in order to help make an informed choice

- The primary purpose of screening should be to offer benefit to the person being screened. If there is no possibility of benefit to the person being offered screening then it should be considered no further as a screening programme

The UK National Screening Committee terms of reference state that they will be reviewed every three years. This last occurred in 2015.

The UK NSC is accountable to the four Chief Medical Officers of the home nations, who agree work plans for the UK NSC on an annual basis. Progress against these work plans is reviewed by the Department of Health and Social Care in conjunction with the other UK Health Departments.

The UK NSC usually meets three times a year, with two of the meetings held in London and the third in one of the other UK countries on a rolling basis.

UK NSC meetings are not open to the public. According to the UK NSC Code of Practice ‘this allows members to have a free and open debate before coming to any conclusions, which will be fully explained in the minutes or statements when these are published.’

Decisions are by consensus, though if a unanimous view cannot be reached, a vote may be taken with a simple majority of the Committee voting members (excluding the Chair) required.

Membership

The UK NSC Code of Practice states that Committee membership normally includes individuals from public life, academia and practising clinicians who have expertise in one or more of the following areas:

- | | |
|--------------------------------|----------------------------|
| - public health (screening) | - health economics |
| - general practice | - laboratory services |
| - paediatrics and child health | - nursing and midwifery |
| - obstetrics | - epidemiology |
| - cancer | - medico-legal |
| - genetics | - social Science |
| - ethics | - patient and public voice |

The UK NSC currently has 18 members, plus a number of non-voting observers. The breakdown of their areas of expertise is as follows:

- | | |
|--------------------------------|---|
| - cancer/public health (chair) | - genetics/cancer/epidemiology |
| - paediatrics/ (vice chair) | - nursing and midwifery |
| - nursing and midwifery/cancer | - health economics |
| - medico-legal/social science | - medico-legal |
| - obstetrics | - public health/epidemiology |
| - laboratory services | - general practice |
| - cancer/public health | - social science/ethics |
| - cancer/epidemiology | - patient and public voice (three places) |

There is also a Fetal, Maternal and Child Health Reference Group, with eight members:

- public health
- paediatrics (two places)
- social science/ethics
- genetics
- health economics
- obstetrics
- patient and public voice

The membership of the UK NSC is heavily weighted towards experts in public health/epidemiology and cancer. Since the UK NSC's remit covers all population health screening, and three of the eleven current screening programmes are for cancer, this concentration of expertise makes sense. However, this means that there is little space for specialist expertise relevant to newborn screening and the rare conditions tested for with this role being mainly covered by a single generalist paediatrician.

The UK NSC has three patient and public voice (PPV) members, one of whom also serves as the sole patient and public voice representative on the Fetal, Maternal and Child Health Reference Group. While there is very little publicly available information about the backgrounds and experiences of two of these three, we have been informed that despite the name, all PPV representatives have been recruited to represent the perspectives of 'users' of screening, which the UK NSC considers to be members of the general public.

There is no member of the Committee or Fetal, Maternal and Child Health Reference Group who acts to represent the perspective of patients, or people living with rare diseases. In contrast, for example, the Adult Reference Group has three PPV representatives, two of whom are breast cancer survivors. This situation conflicts with the approach of other healthcare decision-making bodies, the vast majority of which consider patient voice to be an important factor in decision-making. This difference reveals who the UK NSC considers to be their key stakeholders and primary concern. In contrast the US Newborn Screening Expert group has explicitly stated that 'newborns screening policy development should be driven primarily by the interests of affected newborns, with secondary consideration being given to the interests of unaffected newborns, families, health professionals and the public.'

Unlike the vast majority of decision-makers in rare disease, the UKNSC does not involve rare disease patients in their work, this is likely to be a factor in the relatively low number of rare disease screening programmes approved in the UK.

HOW ARE DECISIONS ON NEWBORN SCREENING MADE IN THE UK?

The UK NSC website states that it will review the evidence for screening in the following circumstances:

- a regular review when the current recommendation is not to offer population screening is due
- a regular review when the current recommendation is to offer population screening
- when new evidence is published which brings into question a current recommendation on screening
- when a proposal is made to modify, or make big changes to, a current screening programme
- when a proposal for a new topic which has not been previously reviewed by the UK NSC is submitted

The procedure followed in each of those circumstances is shown in figure 2.

The UK NSC has a publicly stated commitment to update each recommendation every three years. The UK NSC currently regularly reviews a large number of conditions for continued or proposed inclusion in the newborn screening programme, termed the legacy list.

While the UK NSC's methodology states that the UK NSC will consider an early topic update at the request of stakeholders if significant evidence is published in between reviews, this will only be taken forward if the paper is judged to alter the overall recommendation on whether screening should or should not be recommended. This decision is taken by the chair of the UK NSC on the advice of the evidence team. If the new evidence is judged likely to change a review's conclusion on one criterion but not to alter the overall conclusion, the papers will be considered for inclusion in the next regular update.

The UK NSC conducts an annual call for new topics, starting in the first week of September and lasting for three months. Any individual or organisation can submit a topic for consideration as long as they meet the UK NSC's requirements on length, format and content. The UK NSC is currently in the middle of its third annual call, however so far no proposal made as part of the annual call has passed the triage stage.

The House of Commons Science and Technology Committee's inquiry into National Health Screening in 2014 recommended that the UK NSC clarify and publish its evidence review processes. Since this has occurred, the only proposed NBS programme to have progressed to Step 4 on the above flowchart was severe combined immunodeficiency (SCID), for which a systematic review and costs effectiveness review were carried out before the recommendation for a pilot was made.

Stakeholder involvement

There is very limited opportunity for stakeholder involvement, including both patient and clinical expert groups, as part of the UK NSC's decision-making process. Although stakeholders are identified as part of the rapid review commissioning stage, they are not contacted at this point. There is no



Figure 2 – the UK National Screening Committee’s procedure for deciding whether to review evidence for screening

stakeholder involvement in decision-making about the scope, questions and search strategy of the rapid review, nor in the development of the rapid review itself.

