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Newborn Screening in the United Kingdom:

The UK Newborn Screening Collaborative is a working group of 17 patient organizations and Genetic Alliance UK, advocating the urgent extension of the current UK newborn screening programme to include a greater number of appropriate rare and inherited metabolic diseases.

Whilst welcoming the UK Government's commitment to whole genome sequencing in the United Kingdom and the proposed financial investment to consider offering whole genome sequencing to newborn babies, the work of the Newborn Genomes Programme (NGP) cannot progress sufficiently quickly to prevent the death and disablement of many newborns over the coming years. This exciting new proposal therefore cannot be allowed to negate further considerations on expansion of the current newborn screening programme in the UK at this time.

Purpose of this Briefing Paper

This paper is to advise Government and health officials on the benefits of improving and extending our existing newborn screening programme, whilst also identifying the issues and challenges in respect of whole genome sequencing of newborns. It aims to describe why the current important focus on whole genome sequencing of newborns should not detract from improving and extending our existing newborn screening programme now.

Background to the current position in the United Kingdom (UK).

Very early detection of a disease can enable immediate curative treatment of the child or can provide for a significant improvement in the clinical care of a child. Early detection of a disease is an opportunity for a child to live a fulfilled life i.e. rather than at worse death, or at best a life living with a complex health condition and/or disability. Early diagnosis not only improves the clinical care of the child, however can consequently improve the health, mental wellbeing and the socio and economic circumstances of the rest of the family, including any siblings of an affected child. The impact on the family of the death of a child or caring for a child with a lifelong disability has been well documented.

For some 15 years, patient organizations have been advocating for the extension of the existing newborn screening programme in the UK, together with a call for an improvement in public health decision making on screening babies. This has included the need to change policy and procedures surrounding the decision making on which diseases are to be added to the newborn screening programme. Since 2006, many countries worldwide, including Europe, have significantly extended their newborn screening programmes, benefiting many children. The USA screens for over 50 conditions and Italy, Hungary, Austria and the Netherlands screen newborns for over 20 conditions. During this same 16-year period, the UK has extended their newborn screening programme by only 5 disorders. An additional disorder (SCID) commenced a pilot phase in September 2021. Submissions for screening for a number of other individual disorders have been rejected by the UK National Screening Committee and the Government over this same period. The health of babies in the UK has been severely impacted as a result of the UK Government's lack of attention to the screening of newborns and their reluctance to learn from experiences in other countries.

Submissions to the UK National Screening Committee (UK NSC) to add new disorders to the UK programme have been made, only to be considered and rejected. Due to the failure to screen babies for more disorders, during the past 5 years, significant numbers of children have been diagnosed with a disorder absolutely too late to receive life saving treatment. The UK NSC has recently reviewed and rejected screening for Spinal Muscular Atrophy (SMA). Based on current statistics, over 300 children in the UK could have benefitted from early diagnosis through newborn screening and immediate treatment and care. Between 16 and 20 babies per year are born with SCID, yet it has taken 11 years to get newborn screening for SCID approved as a pilot.

In recent years, whole genome sequencing has presented a phenomenal opportunity for the early diagnosis of both rare and previously undetectable diseases. Following on from successes in the United Kingdom such as the 100,000 Genomes Project, considerations are now moving towards addressing the role that whole genome sequencing might play in the early detection of rare diseases in newborn babies.

However, there is a danger that the current spotlight on whole genome sequencing of newborns will detract important attention away from extending the current programme now, with fatal consequences for many children. Improvements to the current system now would

also benefit whole genome sequencing of newborns, which will inevitably require updated bureaucracy to support the many additional conditions which it will add to the programme.

Benefits and Challenges for implementing the Whole Genome Sequencing of Newborns in the UK

In 2021 Genomics England published their Vision document for the Newborn Genomes Programme and their proposal for a pilot research project, view here: **https://files.genomicsengland.co.uk/documents/Newborns-Vision-Final_SEP_2021-11-02-122418_jjne.pdf**

Genomics England also commissioned a public dialogue on the implications of the whole genome sequencing of newbornscreening, which was undertaken in 2021 in partnership with the NHS and the UK National Screening Committee, view here: **https://www.genomicsengland.co.uk/news/public-dialogue-genomics-newborn-screening**

The NGP pilot, in partnership with NHS England, will look for a set of childhood onset genetic conditions which may affect their health in early years and that we can do something about. Work has already begun to identify the types of conditions that might be looked for and Genomics England are working with scientists, clinicians, and the rare disease community to determine what diseases might be included. Genomics England will be looking for and feeding back to families on a specific set of well-characterised childhood onset, actionable conditions.

