

Whole genome sequencing of babies



OVERVIEW

- Whole genome sequencing is cheaper and faster than ever, but interpreting the results is difficult, time-consuming, and expensive.
- Whole genome sequencing is starting to be used in the NHS to help obtain a diagnosis for some seriously ill babies.
- What genetic information should be shared with parents, and how genetic data should be stored, accessed, and used requires further public consideration.
- There is debate about whether genome sequencing could be used to expand NHS newborn screening to include additional genetic conditions.
- There is broad agreement within the genetics community that it is not acceptable to use whole genome sequencing to look opportunistically for a broad range of conditions in babies. However, some parents express a desire for this kind of information and might be able to access commercial whole genome sequencing in the future.

WHAT IS WHOLE GENOME SEQUENCING?

Whole genome sequencing is the process of identifying a person's entire genetic code. Obtaining this code from a sample of blood or saliva takes around four weeks and costs approximately £1,000.¹ However, interpreting the code is difficult, time-consuming, and expensive. Whole genome sequencing can help to identify single gene changes associated with rare diseases such as cystic fibrosis and certain

cancers, but the significance of large amounts of the genetic code is unknown. Sequencing the genomes of an individual's biological parents as well – called 'trio testing' – can help with interpretation. Another approach is to sequence only the 'exome'. The exome makes up less than two per cent of the genome, but is thought to contain 85 per cent of the gene changes that cause genetic disorders.

REASONS FOR USING WHOLE GENOME SEQUENCING IN BABIES

There are a number of possible reasons for carrying out whole genome or exome sequencing in babies, including:

- Seeking a diagnosis for a seriously ill baby with a suspected genetic disease.
- Predicting how a baby will respond or react to medicines they might need now or in the future.
- Predicting a baby's chance of developing disease in childhood or adulthood.
- Finding out about genetic factors that could

affect other children that the parents or other family members might go on to have.

- Creating research databases of individuals' genome sequences in order to study genetics and disease for the benefit of others.

As well as information about diseases of different types, whole genome sequencing has the potential to reveal information about non-health traits, family relationships, and genetic variations of uncertain or unknown significance.

WHICH BABIES COULD HAVE THEIR GENOMES SEQUENCED?

SERIOUSLY ILL BABIES

When healthcare professionals have not been able to identify the cause of a baby's ill health, whole genome or exome sequencing offers a way of searching simultaneously across large parts of the genetic code for genetic causes of disease.² The data can be filtered, with only the data that are likely to be relevant to the patient's condition being analysed. This approach is being used in some hospitals in the UK, although it is not yet widely available across the NHS.³ This is likely to change after the completion of the Government's 100,000 Genomes Project, which aims to create a genomics service ready for adoption across the NHS (see Box 1).

BABIES WHOSE PARENTS ACCESS COMMERCIAL TESTING SERVICES

Parents of babies in the UK and elsewhere might be able to access whole genome and exome sequencing through commercial providers

in the future. Whole genome sequencing is already available to adults through several US-based companies. For a fee of £700–£1,800, the companies claim to be able to provide information about the person's predisposition to disease, medicines they might be sensitive to, and whether they carry any disease-causing genes that could be passed onto their children.⁴ Several companies offer, or are planning to offer, newborn screening tests that search for large numbers of genetic conditions.⁵

ALL BABIES

In the NHS, the newborn blood spot screening test is offered to parents of all newborn babies. The test looks for nine medical conditions, including cystic fibrosis and sickle cell disease.⁶ Some suggest that the programme should be expanded to include more childhood conditions, and that using whole genome or exome sequencing could become a cost effective way to achieve this.⁷

BOX 1 THE 100,000 GENOMES PROJECT

The UK's 100,000 Genomes Project aims to sequence 100,000 genomes from adults and children who have rare diseases and cancer by the end of 2018. Some patients will receive a diagnosis through the project, but the project's aims are to create a resource for research and to develop an infrastructure for genomic

services in the NHS.⁸ To make this a reality, the Government's Chief Medical Officer for England suggests we need to "embed national standards; streamline laboratories; and, in a secure environment, agree to use of data for our own benefit and others".⁹

LAW, GUIDANCE, AND ADVICE

The Human Tissue Act 2004 makes it unlawful in England, Wales, Scotland, and Northern Ireland to store and use a child's tissue for DNA analysis without the consent of a person who has parental responsibility for them.