The first and only opportunity for stakeholder involvement as part of the formal evidence review process is a three month public written consultation, in which stakeholders are invited to comment on the evidence review report and its conclusions. These documents are typically well over 100 pages in length.

Following the public consultation the evidence team discusses the submissions with the external review group to consider whether they consider any changes to the review are required. All submissions to the public consultation are also provided to members of the UK NSC as part of the papers for the UK NSC meeting at which the review is being discussed. Neither the evidence team, reviewing group or UK NSC is required to respond to the comments received individually. Nor are stakeholder groups able to present their evidence, due to the closed nature of UK NSC meetings. This makes it very difficult to determine the extent to which stakeholder evidence is being taken into account. Instead, stakeholders are informed of the outcome of the review following ministerial decision relating to the Committee's recommendation. There is no process for appealing a decision of the UK NSC, other than via an application for judicial review.

In contrast, most other arms length bodies making access or care decisions involve patients and other stakeholder groups much earlier and more comprehensively in their work. For example, in all NICE programmes expert stakeholders contribute to the development of the scope for each new product, as well as providing written and verbal evidence throughout the development of the guideline or technology appraisal. Decisions about recommendations are made in public meetings, to which stakeholder groups have been specifically invited to participate. Following the publication of a draft guideline or technology appraisal, this is also put out for public consultation, following which stakeholders also have the option of appealing the decision that has been made.

Decision making criteria

As with most screening programmes around the world, the UK NSC Criteria for appraising the viability, effectiveness and appropriateness of a screening programme are based on the ten criteria developed by J M G Wilson and G Jungner in the mid-1960s. Although these criteria were designed for the screening of adult-onset conditions, they have been applied to all forms of population health screening, including newborn screening programmes.

Since the original criteria were published public health bodies have made adaptations to the criteria. In the UK a further ten criteria have been added. The most recent change being made in 2015. These changes in the UK and elsewhere have meant that there are now some significant differences between the UK criteria and both the Wilson & Jungner criteria and the criteria used by other similar bodies in other countries.

The UK NSC requires all of their criteria to be met before it will recommend a screening programme.

Key criteria that adversely affect screening for rare conditions

UKNSC criterion 1: The condition should be an **important health problem** as judged by its frequency and/or severity. The **epidemiology, incidence, prevalence and natural history** of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Original Wilson and Jungner criterion 1: The condition should be an **important health problem**

Original Wilson and Jungner criterion 7: The **natural history** of the disease should be adequately understood

Though most rare conditions would pass the first clause of criterion 1 on the basis of severity, the natural history of rare conditions have been a sticking point, as the term adequately was removed from the UKNSC criterion in 2015. Rare conditions are highly variable and their case numbers are very low. The untreated natural history may also be required, which may not be available because of a long-standing treatment programme.

UKNSC criterion 10: There should be an **effective intervention** for patients identified through screening, with **evidence that intervention at a pre-symptomatic phase** leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered

Original Wilson and Jungner criterion 2: There should be an **accepted treatment** for patients with recognised disease

Requirement for an 'effective intervention' is a much higher bar than the Wilson and Jungner 'accepted treatment' or many countries which are willing to consider any beneficial management and care. Benefits such as diet, lifestyle advice, avoiding complications and any measures to improve the health status and quality of life of the child can be ignored. Criterion 19 makes it clear that the bar is even higher: the intervention must be 'preventative'

UKNSC criterion 19: Evidence-based information, explaining the purpose and potential consequences of screening, investigation and **preventative** intervention or treatment, should be made available to potential participants to assist them in making an informed choice.

The word preventative was added in 2015.

A full analysis of the UKNSC criteria, how they compare to other nations and how they disadvantage screening programmes for rare conditions is available as an annex to this report.

The UK NSC's evidence review process

The evidence summaries used by the UK NSC are developed using rapid review methodologies. These are intended to 'provide and evaluation of the volume and direction of the literature on a single question or set of questions on a given screening topic'.

Evidence reviews are commissioned on behalf of the UK NSC by the evidence team, part of the UK NSC Secretariat. Evidence reviews are commissioned from external groups considered to be experts in review methods and techniques, not in the condition under consideration.

UK NSC evidence summaries are not carried out using a particular standardised methodology, instead the review strategy and approach is agreed between the evidence team and the reviewing organisation at the start of the process of developing each evidence review. This means that there can be substantial variations between reviews on the comprehensiveness of the literature search, arrangements for literature selection, inclusion of evidence synthesis and quality control.

However, in general:

- The UK NSC will only consider evidence published in peer reviewed journals. Stakeholders are advised that all information provided, whether in a proposal or consultation response, should be based on referenced publications of this type.
- External review groups are also advised that they have the opportunity to restrict their literature search to papers specifically relating to the population covered by the review (i.e. the UK condition-specific patient population), as well as excluding articles not published in English or which relate to case reports or conference abstracts, in order to limit the number of references retrieved and therefore cut down the time needed for the literature search. Restricting the literature search in this way becomes more restrictive the rarer the disease proposed for inclusion in the programme is. It is widely acknowledged that in rare diseases the most robust methodology will normally include the analysis of data drawn from overseas and multinational studies.
- In effect, three types of evidence only are regarded as sufficiently strong to use as the basis for making recommendations: systematic reviews, randomised controlled trials and population-based studies
- If the evidence review is part of a regular update, the evidence review will only consider papers published after the previous search ended.
- When the UK NSC publishes a recommendation the recommendation statement will highlight what the committee considers to be key areas of uncertainty. Regular updates will primarily search for and consider new evidence relating to these previously identified uncertainties.

As the UK NSC website only hosts the most recent set of documents about a proposed screening programme, this can make it very difficult to understand what evidence has previously been considered and not judged to resolve uncertainty about a specific criterion. Instead, stakeholders must rely on the summary provided in the most recent evidence review.

