

Genomic newborn screening: current concerns and challenges



60 years ago, the first newborn screening test for phenylketonuria, a rare inherited metabolic disease, was developed. The heel prick test, devised by Robert Guthrie, enabled babies with the condition to be identified soon after birth and begin a diet low in foods containing phenylalanine, thereby preventing them from developing intellectual disability, seizures, and behavioural problems. Since Guthrie's breakthrough, blood-based screening programmes have been expanded to cover more genetic disorders. The number of diseases covered varies: the USA currently screens for 63 disorders, the UK screens for nine, and Australia screens for 27. Yet implementation of newborn screening programmes is highly variable in low and middle-income countries, particularly on the African continent. Such inequity needs to change. The development of genomic sequencing technologies now offers an unprecedented opportunity to expand screening programmes. More than 4000 genes have been associated with recognisable monogenic diseases affecting an estimated 400–700 million people worldwide. In the US, health-care costs and utilisation of services by patients with these rare diseases accounted for an estimated US\$768 billion in inpatient costs alone in 2016. Why then do we not screen the whole genome of all newborns, given the wealth of information and potential benefits it could provide?

The question has been the subject of much debate and is soon to be explored further by a UK-based project, the Newborn Genomes Programme, which is currently aiming to sequence the genomes of up to 100 000 newborn babies. Details of the £105 million project remain incomplete. The aim is to provide information to parents on between 200 and 400 rare diseases. The exact figure will be revealed when experts from different specialities can finally agree on whether acceptable treatments are currently available for the individual conditions. Sequencing will be carried out at the time that the current heel prick test is done, and the results will be stored and then reanalysed as needed. Several ongoing research projects—including the US-based Newborn Screening in Genomic Medicine and Public Health programme and the BabySeq Project—have identified important ethical, technical, and financial dilemmas which all potential stakeholders ought to be aware of.

Firstly, interpreting whole genome data has notable challenges. Some mutations, although known to cause a recognised disease in childhood, might only result in the person developing the disease later in life, or in some cases, not at all. Additionally, sequencing the whole genome of newborn babies will identify possible genetic changes of unknown importance. Where outcomes are uncertain, this will necessitate lengthy, costly follow-up, with accompanying psychological harms. Secondly, using a whole genome approach restricted to only those diseases where there are currently recognisable and affordable treatments available would have no advantage over simply expanding current screening programmes by using targeted gene panels covering the additional diseases. Thirdly, whole-genome sequencing has been shown to have a considerable false negative rate compared with current conventional screening tests employing mass spectrometry and other laboratory investigations. Ethically, obtaining informed consent from parents to take part in such screening programmes, particularly where outcomes are sometimes of uncertain importance, is difficult enough in the short term. For the longer term, parents cannot give consent, nor can they know the wishes of their grown-up child about participating in such a programme.

Keeping large, clearly identifiable data safe is problematic and potentially exploitable; inappropriate sharing of such information with secondary agencies, including insurance and pharmaceutical companies and law enforcement, remains a realistic possibility. Economically, the implications of a newborn screening programme involving whole-genome sequencing are substantial: not only the cost of prolonged follow-up and monitoring of babies with identified mutations and variants but also additional costs that might include genetic testing of the parents. Genomic sequencing could screen for many more conditions than current conventional programmes, but the risk benefit balance remains uncertain. Given such uncertainties, focusing on improving screening by upgrading targeted gene panels might be more sensible in the short term. Whole genome sequencing in the long term deserves thorough examination and universal caution. ■ *The Lancet*



For more on the **Guthrie's heel prick test** see *Pediatrics* 1963; 32: 338–43

For more on the **disorders screened for in the USA** see [https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp#:~:text=The%20RUSP%20is%20a%20list,newborn%20screening%20\(NBS\)%20programs](https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp#:~:text=The%20RUSP%20is%20a%20list,newborn%20screening%20(NBS)%20programs)

For more on **newborn screening in the UK** see <https://www.nhs.uk/conditions/baby/newborn-screening/overview/>

For more on the **disorders screened for in Australia** see <https://www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened>

For more on **newborn screening in Africa** see *J Community Genet* 2020; 11: 253–68

For more on the **Newborn Genomes Programme** see <https://www.genomicsengland.co.uk/initiatives/newborns>

For more on the **Newborn Screening in Genomic Medicine and Public Health programme** see <https://www.genome.gov/Funded-Programs-Projects/Newborn-Sequencing-in-Genomic-Medicine-and-Public-Health-NSIGHT>

For more on the **BabySeq Project** see <https://www.genomes2people.org/research/babyseq/>

For more on the **pros and cons of genome sequencing in newborn screening** see <https://www.genomicseducation.hee.nhs.uk/blog/newborn-screening-the-pros-and-cons-of-genome-sequencing>