Benefits

Whole Genome Sequencing can enable the earliest detection of a very significant number of different diseases in newborn babies. This can result in the prompt and appropriate life saving or life enhancing treatment and care of a child. Genomics England has estimated that approximately 80% of rare diseases have genetic origins and almost 30% of children with a rare disease die before their 5th birthday. It is clear what benefits WGS can bring to newborns.

Genomics England have said that they are committed to undertaking this research project transparently and correctly and will fully address all the issues and concerns raised both within the Public Dialogue and the research project itself. (Genomics England Newborn Genomes Programme Vision doc.) In addition Genomics England has confirmed that their research

programme will need to fit into the broader strategy for newborn screening development. GE is committed to supporting research that can inform decision making on current policy and practice in screening more broadly.

Challenges

Significant work on the Newborn Genomes Programme is in progress. The timetable for the research project indicates that recruitment of families and pilot work is not due to commence before April 2023. It is proposed that some 100,000 newborns will be part of the 3 year research programme. It is unclear when the results of the review will be evaluated and indeed when implementation of WGS for newborns will be embedded fully within the NHS beyond 2026. It is also unclear which diseases can successfully be implemented. Consequently full implementation of some diseases might be at least some 5-10 years away. Simon Wilde, Engagement Director for Genomics England, in response to concerns raised in the Guardian in December 2021 said that Genomics England recognized the uncertainty of the benefits and the research outcomes, which is why they are taking things slowly. This further indicates that we are some way away from any National Rollout.

It is accepted that Genomic sequencing will bring challenges and these will be addressed in any pilot phase. WGS will be unable to detect some key diseases without the associated biochemical testing that we currently utilize. An example is Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD). Biochemical screening enables detection of the more severe phenotypes and avoidance of referring the milder disease or heterozygotes. Cases of the diseases Long Chain 3-Hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and Propionic academia in children have been identified that were biochemically abnormal, yet no actual gene mutation was found. A combination approach with biochemical testing and genomics should allow further integration of newer sequencing technologies into routine use and without necessarily disrupting the existing screening programme. Newborn Genome Sequencing, at least for the foreseeable future, will need to run alongside rather than replace current screening modalities.

There is also a risk of greater numbers of false positive results from whole genome sequencing which may put children on a clinical care pathway quite unnecessarily. The NGP will seek

variants that are known to cause disease to mitigate this risk of false positive results although some affected cases may be missed as a consequence.

To date the existing 100,000 Genomes Project has looked at children or adults where a clinical or health problem has already been identified. There are huge ethical, parental consent and data retention/sharing implications for using genomic sequencing for whole population screening. Data gathered through WGS could have significant implications for the rest of that child's life.

Whole genome sequencing could identify variants of unknown significance (VOUS). In essence we just do not know what these genetic variants mean. The NGP will develop clear principles for how the genes and variants they will look for are selected to avoid wherever possible identification of VOUS. Any disorder where there is a biochemical diagnostic test and the genomic screen has identified novel previously undescribed variants will require biochemical clarification. We do not yet know enough about the function of particular genes. Using a genome is highly complex with issues due to penetrance. Naturally the research pilot will identify the implications of this, however this is likely to create significant dilemmas**.** Environmental factors can also affect gene expressions**.** Whole genome sequencing could raise ethical issues on diseases that are identified at birth and which may not present until later life or indeed never present at all. This will be addressed by the NGP only looking at childhood onset actionable conditions.

Scientists have already raised concerns on the focus on whole genome sequencing when newborn screening for babies can be significantly improved in the UK by alternative, more targeted and less costly testing. In essence building and improving on what we already have. Genomics has become a national flagship and consequently expansion of our existing programme is being sidelined. (Article in the Guardian. Thursday 2.12.2021 'Scientists raise concerns over UK baby genome sequencing plan').