The evidence standards are applied across the portfolio of possible screening programmes. This means that a proposal for a rare condition to be added to the newborn screening programme is expected to meet the same level of evidence as a proposal to modify the breast cancer screening programme, despite the vast differences in prevalence of the conditions and ability to collect evidence of this type.

Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. While information from clinicians and patients may not be published, it represents the most

recent and relevant information on a condition coming from those that either directly manage or are affected by the condition today.

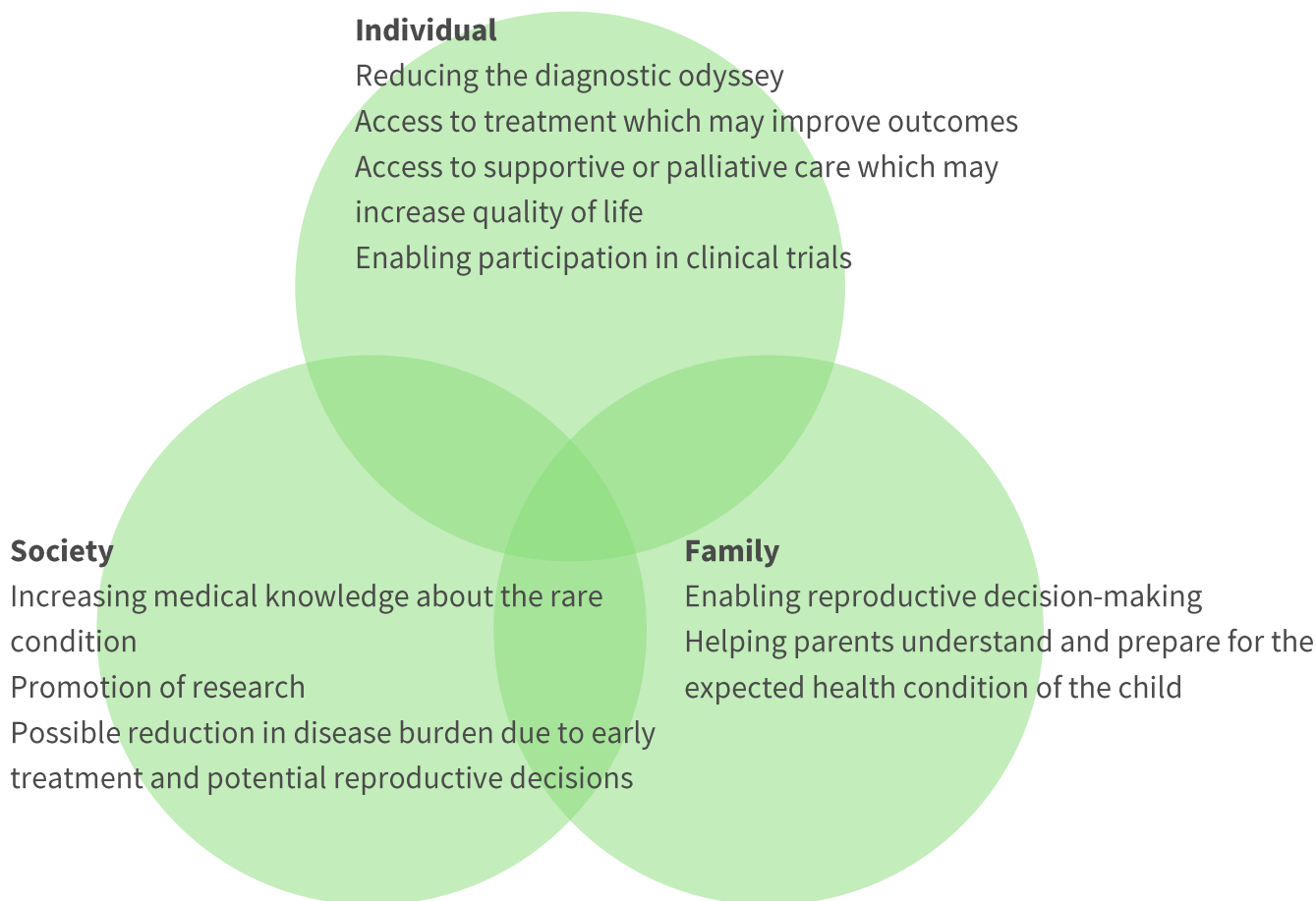
Not taking this type of information into account during a review of the evidence is out of step both with other institutions with responsibility for decisions regarding public health, such as NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency, and with accepted practice in dealing with rare disease issues. All three of these agencies, and more, have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community.

Benefits and harms of screening programmes

A key aspect of decision making on screening programmes is a weighing of the potential benefits and harms from implementing a programme. The question of which benefits and harms are taken into consideration is one of the key differences between different countries' decision making on screening.

The UK NSC's decision making primarily considers there to be benefit from a newborn screening programme if a baby diagnosed with a condition through the newborn screening programme will then be able to access an effective intervention, which is able to largely prevent or avoid the harm of the condition, with clear and extensive evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.

Potential benefits of screening



Potential harms of screening



However, there are a number of other potential benefits that can be gained from newborn screening, not only for the baby picked up through screening but also for their parents and family members and to broader society. Some examples are shown in the figure above.

It is clear then, that in expertise, criteria for decision-making and in evidence collection, people living with rare conditions are entitled to feel disadvantaged in this decision making process.

FIXING THE PRESENT

Findings and recommendations

Screening in the UK has been left behind by most comparable countries. Both the community of people living with rare conditions, and the research and treatment development sector are being significantly disadvantaged by UK policy in this area. The UK National Screening Committee has failed to adapt its policy and methodology to treat rare diseases fairly, leaving the UK out of step with the majority of high income countries.

