The Generation Study:

Is genome sequencing good for babies?

GeneWatch UK

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In December 2022, the UK Government announced the launch of a new genetics project for England, the Newborn Genomes Program, which has now been renamed the Generation Study.[1,2] The study is run by a UK Government-owned company called Genomics England. It aims to sequence the genomes of 100,000 newborn babies. When it was launched in 2023, it was described as a pilot study which could be rolled out to all newborn babies in the future, potentially building the first DNA database of a whole population from birth.[3] Government funding for the study is confirmed until April 2025.[4]

A genome is all the chemical letters that make up a person's DNA (around 3 billion pairs). DNA occurs in every cell in a person's body (in blood, saliva, or bodily organs, for example) and is inherited (half from each of a person's biological parents). As well as containing some information that may be relevant to a person's health, whole genomes can be used like a 'genetic fingerprint' to identify people and their relatives (including non-paternity), if they are stored in a genetic database.

Many medical professionals are sceptical about the Generation Study, because they doubt it will be good for babies' health or have concerns about how the information might be misused in the future.[5,6] Underlying this is a concern that whole genome sequencing (WGS) is being rolled out to healthy babies because the technology exists – and because some hope to profit from it – rather than because it's in the best interest of these babies.[7]

This briefing highlights the key questions that the project raises.

1. Will the study help every baby taking part?

The chance that the study directly helps an individual baby is very low. This is because the genetic disorders it is looking for are very rare. The Generation Study estimates that some 500-800 children will have a positive screening result (a 'positive' result means something has been found that might mean the baby has a genetic disorder).[8] This is less than 1 in 100 participants (1,000 out of 100,000 babies in the study). This means that most babies in the study (the 99% or more that receive 'negative' results) will not be helped directly. In addition, a positive screening result does not mean that the baby necessarily has a genetic disorder or will develop any symptoms. In fact, Genomics England expects that only 4 in 500 children who receive a positive screening result using whole genome sequencing (WGS) will actually be diagnosed with a genetic disorder, with the remainder (496 out of 500 babies) receiving 'false positive' results that could lead to unnecessary further tests and perhaps unnecessary treatment (this is discussed in Section 2 below).[9] Thus, only between 4 and 6 out of 100,000 babies in the study are expected to benefit (up to 0.006%, or less than 1 in ten thousand babies tested).

2. Will the study help some babies?

"*If technology capacity is allowed to drive genetic screening activities in the absence of evidence for benefit, a growing number of asymptomatic individuals will receive a genetic diagnosis yet will remain uncertain about whether their test results represent a legitimate diagnosis, overdiagnosis, or a false positive finding. This will in turn drive additional medical work-up and treatment, resulting in costs to the healthcare system and the risk of iatrogenic* [medical] *harm*". Dr Laberge and Professor Burke. Experts in genetics and bioethics in the USA and Canada, 2017.[10]

"*It will screen 100,000 newborn genomes starting in 2024 and it's roughly estimated that will lead to about 500 positive results per annum and that will involve quite a lot of work and will emphasise the importance of clinical multi-disciplinary teams to discuss the positive results because it is estimated that it will distil down to 2 positive results a year that will truly inform monogenic* [single gene] *disease that would be fed back to parents, so there will be quite a lot of filtering of variants that occur and patients that have, if you like, false positive results – variants of unknown significance – that require discussion. That will involve clinical genetics time and genetic counsellors and it's going to be very important to evaluate that in the study to inform newborn screening using these technologies going forward. As emphasised, within this study there are going to be some confirmatory tests for some diseases, such as tandem mass spec* [spectrometry] *in inherited metabolic disease and it's going to be very important to evaluate both*…" Professor Mark Kilby, then Professor of Foetal Medicine at the University of Birmingham, a consultant in foetal medicine at Birmingham Women and Children's NHS Foundation Trust, and (at the time of speaking) a clinical scientist for medical genomic research at Illumina, discussing the Generation Study.[11,12]

A so-called 'positive' screening result would mean that a baby has been identified as having a rare genetic variant that could cause one of more than 200 rare diseases. Genetic variants include mutations (a change in a single chemical letter in the DNA), or more complex changes, such as short deletions or insertions of DNA (known as 'indels'), or structural variations (such as copy number variations, where short sections of DNA are repeated multiple times). Sometimes these genetic variants cause a genetic disorder, which can have serious symptoms or even lead to death. However, it is not straightforward to interpret what these genetic variants mean for a baby's health.