Current UK and international professional guidance and advice broadly agrees that it is acceptable to use whole genome or exome

sequencing in the clinical care of seriously ill babies. However, the guidance and advice suggests that using this technology to look opportunistically for a wide range of genetic conditions and traits in babies, either through a newborn screening programme or commercial services, is not justifiable or acceptable (see Box 2).

BOX 2 PROFESSIONAL GUIDANCE AND ADVICE

On using **whole genome sequencing in the care of seriously ill babies:**

- British Society for Genetic Medicine: where testing aids immediate medical management, it is unlikely to be contentious.¹⁰
- European Society of Human Genetics: it is preferable to use a targeted approach first in order to avoid unsolicited or uninterpretable findings.¹¹
- American College of Medical Genetics and Genomics: parents should be given the option of finding out about additional, specific genetic disorders.¹²

On **direct-to-consumer genetic testing of children:**

- Nuffield Council on Bioethics (UK): companies should not carry out on children DNA tests that do not meet the criteria of the UK National Screening Committee.¹³

- Human Genetics Commission (UK): direct-to-consumer genetic tests in respect of children should normally be deferred until the attainment of capacity.¹⁴
- European Society of Human Genetics: direct-to-consumer genetic tests should not be offered to individuals who have not reached the age of legal majority.¹⁵

On using **whole genome sequencing in population newborn screening:**

- Groups from Europe, the US, and the UK broadly agree that current knowledge does not justify the use of untargeted whole genome sequencing in population newborn screening. Newborn screening should be limited to gene variants conferring a high risk of specific conditions that can be effectively treated or prevented in childhood.¹⁶

ETHICAL ISSUES

Some of the ethical issues to consider with the increasing use of whole genome sequencing in babies are summarised in this section.¹⁷

WHO IS AFFECTED?

Different parties could be affected by the use of whole genome sequencing in babies:

- **Babies** who are ill might receive immediate health benefits from genome sequencing, but there are potential harms to be considered as well, such as false positive results, uncertain results, and over-treatment. In the prediction of future disease, a child's right to an open future and their ability to make their own choices later about accessing their genetic information should be factored in.
- **Parents** might feel entitled to know, or not know, genetic information about their child, particularly as it might reveal information relevant to their own health and that of any other children they may have. But the difficulty of interpreting genetic information means that some results might lead to uncertainty, which could cause parents confusion and anxiety. Information obtained at birth could affect family expectations and how the child is raised.
- **Other family members**, such as siblings, have interests in knowing information that could be beneficial to their health. Equally, they might wish not to know their genetic information, and may prefer to keep it private.
- **Healthcare professionals** have responsibilities to ensure their patients receive high quality care and treatment, which they might feel includes giving them access to genome sequencing. But they might not appreciate its limitations, nor be adequately trained to interpret and deliver the results, and genetic counselling may not always be available.
- There are also costs and benefits to **society** that might be weighed, including the potential to reduce the burden of genetic disease in the population, the financial costs of offering genome sequencing in a public healthcare system, and the potential effects on public attitudes towards genetic variation and disability.

WHAT GENETIC INFORMATION SHOULD BE SHARED WITH PARENTS?

While it is difficult to establish a clear picture of international practices, there appears to be a general consensus within the medical genetics community that only information about *childhood* conditions should be shared with parents following whole genome sequencing of sick babies (see Box 2). However, there are different views on which childhood conditions should be included in the information shared with parents. In the US, an emphasis on the parent's entitlement to know is leading practitioners towards reporting results relating to a large number of specified childhood conditions.¹⁸ Practitioners in the UK and Europe have tended towards a more targeted approach, with the focus on determining the cause of a child's current ill health. However, this is changing: parents of children participating in the UK's 100,000 Genomes Project (see Box 1) can opt to find out whether their child has several additional gene changes that can cause childhood conditions, as well as those relating to their existing condition.¹⁹ Concerns have been raised by the British Society for Genetic Medicine about this becoming routine NHS practice without the consequences for patients and healthcare professionals first being properly evaluated.²⁰

Some parents of children involved in genomic research have expressed a strong desire to receive a broader range of health-related results, irrespective of whether or not the results are uncertain, or relate to childhood or adult conditions, and whether or not there are known treatments.²¹ There is no UK legislation that would prevent genome sequencing companies from sharing this information with parents. It has even been suggested that clinical laboratories could have a legal obligation to provide individuals with their 'raw' genomic data on request.²²

SHOULD ALL BABIES HAVE THEIR WHOLE GENOME SEQUENCED AT BIRTH?