The nations to which we have compared the UK all use the same ultimate criteria to make their decisions on approving a newborn bloodspot screening programme. These stem from the Wilson-Jungner screening criteria published by the World Health Organisation in 1968. Most countries have adapted or added to these criteria, (including the UK). These adaptations, where they address considerations specific to rare diseases when taken alongside interpretation and applied thresholds for evidence, account for the difference between nations. When we compare these approaches we see that:

- most countries' 'important health problem' is the UK's 'rare disease';
- most countries' 'well understood natural history' is the UK's 'highly variable condition';
- most countries' 'treatment' includes reproductive choice and medical management, whereas the UK's 'treatment' is a licensed orphan medicinal product or surgical intervention.

In order to adapt decision making to fit rare diseases

Recommendation 1: The methodology for decision making on newborn screening should be adapted in recognition that the conditions being screened for are rare and thus present specific challenges

- Decision making should take account of forms of evidence other than RCTs and systematic reviews published in peer reviewed journals, similar to other bodies such as NICE and the European Medicines Agency, such as grey literature, unpublished registry data, evidence from other countries and evidence from patient and clinical experts
- The inherent uncertainty – comparative to common conditions – in information about rare diseases should be acknowledged and managed.
- Where a screening programme is not recommended due to lack of evidence there needs to be a proactive mechanism for supporting the gathering of that evidence, including local or pilot screening projects.
- Cost effectiveness evaluations should reflect public, patient and governmental support for higher cost effectiveness thresholds in rare diseases

Recommendation 2: Decisions on newborn screening should be made by a body with specific and relevant expertise

- Membership of the decision making body should consist primarily of experts in newborn bloodspot screening and relevant conditions with fewer experts in public health and epidemiology
- The newborn screening decision making body should involve stakeholders at every stage from topic selection to implementation
- Meetings of the newborn screening decision making body should be held in public except where confidential information is being discussed

- Patient and public representatives should be people with experience/knowledge of the screened conditions or of being picked up through screening, not solely members of the general public

Recommendation 3: Benefits to the patient, family and broader society other than preventative interventions should also be considered

- Forms of benefits to the child around improved care not involving a preventative intervention should be explicitly valued in decision making
- Where a screening programme is being considered which does not offer improved health outcomes to the diagnosed child, the role of consent and education should be explored

In order to embrace the potential of screening as a rare disease identification system

Recommendation 4: Newborn screening should be recognised as a mechanism for earlier diagnosis as part of a broader care pathway, keeping step with progress in disease identification and diagnosis in symptomatic patients

- Screening programmes should examine the quality of information and service provision following a positive screen to improve patient and family experience and remove geographical inequities
- Care pathways should be developed for any conditions detected during newborn screening, including those found as incidental findings
- Surrounding infrastructure, including specialised clinics and registries should be developed
- The newborn screening decision making body should work with the NHS and health technology appraisal bodies to best deliver screening, rather than duplicating their analyses and remit

In order to Take full advantage of developments in technology

Recommendation 5: The Newborn screening programme should be ‘opportunity based’ – based on categories of conditions it is possible to detect through screening, not condition by condition

- Opportunities for cost effective aggregation of technology use should be explored
- Investment in screening infrastructure should be made on the basis of the potential value to the NHS, people living with rare disease and the research and treatment development sector

Recommendation 6: Measures should be taken to address out of date infrastructure and technologies

- UK newborn screening laboratories should be supported to gain the technology and expertise necessary to screen for a broader range of conditions
- The important role of second tier testing in improving screen test accuracy should be recognised (screening as a process not a test)

BUILDING FOR THE FUTURE

Newborn screening for rare conditions

Background

The 100,000 genomes project has completed its recruitment of patient participants with 70,000 of these genomes collected from families affected by rare conditions. Though research is ongoing, with many more diagnoses expected from the rare disease cohort, the project has delivered sufficient indication of the value of its approach to pave the way for the Genomic Medicine Service (GMS) in England. In some circumstances this service will deploy whole genome sequencing as a first line tool to deliver a diagnosis for patients.

The diagnostic odyssey currently lasts for four years for the median rare disease patient during which time they are likely to see five doctors and receive three misdiagnoses. This time period is long, frustrating and painful for most people living with rare conditions – treatment opportunities may be missed, and mental health can be badly affected. The advent of the GMS plus less mature undertakings in Wales and Scotland, herald a step change in expectations for the diagnosis of rare conditions with a genetic component. These initiatives will both shorten the time for a diagnosis of rare conditions for which the genetic component is already identified, and – through integrated research – increase the proportion of rare conditions for which the genetic component has been identified. Genomic medicine reflects the crucial value of a diagnosis, a view that is increasingly out of step with the UK's approach to newborn bloodspot screening.

With the potential for the diagnostic odyssey to be shortened for symptomatic patients through genome sequencing being realised, now is the time to ask why we must wait for symptoms to present themselves. As the case studies in this document show, for many rare genetic conditions, treatment is best delivered before symptoms present and for some patients pre-symptomatic treatment can tip the balance in terms of the ultimate outcome, including whether a patient lives or dies.

The increasing use and availability of genome sequencing in different domains of healthcare has led many stakeholders in the UK to consider whether this technology could be used in newborn screening. This idea was first discussed seriously in the UK in the genetics white paper 'Our Inheritance, Our Future' (2003) which stated that genetics 'will bring new challenges as well as opportunities for screening programmes' and identified the possibility of screening 'babies at birth as part of the standard postnatal checks and to produce a comprehensive map of their key genetic markers, or even their entire genome'. The paper recognised the 'wide range of ethical and social concerns' which it asked the Human Genetics Commission (HGC) to examine.

The HGC report, 'Profiling the Newborn' (2004) acknowledged the potential benefits that genetic screening of newborns could deliver, identifying advance planning in the NHS and the potential of personalising healthcare to a patient's genetic makeup. However, the report's conclusion was that the technology would not be affordable in the NHS within 20 years, and that the important ethical and social issues need to be reassessed in five years' time.