It is important that babies with rare genetic diseases are diagnosed early because this could help their treatment. But some medical professionals have serious doubts that using whole genome sequencing in a large group of healthy babies is the best way to find the children with these rare diseases.[13] The reason is that this type of testing will not give clear results about which babies are really sick, or, if they are ill, what is wrong with them. In particular, many babies without symptoms (known as 'asymptomatic') will be identified as having a possible genetic disorder, even if they don't. This is because:

- Most children with a genetic variant believed to cause disease never develop any symptoms of that disease;
- Of the babies who develop symptoms, many will have only a mild form of the condition and, in some cases, treatment could do more harm than good.

This means that babies who are identified as potentially having a genetic disorder will have extra tests and medical appointments that could lead to anxiety, uncertainty (because it may not be known whether the genetic variant found is harmful), and over-treatment (which could harm babies who would never have developed symptoms).[14] Because resources are limited, there is also concern that adding these 'asymptomatic' babies to the waiting list may compromise the time and resources available to children who are already ill.[15]

Because screening programmes can cause harm (see Box A), medical organisations have developed 'screening criteria' to try to make sure that screening programmes do more good than harm.[16] In the UK, the National Screening Committee normally does careful studies to find out whether a new test should be added to the newborn screening programme.[17] But the Generation Study is bypassing this process, so no assessment has been made of the likely benefits compared to the likely harms.

Box A: How screening can cause harm
All medical tests work much better in people with symptoms of a disease (known as diagnostic testing) and are much poorer at finding people with a specific disease in a group of healthy people (known as screening). Used in a screening programme, most medical tests will miss some cases of disease (known as 'false negatives') and find some cases of disease that don't really exist (known as 'false positives'). In addition, some people could get very mild versions of the disease that are better left untreated (finding these people is known as 'over diagnosis'). Although some people can benefit from screening programmes, because they get an early diagnosis, many other people can be harmed, due to false positives and over-diagnosis, which can lead to unnecessary anxiety and perhaps unnecessary treatment, which can cause physical harm or nasty side effects. This harm is not rare or unlikely: it is summed up in the quote "*All screening programmes do harm; some do good as well, and, of these, some do more good than harm at reasonable cost*".[18]

An important question is: what is already known about the harms of screening using whole genome sequencing (WGS)?

Many genetic disorders are known to be caused by rare genetic variants in specific genes, but finding one of these genetic variants doesn't necessarily mean a person will get sick. The 'penetrance' of a genetic variant is how likely a person with that genetic variant will actually develop the disease. When scientists looked for genetic variants only in families with symptoms of a genetic disease, they thought the penetrance of most genetic variants thought to cause diseases (so-called 'pathogenic' variants) was quite high. But now, they know that the penetrance of these genetic variants in the general population is much lower than originally thought.[19,20] This means that most people with a genetic variant thought to cause disease will never actually develop it. In addition, some people who do develop a condition will have severe symptoms whilst others will have symptoms that are mild – in some cases, these people could be harmed by 'over-treatment'. For example, rare mutations known to cause serious developmental disorders in some families lead to only mild symptoms in others.[21]