The UK National Screening Committee advises the Government on NHS screening programmes. It stipulates that screened-for conditions must be serious and treatable, the test must be precise, and there should be evidence that

screening will reduce ill-health or death. This would rule out using whole genome sequencing to look opportunistically for a wide range of different kinds of genetic conditions in all babies. However, there is debate about whether genome sequencing could be used to expand NHS newborn screening to include additional specific genetic conditions, and how the benefits and harms of screening programmes should be weighed. Some researchers suggest that notions of the benefits of newborn screening are evolving and could include providing parents with information relevant to other children they might go on to have.²³ Others argue that only by expanding the newborn screening programme can evidence of benefit be amassed, particularly for rare diseases.²⁴

HOW CAN PARENTS BE SUPPORTED TO MAKE INFORMED CHOICES?

Facilitating informed choice in the context of genome sequencing is challenging. Tests offered as part of screening programmes are often seen by parents as routine or automatic,²⁵ and healthcare professionals caring for sick babies might not have specialist genetics knowledge to help talk parents through their options. Commercial providers have been criticised for providing misleading information and claims about their tests in some other areas of genetic testing.²⁶ There are calls for standardised catalogues of disease-causing genes, for training to help doctors interpret genomic results, and for genetic counselling to be informed by the experiences of people with genetic conditions and their families.²⁷ Other sources of information for parents, such as websites and parenting manuals, could also play a role in informed decision making.²⁸

WHAT MIGHT BE THE IMPACT ON TREATMENT AND CARE?

Using whole genome sequencing to diagnose a sick baby could help reduce a long and distressing journey of tests, and inform decisions about appropriate clinical care, be that active treatment or palliative care. However, there is a risk of false positive results that might result in unnecessary or inappropriate treatment.²⁹ Even if a genetic condition is diagnosed, the prognosis can be uncertain, meaning genome sequencing

will not always help families and healthcare professionals to decide on the best care.

If a gene change associated with a particular disease is found in an apparently healthy baby, it might enable preventative action to be taken. But there is often no certainty that the baby will become ill, and it has been suggested that this kind of result could adversely affect bonding between the parents and child in what otherwise would have been a care-free period.³⁰

HOW SHOULD GENOMIC INFORMATION BE STORED AND ACCESSED?

Babies who have had their genome sequenced at birth might grow up to find that their genetic data has been stored in some format. They might want to access this themselves. Some genome sequencing companies refer to genome sequencing as a resource for life and offer to regularly re-analyse their customers' data in light of new genetic knowledge.³¹ Within the NHS, discussions are taking place on what kind of new knowledge would warrant re-contacting a patient who has had genomic testing, and whose responsibility this would be.³² However, as sequencing standards and IT systems change over time, it is possible that today's sequencing data will be too crude to be of use in a few years' time.³³

Other parties - such as family members, researchers, and companies - might have an interest in accessing genomic information.³⁴ There are debates about the ownership and control of genomic information, with some researchers suggesting a public ownership model is most appropriate.³⁵ It is recognised that NHS care could be greatly improved by encouraging research activity on health data, but achieving this with the support of the public requires careful thought.³⁶ Data governance and access arrangements have been developed by the 100,000 Genomes Project.³⁷ The Nuffield Council on Bioethics has recommended that there should be public consideration of whether these arrangements represent the optimal model before they are used as a template for similar initiatives.³⁸ The transparency of the data handling activities of some genome sequencing companies has been found to be lacking.³⁹

WHAT COULD BE THE IMPLICATIONS FOR WIDER SOCIETY?

There are differences of opinion about whether an increased uptake of genome sequencing would lead to more positive or more negative views of genetic variation, disability, and poor health. Some caution that if genome sequencing becomes associated with palliative care this might send a harmful message to people with genetic conditions and their families, and fuel distrust toward the use of genetic technologies in clinical care.⁴⁰ It has been suggested that population genome screening should not be contemplated without first tackling discrimination, exclusion, and negative societal attitudes experienced by disabled people.⁴¹

Increased uptake of genome sequencing at birth could lead to the creation of a population-wide genome database. As well as a resource for research, such a database could have a myriad of other possible uses, such as crime detection, border control, and insurance and employment screening. These kinds of uses of genomic information are controversial and have

been the subject of academic and public debate. Proposals to create a comprehensive, UK-wide police DNA database have raised concerns about balancing the protection of individual liberty with the need to prevent crime.⁴² Using DNA databases for employment or insurance purposes is widely thought to represent an unjustified intrusion of privacy.⁴³

WHAT COULD BE THE IMPLICATIONS FOR THE NHS?