In September 2018, the Secretary of State for Health announced a vision for the UK to deliver 5 million genome analyses within five years. The National Genomics Board has a suite of workstreams addressing this plan, one of which includes a Genomic Analysis in Children Task and Finish Group chaired by Professor Sir Mark Caulfield, which will advise the National Genomic Board on matters from genomic diagnosis for acutely ill children (expected to be delivered through the GMS) through to a possible future scenario where all children are offered a genomic analysis as an extension of the existing newborn screening programme.

A chapter of the 2016 Chief Medical Officer's report 'Generation Genome' was devoted to genomics in newborn screening. A series of challenges, opportunities, questions and acknowledgements were raised, which were discussed at the 2018 Genetic Alliance UK workshop and which will be examined here from the perspective of patients and families living with rare conditions. The report recognised the fundamental value of genomics in the context of newborn screening, that of a much higher potential number of conditions tested and a greatly reduced need for follow up testing.

At Genetic Alliance UK's workshop in 2018 we invited participants to examine the challenges and opportunities arising from whole genome sequencing in the newborn from the perspective of people living with rare conditions. We present here a summary of views and discussions.

SHOULD WE EXAMINE THE POSSIBILITIES OF GENOME SEQUENCING FOR NEWBORN SCREENING?

Workshop participants were in favour of examining the use of genome sequencing in newborns in recognition of its potential to **vastly increase the number of rare conditions** that could be identified at birth because:

- **The number of conditions that can be identified is much greater than when using traditional metabolic screening technology**

The number of identified conditions is much larger because detection is possible before symptoms occur. Traditional technology relies on early metabolic indication of the condition, and a methodology to detect this signal. Genomic technology can detect a genetic change that may not cause illness until weeks or months after birth. Other confounding factors such as illness, transfusion, medicines, and food do not affect the results. This is corroborated by the US based research project 'BabySeq' has created a curated list of gene-disease pairs collecting 1,514 gene-disease pairs (at time of publication) from a variety of sources. These conditions are divided into three categories:

- category A – gene-disease pairs with definitive or strong evidence to cause a highly penetrant childhood-onset disorder, this category had 884 gene-disease pairs in it;
- category B – gene-disease pairs included based on actionability during childhood, this category had a further 70 gene-disease pairs listed, composed mainly of conditions that could be managed with non-invasive screening methods such as cardiomyopathies and cancer syndromes; and
- category C – gene-disease pairs which do not meet the required threshold of penetrance or which manifest in adulthood.

- **The Use of Whole Genome Sequencing would deliver efficiency within the system**

The follow-up pathways for genomic newborn screening are likely to be much shorter than within the current system. Whereas the traditional methods use a pathway of repeating sample evaluation (sometimes ending in a genetic test) that can take weeks, for gene-disease pairs with a definitive link, completing the pathway for confirming the screening result can be much more straightforward. This can deliver the identified condition to a pathway for management more quickly, providing an opportunity for better outcomes.

Currently, four spots of blood are collected using the Guthrie card for newborn screening. To drastically scale up the number of conditions screened for in the UK would require an increase in the sample of material collected. Though the four spots currently collected would be insufficient for genome sequencing, once a sufficient amount of blood has been collected, this sample size will not have to be adjusted to allow for an increase in the number of conditions screened for.

It is important to recognise that the increase in number of conditions that can be screened for amplifies the benefit of screening to the rare disease community. All of the benefits identified in the first section of this report would apply:

- Entry to a care pathway as soon as necessary to minimise the impact of the condition, including access to curative treatments and medicines before symptoms such as intellectual disability can have any effect.

- Provision of information to parents of a child with a rare condition as soon as possible, providing an understanding of what the future may hold for the family, how their child's health will progress allowing families to plan, make adjustments to their lifestyle, home, location or career so that they can best manage the condition that will affect their family.
- Prevention of a lengthy, agonising and frustrating diagnostic odyssey, that can take years and may involve unsafe misdiagnoses.
- Delivering the opportunity to exercise reproductive choices, with information about the chance of their next child having an inherited condition.
- The opportunity to build a platform to deliver new treatments including registries and clinical trials.

In the context of using genomics to drastically reduce diagnostic timescales for unwell adults and children, it will become increasingly difficult to against deploying the same technology to identify conditions before they cause sickness. This is especially true if we do not significantly increase the number of conditions that are detected using traditional technologies.

– **Examining the potential of a repository of genomic information for life**

The concept of storing an individual's genome sequence, and interrogating it at appropriate times for appropriate health risks has been around for as long as the concept of sequencing a genome. This is not a popular concept within either clinical or patient and family communities. The argument for or against this would be strengthened with some formal analysis.

The 100,000 genomes project allowed for a detailed exploration of this topic in the context of high unmet health need in patients and families affected by rare diseases and cancer. There is an enormous amount of valuable learning that has come from this with respect to: information and communication, that may be adapted to support this work. Some of the learning too may be adapted.

It is important to note though, that patient, family and public perception of the acceptability of storage and sharing of genome sequence is likely to be different according to the status of the subject of this data. Support within attendees at our workshop was notably higher for people with high unmet health needs than for healthy newborn subjects. The scale of this difference should not be underestimated. Workshop participants expressed serious concern for the public perception of the storage of sequence data for newborns, and recommended that a large scale engagement programme would be necessary to support any such activity.

It is worth noting that these warnings and concerns come from a community that understands well, and strongly supports the sharing of this type of data in the context of high unmet health need.

Attendees at our workshop were persuaded most strongly by the opportunity to deliver the benefits of screening more widely to communities affected by rare conditions.

SHOULD WE EXAMINE THE POSSIBILITIES OF GENOME SEQUENCING FOR NEWBORN SCREENING NOW?

Workshop participants were in favour of beginning work to examine the possibilities of genome sequencing for newborn screening as soon as possible.