The scale of this problem is potentially enormous because most people have at least one genetic variant in one of the genes linked to single gene disorders (one of the 500 or more genes which can potentially cause a genetic disorder), that is predicted to alter the gene product.[22,23] A gene product is a biological chemical (such as a protein or a type of molecule called RNA) which plays a role in the human body. For example, one study looked at 'pathogenic' mutations and 'loss-of-function' genetic variants (thought to result in symptoms of some kind) in adults. In this study the average (mean) penetrance in the general population was only 6.9%.[24] This means that, in this study of adults, less than 7 out of 100 people with genetic variants that were expected to be harmful actually developed the expected condition. There is also evidence of the scale of this problem in studies of children. In particular, whole genome sequencing (WGS) is already used for some children with suspected genetic disorders in the NHS. One study looked at 156 cases selected because a strong genetic component was suspected but prior genetic screening had failed to identify any pathogenic (disease-causing) genetic variants.[25] It found multiple unaffected individuals with genetic variants in genes that would have been interpreted as causing a genetic disorder had those individuals presented with symptoms of the disorder in question. For

example, 96% of individuals carried at least one genetic variant in genes involved in brain development and function. The authors note, "*Every individual carries multiple rare variants that could potentially be assessed as pathogenic for a given disorder on the basis of biological information about the gene, the coding consequence of the variant and its frequency within the population*". In addition, they find that filtering out some genetic variants can lead to 'false negatives' (cases in which sick children do not receive a diagnosis). It is important to be aware that although WGS has already helped to diagnose some sick children in the NHS, it currently helps only about a third of patients tested: in most studies diagnostic yield (the proportion of patients given a diagnosis) is typically 25 to 30%, increasing to 35% if more complex genetic changes are considered.[26]

This does not mean Whole Genome Sequencing (WGS) is useless, just that it must be used with care. In particular, additional information about the child's symptoms and testing for the same genetic variants within their family are important ways to improve diagnostic accuracy.[27] Using WGS as a screening test in large numbers of healthy babies will significantly increase the number of false positives, over-diagnosis and unnecessary tests and treatments. This is because, in a screening programme, many more abnormal test results will occur in healthy babies. Thus, an important way to limit harms is to select a smaller, higher risk group of babies to have their genomes sequenced: for example, based on their symptoms or because they are thought to be at higher-than-average risk of having a genetic disorder. This is discussed further in Section 3.2.

Some studies in the USA have already looked at the problem of false positives that might be expected when using whole genome sequencing (WGS) for newborn screening. Of several different studies that have been reported, only one (the BeginNGS study) has reported attempts to reduce false positive results, restrict the findings to childhood-onset disorders, and demonstrate potential health benefits to sequencing before symptoms develop.[28] This study reports numerous conflicts-of-interest (four of the authors are employees of Illumina, see Section 7, and several are employees and or shareholders of other companies). Nevertheless, the data in the study can give some indication of the number of false positives that might be expected. The study involved developing a whole genome sequencing (WGS) method which was then tested in 4,376 critically ill children (not the mostly healthy children likely to be recruited in the Generation Study) and their parents. The authors argue that if whole genome sequencing had been used earlier in these children, symptoms could have been avoided completely in seven critically ill children in this group, and reduced in others. This study accepts that false positive results are a major problem, so it uses evidence from a study of 454,707 middle-aged people recruited from the general population (UK Biobank) to remove reports of genetic variants that appear to lead to people not showing any symptoms. In this comparison, 2,982 UK Biobank participants were found to have genetic variants relevant to 388 genetic disorders, but only 172 of these people were thought to actually have the disorder (111 with a standard diagnosis and 61 with late onset or mild disease, i.e., 172 'true positives'). To try to reduce false positives, 94 genetic variants in 338 genetic disorders were blocked and thus not reported in the diagnosis, limiting false positives in the UK Biobank population to 1,214 people.[29] By doing this, the authors hope to increase the Positive Predictive Value (PPV) of the tests. The PPV is the proportion of positive results that are true positives (i.e., the proportion of people with the genetic variant who go on to develop symptoms of the disease). After blocking the variants thought to lead to most false positives, the study reports a positive predictive value (PPV) of 12.4% for the 388 genetic disorders in the study (this is the proportion of middle-aged adults with a positive test result that they expect to show symptoms of disease). This PPV means most of the babies receiving positive results (87.6%, or nearly 9 out of ten people) will <u>not</u> go on to develop symptoms of the diagnosed disease. Although the paper argues that the real PPV may be higher, and might be increased further, this illustrates the likely scale of the problem with false positive results, even after many variants known to cause false positives have been removed from the results. In addition, this study could have missed some false positive