There are concerns about the ability of the NHS to deliver an effective genomics service. Deciding which patients will benefit from genomic testing, obtaining consent for testing, and interpreting results take specialist knowledge and time, and remain a significant challenge in mainstream medicine.⁴⁴ NHS genetics laboratory services will also play an important role, but there is uncertainty about how they will be configured in the future.⁴⁵ If whole genome sequencing was offered to parents of *all* newborn babies, the scale of counselling and other NHS services required might be unmanageable.⁴⁶

CONCLUSIONS

Whole genome and exome sequencing has the potential to improve the care and treatment of seriously ill babies, and the NHS will use this technology increasingly in future. The consequences of sharing any additional findings with parents are not yet known, and how genomic data should be stored, accessed, and used requires further public consideration. There is ongoing debate about whether genome sequencing could be used to expand NHS newborn screening to include additional specific genetic conditions,

and how the benefits and harms of screening programmes should be weighed. Using whole genome sequencing to look opportunistically for a broad range of conditions and traits in babies who are not ill is widely thought to be unacceptable within the medical genetics community. However, some parents express a desire to receive a broad range of health-related results from whole genome sequencing and they might be able to access such results from commercial providers in the future.

REFERENCES

- 1 Faster methods of whole genome sequencing are being developed but require specialist equipment and expertise, and are currently expensive. See, for example, Miller *et al.* (2015) A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases *Genome Med* **7**: 100.
- 2 The usefulness and implications of whole genome sequencing of newborns is being explored in a US\$25 million study funded by the National Institutes of Health in the US. The [Newborn Sequencing in Genomic Medicine and Public Health \(NSIGHT\) study](#) involves four hospitals and is running for five years from 2013.
- 3 For example, the NHS clinical laboratory in Exeter offers an exome sequencing service, see www.exeterlaboratory.com/test/exome-sequencing-services.
- 4 See, for example, www.suregenomics.com and www.veritasgenetics.com/mygenome.
- 5 See: www.babygenes.net, www.mybabygenome.com, and www.veritashealthystart.com/myNewborn.
- 6 See: www.nhs.uk/conditions/pregnancy-and-baby/newborn-blood-spot-test.
- 7 Taylor-Phillips *et al.* (2014) *The ethical, social and legal issues with expanding the newborn blood spot test*, pp25-6.
- 8 See: www.genomicsengland.co.uk/the-100000-genomes-project.
- 9 Department of Health (2017) *Annual report of the Chief Medical Officer 2016: generation genome*, chapter 1.
- 10 British Society for Genetic Medicine (previously known as British Society for Human Genetics) (2010) *Report on the genetic testing of children*.
- 11 van El CG *et al.* (2013) Whole-genome sequencing in health care: recommendations of the European Society of Human Genetics *Eur J Hum Genet* **21**: S1-S5.
- 12 Kalia SS *et al.* (2017) Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics *Genet Med* **19**: 249-55.
- 13 Nuffield Council on Bioethics (2010) *Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age*.
- 14 Human Genetics Commission (2010) *A common framework of principles for direct-to-consumer genetic testing services*.
- 15 European Society of Human Genetics (2010) *Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes*.
- 16 US President's Council on Bioethics (2008) *The changing moral focus on newborn screening*; Howard HC *et al.* (2015) Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes *Eur J Hum Genet* **23**: 1593-600; Friedman JM *et al.* (2017) Genomic newborn screening: public health policy considerations and recommendations *BMC Medical Genomics* **10**: 9.
- 17 These issues are discussed extensively in the academic literature. See, for example, Wilkinson DJ *et al.* (2016) Genomic intensive care: should we perform genome testing in critically ill newborns? *Arch Dis Child-Fetal* **101**: F94-F8.
- 18 Ceyhan-Birsoy O *et al.* (2017) A curated gene list for reporting results of newborn genomic sequencing *Genet Med* **19**: 809-18; Kalia SS *et al.* (2017) Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics *Genet Med* **19**: 249-55.
- 19 See: www.genomicsengland.co.uk/taking-part/results.