The policy imperative that arises from the Secretary of States vision for the future of genomics in the UK – when taken with the vision contained within Generation Genome – provides more than enough of a mandate for us to consider a pilot of this technology. Additional to this is the growing risks that come from couples making their own judgement on the value of this technology and purchasing commercial screening solutions.

Consumers' choices are difficult here, as a high degree of expertise is required to judge the value, quality and comprehensiveness of these services. Direct to consumer screening services are by definition poorly connected to the National Health Service and identified conditions will place pressure on the NHS whether or not they are correct.

In the current context of increasing awareness of consumers about genomic technology, increasingly high-profile success of the technology in other domains, and marketing of direct to consumer genomic screening solutions, the chance of consumer frustration and/or negative outcomes is rising. The value of newborn screening to the rare disease community is clear, and the basis for the long-held arguments against changing the status quo urgently need to be addressed.

WHY SHOULD WE EXAMINE THE POSSIBILITIES OF GENOME SEQUENCING FOR NEWBORN SCREENING IN THE UK?

The successes of the 100,000 genomes project include the creation of a nationwide infrastructure for analysis of genome sequences. Though the challenge of analysing healthy newborn genome sequences at a population level is quite different – the UK birth rate of more than 0.6 million births a year is much greater than the 100,000 genome project – there might be no country better placed to be considering a pilot of genomic technology for newborn screening.

WHAT ARE THE CHALLENGES THAT MUST BE ADDRESSED?

Where does newborn screening using genome sequencing fit within the system?

Here there is a distinction between the methodology envisaged for the ultimate fully realised system, and that used initially during piloting and/or roll out. Our workshop discussed whether genome sequencing can replace the current technology, whether it should become a second line technology, or whether it should sit in parallel to the existing screening methodology.

The workshop concluded that any pilot should be provided in parallel with the existing screening programme, not least because genome sequencing cannot detect all forms of conditions that are currently tested for. Eg there are some genotypes for cystic fibrosis that are not characterised yet. There are also metabolic conditions that cannot be detected using genome sequencing that are screened for in other countries, but that are not yet approved for screening in the UK such as maternal B12 deficiency. This raises the question as to whether a pilot should be delivered alongside an expanded metabolic screening programme.

The question as to whether genome sequencing methodology could be used as a second line on cases identified using the current methodology is straightforward to answer from the perspective of those affected by rare conditions. To do so would be to drastically limit the potential of a technology which is being considered precisely because of its enormous potential. Even in the context of a much more permissive decision-making body, this choice would stifle the opportunity that genome sequencing offers as a screening technology.

The workshop concluded that a pilot should be delivered alongside the existing screening programme, in parallel, with the two technologies supporting each other to account for their weaknesses, rather than depending on each other. The ambition should be to work towards examining the full potential of the new technology.

Would the use of genome sequencing in newborn screening be cost-effective?

The more important question is at what cost would such a programme be considered cost effective? To answer this it will be crucial to fully map out all of the potential costs, and all the potential benefits of such a service. Establishing the cost burden of rare conditions to the NHS and more widely is a difficult task, a failure to engage with this challenge may leave the service appearing to be less cost-effective than it may be.

The negative impact of a long diagnostic odyssey on the NHS is likely to be a major source of savings from a newborn screening programme covering a wider set of target conditions. This is likely to be felt across specialised paediatric medicine, where services will be able to devote less of their resource to case identification and more on treatment and care. Diagnoses will facilitate timely coordination of care, which can ease the chaotic care needs of children with serious undiagnosed conditions. This burden can be higher than expected, and more research is required to understand this. A single day's audit in Birmingham Children's Hospital showed that a third of inpatient referrals from other hospitals did not have a diagnosis for their condition.

Long diagnostic odysseys have less tangible impact on health services too. Research from Genetic Alliance UK has shown that both a long diagnostic odyssey and uncoordinated care provision significantly harms the mental health of families living with rare conditions.

Some of the value of this system will come from feeding patients into establishing pathways that deliver optimum care for babies who are identified as being at risk of a rare condition. Work to understand the cost-effectiveness of this programme should take into account the likelihood that many of these pathways will not yet exist or may not yet be fully realised.

A further question is how to capture the indirect economic benefit that this programme may deliver in building a platform for research within the UK. This is both in the context of the potential large scale aggregation of genome sequences for research purposes, and in the context of case identification for registry and clinical trial purposes. There are an increasing number of treatments in development for which clinical trials would be impossible in the UK without an appropriate screening programme to identify cases. For conditions where metabolic screening case identification is not possible, this is an area where the UK could have a competitive advantage against other nations.

The direct advantage to people living with rare diseases of registries and clinical trials in the UK is keenly felt, and this was a priority for those attending the workshop.

Should genome sequences be stored? How and under what terms?

One of the major benefits of implementation of genome sequencing in newborn screening would be for the collection of genome sequences for research purposes from those who consent to share their child's genome sequence. This advantage would go some way to deliver the Secretary of State for Health and Social Care's vision for sequencing 5 million genomes in the next 5 years.

Attendees at the workshop were fully behind the concept of sharing health data relating to people living with rare disease for the purpose of research as espoused by the 100 genomes project among other programmes. This opinion matches a well understood positive orientation to research and the sharing of health data from people with serious unmet health needs. However, the workshop participants felt that to collect and store genome sequencing from newborns was a very different undertaking. There was concern as to how this might be perceived by the public, and that the activity might be considered 'scary'.

Participants noted that we ‘are struggling to adequately inform patients and families about the screening we do now within the NHS’ but felt that ‘we should press on, but recognise that communication and information standards need to improve’. In general good quality communication and education combined with a consenting process that provides information to participants was felt to be the pathway forward. It was felt that work to ensure public understanding of the value of storing whole genome sequences should be prioritised.

Many of the technical, governance, security and communication challenges have been addressed by the 100,000 genomes project and others, and this was not felt to be a particular challenge.

Which conditions should be screened for? How should they be selected?