There are massive implications on how we would achieve a trusted and future-proofed genomic data storage and usage system that is acceptable to the public.

How do we assure the public that genomic screening is definitely going to improve diagnosis and the treatment/care of newborns, as opposed to being a future UK population health data collection and storage for other purposes?

In the whole genome sequencing of newborns, how would we provide a scalable and sustainable programme for the NHS i.e. financially, the workforce implications, staff training and many other considerations.

There are ongoing backlogs on diagnosis within the existing 100,000 Genomes Project. Is this likely to be a similar issue for the genomic sequencing of our newborn babies, particularly when we will be screening for some 600,000 live births a year? The Government has standards for genomic analysis (TAT Standards). However, the standards do illustrate the challenge that genomics newborn screening will face in terms of delivery.

Genomic sequencing of newborns will still need consideration of the World Health Organisation (WHO) criteria for determining which disorders should be screened for. The UK follows the WHO criteria. This is particularly relevant to whether there is treatment available to the child, or in Genomics England words 'that we can do something about it' and of course the financial/resource implications.

A system that is already lacking the required bandwidth to efficiently assess and support a very small number of disorders cannot possibly have the capability to support the burgeoning slate which will result from the whole genome sequencing of newborns research.

Extending the current newborn screening programme

The importance of extending the existing newborn screening 'heel prick' programme in the UK cannot be underestimated. Improving the decision making processes will support this. Extension of the newborn screening programme over the next 12-18 months would also be a less costly measure. If we were to wait for the outcomes of the Newborn Genomes Programme research, many babies with a disease that could have been identified and treated will go undiagnosed.

The UK's newborn screening programme is not synchronized with many countries in the world, particularly similar European countries. There is an opportunity to bring the UK in line with other countries without having to wait a further 5+ years.

There is no guarantee that the whole genome sequencing of newborns research programme will produce workable and sustainable solutions for the UK and the NHS. There is a real risk that we will put improvements to and the development of the existing screening programme on hold pending the research outcomes. This will result in the loss of even more children's lives and additionally little development of our existing programme.

There are adaptations that could be made within the existing 'heel prick' programme and within the next 12-18 months which would be beneficial for children and families and that will be less costly and less disruptive to existing healthcare pathways.

Examples of suggested improvements are:

1. By the end of 2022, formation of a **dedicated team of newborn screening experts** to solely evaluate conditions to be added to the newborn screening programme and to undertake the formal engagement of consultees, including clinical and scientific **experts relevant to the condition/group of conditions being appraised**.

2. By the end of 2022, establishment of a **streamlined evidence review process** for evaluation of conditions to be added to the UK newborn screening programme, which is **relevant to rare diseases** and automatically accepts a wide range of evidence currently available from validated and reputable sources.

3. By the end of 2022, the process of evaluation of adding conditions to the UK newborn screening programme to incorporate **specified timescales** to ensure appropriate **efficiency and accountability.** (An excellent example of the lack of defined timeframes for decision making is SCID which only went into pilot in the UK in September 2021 yet was in the consideration and review system with the UK National Screening Committee for some 11 years.

There is more background information on these areas of improvement available on the ArchAngel Trust website at: https://www.archangel.org.uk/newborn-screening-campaign

It should be noted that there is marked concern amongst the rare disease community that the DHSC's 2022 'Rare Disease Action Plan' has not actually addressed the serious flaws in the current system which the NBS Collaborative have identified as above.

Conclusion

We are asking that the extension of the existing newborn screening 'bloodspot' programme for appropriate diseases and neccessary improvements to current bureaucracy are not put on hold or sidelined pending the results of the new whole genome sequencing of newborns research. It is acknowledged that the possibilities of using whole genome sequencing in detecting rare disorders in children at birth can ultimately lead to significant health improvements. However, any delay in extending the current programme will lead to unnecessary disability or loss of life for many children. Any expansion of the current programme now will not only save and dramatically improve lives, but it will also result in the betterment of bureaucracy which is essential to support whole genome sequencing of newborns.

Pat Roberts

Director of the Newborn Screening Project

ArchAngel MLD Trust & UK NBS Collaborative