- 20 [Letter from the British Society for Genetic Medicine to Sue Hill](#) (CSO England), Mark Caulfield (Chief Scientist, Genomics England) and Ellen Graham (Deputy Director, Genomics), 20 February 2018.
- 21 Fernandez CV *et al.* (2014) Attitudes of parents toward the return of targeted and incidental genomic research findings in children *Genet Med* **16**: 633-40.
- 22 Thorogood A *et al.* (2018) APPLaUD: access for patients and participants to individual level uninterpreted genomic data *Hum Genomics* **12**: 7.
- 23 Bombard Y *et al.* (2010) Reconsidering reproductive benefit through newborn screening: a systematic review of guidelines on preconception, prenatal and newborn screening *Eur J Hum Genet* **18**: 751-60.
- 24 See discussion in Taylor-Phillips *et al.* (2014) *The ethical, social and legal issues with expanding the newborn blood spot test*, pp29-31. It should be noted that whole genome sequencing cannot replace some newborn screening tests, such as the test for congenital hypothyroidism which measures hormone levels.
- 25 See, for example, Nicholls SG (2012) Proceduralisation, choice and parental reflections on decisions to accept newborn bloodspot screening *J Med Ethics* **38**: 299-303.
- 26 See, for example, FDA (2013) [Warning letter to 23andMe, Inc.](#); Nuffield Council on Bioethics (2017) *Non-invasive prenatal testing: ethical issues*, paragraphs 4.21-33.
- 27 Deem MJ (2016) Whole-genome sequencing and disability in the NICU: exploring practical and ethical challenges *Pediatrics* **137**: S47-55; Ceyhan-Birsoy O *et al.* (2017) A curated gene list for reporting results of newborn genomic sequencing *Genet Med* **19**: 809-18; Department of Health (2017) *Annual report of the Chief Medical Officer 2016: generation genome, chapter 1*.
- 28 Davis DS (2013) Opportunistic testing: the death of informed consent? *Health Matrix Clevel* **23**: 35-54.
- 29 Berg JS *et al.* (2011) Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time *Genet Med* **13**: 499.
- 30 Harrell H (2009) Currents in contemporary ethics: the role of parents in expanded newborn screening *J Law Med Ethics* **37**: 846-51.
- 31 See, for example, www.suregenomics.com and www.veritasgenetics.com.
- 32 These questions are currently being considered as part of an ESRC-funded project led by Professor Susan Kelly at the University of Exeter. See: Dheensa S *et al.* (2017) A 'joint venture' model of recontacting in clinical genomics: challenges for responsible implementation *Eur J Med Genet* **60**: 403-9.
- 33 Clarke A (2016) Genetics, genomics and society: challenges and choices, in *Genomics and society: ethical, legal, cultural and socioeconomic implications* Kumar D and Chadwick R (eds).
- 34 See, for example, Parker M and Lucassen AM (2004) Genetic information: a joint account? *BMJ* **329**: 165-7.
- 35 Montgomery J (2017) Data sharing and the idea of ownership *New Bioeth* **23**: 81-6.
- 36 Department of Health (2017) *Annual report of the Chief Medical Officer 2016: generation genome*, chapter 16.
- 37 See www.genomicsengland.co.uk/the-100000-genomesproject/data/ and www.genomicsengland.co.uk/taking-part/consent/.
- 38 Nuffield Council on Bioethics (2015) *The collection, linking and use of data in biomedical research and health care: ethical issues*.
- 39 Niemiec E and Howard HC (2016) Ethical issues in consumer genome sequencing: use of consumers' samples and data *Appl Transl Genom* **8**: 23-30.

- 40 Deem MJ (2016) Whole-genome sequencing and disability in the NICU: exploring practical and ethical challenges *Pediatrics* **137**: S47-55.
- 41 See, for example, Human Genetics Commission (2005) [Profiling the newborn: a prospective gene technology?](#); Nuffield Council on Bioethics (2017) [Non-invasive prenatal testing: ethical issues](#).
- 42 Nuffield Council on Bioethics (2007) [The forensic use of bioinformation: ethical issues](#).
- 43 See, for example, Human Genetics Commission (2002) [Inside information: balancing interests in the use of personal genetic data](#); GeneWatch (2013) [A DNA database in the NHS: your freedom up for sale?](#)
- 44 PHG Foundation (2017) [Genomics in mainstream clinical pathways](#); Samuel GN and Farsides B (2017) The UK's 100,000 Genomes Project: manifesting policymakers' expectations *New Genet and Soc* **36**: 336-53.
- 45 British Journal of Healthcare Computing (2017) [NHS England network of genomic laboratory hubs to become operational in 2018](#).
- 46 Taylor-Phillips et al. (2014) [The ethical, social and legal issues with expanding the newborn blood spot test](#).

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