This is a challenging question that should be carefully addressed.

The attendees at our workshop had a clear message that these decisions should be made differently to how the decision to add conditions to the current programme of newborn screening is made. A version of the model designed by Genomics England to decide on conditions that will be reported through genome sequencing is a much more appropriate basis on which to make this decision than the approach that is currently taken by the UKNSC. This means:

- Expert stakeholders should be part of a permanent decision-making body for the inclusion or exclusion of conditions for newborn screening using genome sequencing
- People living with rare conditions should have a voice within the decision-making process
- This list should be designed by setting principles and boundaries for inclusion or exclusion of conditions based on their characteristics, rather than examining conditions individually

One of the key issues to address is the relationship between phenotype and genotype and confidence in the value of identifying cases based purely on their genotype in the absence of a signal from symptoms of ill health. It is important to recognise that the way in which genomic healthcare is currently delivered is led by phenotype, with genotype examined in light of the symptoms an individual presents. To work in the other direction, expecting phenotype to follow genotype is a new approach and one that the clinical genetic community is wary of.

The development of the list should therefore focus on highly penetrant conditions, where a particular genotype is very strongly associated with a predictable phenotype.

Other questions linked to challenges already addressed

Many of the questions raised in relation to the use of genome sequencing in newborn screening are questions that have been discussed and addressed previously in similar contexts. This is not to say that they need not be considered in this new context, but that they are problems that have been solved before and that previously successful approaches, including engagement with stakeholders and pragmatism may be successful again.

These questions include:

- Parental choice and a child's right to make autonomous decisions in the future;
- How to manage a parallel health and research consenting process;
- How to handle findings of unknown significance, incidental findings and unexpected findings; and
- How genetic information will be shared within families.

The parallels with the 100,000 genomes project are enormously beneficial here, and the methodologies used to address them, which were felt to be particularly valuable, are the trio of engagement with the clinical community, with ethical expertise and with the patient community. An addition of a cohort of representatives of the public would be useful in this context.

WHAT DOES THE RARE DISEASE PATIENT COMMUNITY EXPECT FROM A PILOT OF GENOME SEQUENCING IN NEWBORN SCREENING?

Recommendation 7: Having examined the evidence and the views of our workshop participants, Genetic Alliance UK has reached the view that a pilot of genome sequencing in newborn screening should be planned for delivery within the NHS as soon as possible.

This is primarily because of its potential to **vastly increase the number of rare conditions** that could be identified at birth. The opportunity for efficiencies within screening pathways and for a repository of genomic information to be created were considered secondary to this primary benefit.

The aims of this pilot should include:

- **Delivering a clear message on the cost-benefit of such a programme by:**
- **Establishing the breadth of value to the rare disease community, to the NHS and to a rare disease treatment and care in the UK of such a programme.**
- **Establishing the predicted costs of the system, taking into account the efficiencies that may be delivered in other areas of the health service and more broadly.**

An examination of society's attitudes to the storage of genome sequence information collected at birth:

- Addressing the acceptability, methodology and value of storing genome sequences from newborns.
- Examining whether, and to what extent, learning from the 100,000 genomes project with respect to the collection, storage and sharing of genome sequence data collected from individuals with a high unmet health need applies to healthy newborns.

To take advantage of the infrastructural legacies of the 100,000 genomes project.

To address the challenges associated with genome sequencing in newborn screening, including:

- Where does newborn screening using genome sequencing fit within the system?
- Which conditions should be screened for? How should they be selected?
- To what extent do ethical challenges raised in the delivery of a genomic medicine service apply to a genomic screening service, and whether these topics need to be revisited.

Such a pilot should:

- Be offered in parallel to existing biochemical screening to ensure that standards of turnaround times, accuracy and sensitivity can be met
- Be offered in a small number of specialist hospitals where the quality of information provision, consenting and genetic counselling can be carefully monitored, interventions can be evaluated and feedback from healthcare professionals and patients can be evaluated.
- Allow parents the opportunity to be informed of additional results by category based on actionability, age of onset and certainty

- Parents should be offered the opportunity to participate in additional research studies consented separately from screening
- Development and implementation of the pilot should be carried out transparently and with the full involvement of stakeholder groups, including the genetic and rare disease patient community

Any decisions about data storage and sharing in the pilot should be made on the basis of a full public conversation about appropriate safeguards, involving all relevant stakeholders including genetic and rare disease patient groups.

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ANNEX

Analysis of the UKNSC criteria, how they compare to other nations and how they disadvantage screening programmes for rare conditions

UKNSC Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

1. The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Comments

W&J principle 7 requires only that ‘the natural history of the condition, including development from latent to declared disease, should be adequately understood.’ (emphasis ours)

Before the 2015 review the UKNSC criteria also included the word ‘adequately’ but this was removed.

It is often not possible for this information to be gathered on rare conditions due to the small number of affected individuals and the unpredictable or heterogeneous nature of the condition’s presentation and/or progression.

In some past evidence reviews (eg. biotinidase deficiency) this criterion was regarded as not met as children diagnosed with the condition both in the UK and elsewhere have been treated for many years, and so it is not possible/ethical to study the natural history of the untreated condition. This being the case, it is unreasonable to regard the lack of natural history data as a reason not to recommend screening - where a criterion cannot realistically be met, it is unreasonable, and potentially unethical, for this to be required.

<p>2. All the cost-effective primary prevention interventions should have been implemented as far as practicable.</p>	<p>This criterion is less relevant to newborn screening than to other programmes such as cancer screening.</p>
<p>3. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.</p>	<p>This criterion appears to be unique to the UK (Seedat et al 2014)</p> <p>In the absence of a screening programme, carriers would be most likely to be identified following the diagnosis of a relative. It is difficult to see how evidence on outcomes of carriers identified in a screening programme could be collected other than through an existing screening programme or similarly large scale study.</p>
<p>4. There should be a simple, safe, precise and validated screening test.</p>	<p>Based on W&J principle 5, which only states that ‘there should be a suitable test or examination’.</p> <p>‘Validated’ appears to be a particularly difficult standard to meet, as the UKNSC requires RCT evidence (effectively an existing screening programme or similarly large scale study) in a population demonstrably similar in makeup to the UK. This was one of the criteria SCID was judged not to meet in the 2017 review.</p>
<p>5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.</p>	<p>Only the UK and Australia require this (Seedat et al 2014)</p> <p>It is difficult to see how this evidence could be collected other than through an existing screening programme or similarly large scale study, which is difficult in rare disease.</p>

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| <p>6. The test, from sample collection to delivery of results, should be acceptable to the target population.</p> | <p>Based on W&J principle 6, which only states that ‘the test should be acceptable to the population’.</p> <p>The UKNSC requires this to be demonstrated for the specific test and condition, rather than accepting evidence of the acceptability of newborn bloodspot screening programmes in general.</p> |
| <p>7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.</p> | <p>Due to the scarcity of evidence, treatment guidelines in rare disease, where they exist, are usually based on the consensus of expert clinicians. This would not meet the UKNSC’s evidence standards.</p> |
| <p>8. If the test is for a particular mutation or set of genetic variants the method for their selection and the means through which these will be kept under review in the programme should be clearly set out.</p> | <p>No newborn screening is currently carried out using genetic methods, though this criterion may become relevant in future.</p> |

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

Based on W&J principle 2 which requires only that ‘there should be an accepted treatment for patients with recognized disease.’

Before the 2015 review, this criterion referred to ‘effective treatment or intervention’ with ‘evidence of early treatment leading to better outcomes than late treatment’

Requirement for an ‘effective intervention’ is a much higher bar than W&J ‘accepted treatment’ or many countries which are willing to consider any beneficial management and care. For example EU Tender Expert Opinion document lists as examples ‘medication, diet, lifestyle advice, avoiding complications and any measures to improve the health status and quality of life of the child’. Criterion 19 makes it clear that the bar is even higher: the intervention must be ‘preventative’

In the absence of a single effective intervention, early detection can provide benefit in the provision of supportive or palliative care, which may increase quality of life or even improve outcomes (eg. improved growth in CF screen positive children due to extra attention paid to diet and nutrition)

The UK already has a number of HTA bodies specialising in the evaluation of the clinical effectiveness of treatments. Here the UKNSC carries out its own evaluation, with a higher standard to meet clinical effectiveness and a higher evidence bar than all UK HTA bodies. As a result, we see treatments which are regarded as both clinically and cost effective enough for NHS routine commissioning not being considered an effective intervention for this criterion.

Other possible forms of benefit (other than reductions in mortality or morbidity for the child screened include: reducing the diagnostic odyssey; ability to participate in clinical trials; stimulating research; providing reproductive risk information to child or parents.

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| <p>10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.</p> | <p>Based on W&J principle 8, which only states that ‘There should be an agreed policy on whom to treat as patients.’</p> <p>Due to the scarcity of evidence, treatment guidelines in rare disease, where they exist, are usually based on the consensus of expert clinicians. This would not meet the UKNSC’s evidence standards.</p> |
| <p>11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (such as Down’s syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.</p> | <p>It is difficult to see how this evidence (from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity) could be collected other than through an existing screening programme or similarly large scale study</p> |
| <p>12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.</p> | <p>The UKNSC requires this to be demonstrated for the specific test and condition, rather than accepting evidence of the acceptability of newborn bloodspot screening programmes in general.</p> |

13. The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

The evidence base regarding harms associated with screening for specific conditions is often more limited than that for benefits (Goldenberg et al 2016). UKNSC appears willing to relax requirement for RCT evidence on harms only.

Screening programmes using point of care testing (eg newborn hearing screening) more prone to false positives than newborn bloodspot programme where there is the opportunity for samples to be retested and confirmed before the parents are informed.

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

Based on W&J principle 9, which only states that 'The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.'

UKNSC expert group conducts a health economic analysis of the incremental cost effectiveness ratio for screening for the condition in the NHS Newborn Blood Spot Screening Programme compared to not screening. The analysis is undertaken from the perspective of the NHS and Personal Social Services. The analysis focuses on the health benefits to the child expressed in quality adjusted life years, with determining the probability of the screening programme being cost effectiveness at thresholds of £20,000 and £30,000 (reflecting the cost effectiveness thresholds used in NICE appraisals).

Cost effectiveness evaluations are not conducted each time a condition is reviewed. It is not clear what triggers a cost effectiveness evaluation.

<p>15. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.</p>	<p>What constitutes optimised clinical management is quite subjective.</p> <p>Due to the scarcity of evidence, treatment guidelines in rare disease, where they exist, are usually based on the consensus of expert clinicians. This would not meet the UKNSC's evidence standards.</p>
<p>16. All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.</p>	<p>Not required at outset in most countries (Jansen et al 2017)</p> <p>The UKNSC does not have the power to add topics to the NICE or NHS England (for example) work programmes. This means that if the UKNSC decides that a clinical guideline or new service would be a more suitable option than a screening programme, this can lead to the screening programme not being recommended without a clinical guideline or new service being considered or developed/</p>
<p>17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.</p>	<p>Not required at outset in most countries (Jansen et al 2017)</p>
<p>18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.</p>	<p>Requiring staffing and facilities to be available before the recommendation is made and the implementation phase (and funding) begins may be considered premature.</p>

19. Evidence-based information, explaining the purpose and potential consequences of screening, investigation and preventative intervention or treatment, should be made available to potential participants to assist them in making an informed choice.

Word 'preventative' added in 2015 review.

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

This criterion appears to be unique to the UK (Seedat et al 2014; Jansen et al 2017)

This criterion appears to be more relevant to screening programmes in adulthood, where repeated screening is carried out and the balance between sensitivity and specificity can be weighed differently.