results because many of the mutations it is looking for are too rare to show up in UK Biobank: for the majority (206) of the 281 genes included in this comparison, no information on false positives was available.[30] This study is not able to assess the problem of false negatives, but other studies have already shown that filtering out potentially harmful genetic variants (to reduce the number of false positives, as done in this study), increases the number of false negatives (i.e., the number of babies who should receive a diagnosis but do not).[31] Thus, there is no simple answer to improving the performance of WGS in a screening programme.

To meet its own screening criteria, Genomics England has published a list of the genes and conditions it will look for in the genome sequences it collects in the Generation Study.[32] This list includes more than 200 individual conditions caused by genetic variants in around 500 different genes. Unfortunately, this list does not include a list of the genetic variants that the study will be trying to identify. Because many of the genes are different (only 201 of these genes were also included in the BeginNGS study) and the genetic variants are not identified, it is not possible to compare the Generation Study directly with the BeginNGS study results. However, there is no reason to expect any significant reduction in the number of false positive results. Before filtering out any variants, Genomics England expects that only 4 out of 500 children who receive a positive screening result using whole genome sequencing (WGS) will actually be diagnosed with a genetic disorder.[33] Most of the babies with a 'positive' test result (at least 496 babies in the study, perhaps more, because Genomics England expects 500 to 800 positive results[34]) may therefore have unnecessary tests (seeking to confirm a suspected disorder that they do not have), and some could receive unnecessary treatments that could do them harm. Although the number of false positives could be reduced by filtering out some variants in a manner similar to the BeginNGS study, this could defeat the purpose of the study by removing variants that do turn out to cause disease in some of the babies who do have one of these rare disorders (i.e., increasing the number of false negative results).

3. Are there better ways to diagnose genetic disorders in babies or young children?

Advocates of sequencing babies at birth highlight two potential benefits:

(i) Identifying some genetic disorders earlier, when (in some cases) early treatment might prevent serious harm or even death;

(ii) Shortening the long time (often years) that parents have to wait for a diagnosis for a child with a genetic disorder (known as the 'diagnostic odyssey)'.

However, there are alternative approaches that could help with both these problems, without causing the harm to healthy babies highlighted in Section 2 above, or creating a DNA database of every baby with its associated concerns (see Sections 6 and 7). This means considering the options to:

(i) improve the existing screening programme for babies at birth;

(ii) speed up diagnosis of genetic disorders in children with symptoms or at high risk.

3.1 Potential to gradually improve the screening programme for babies at birth

"..*WES [Whole Exome Sequencing] was found to have an overall sensitivity of 88% and specificity of 98.4%, compared to 99.0% and 99.8%, respectively for MS/MS* [Tandem Mass Spectrometry]*, although effectiveness varied among individual IEMs* [In-Born Errors of Metabolism]. *Thus, WES alone is insufficiently sensitive or specific to be a primary screening test for most of IEMs. As a secondary test for infants with abnormal MS/MS screening results, WES could reduce false-positive results, facilitate timely case resolution or suggest more appropriate or specific diagnosis. Hence, NGS* [Next-Generation Sequencing methods] *have a potential advantage as a second-tier screening method to verify the primary*

biochemical testing results. Nonetheless, suitability of WES or whole-genome sequencing (WGS) must be evaluated for each disorder. As a form of screening, sequencing would require weighing of benefits versus costs and societal implications". Researchers at the Institute of Bioinformatics, Bangalore, India, 2021.[35]

In the NHS, every baby is offered newborn blood spot screening, also known as the heel prick test, usually when they are 5 days old.[36] Currently, the NHS newborn screening programme looks for one of 9 rare but serious conditions.[37] These include some of the most common genetic conditions (sickle cell disease and cystic fibrosis), congenital hypothyroidism (which sometimes has a genetic cause), and some rarer conditions. These include phenylketonuria (PKU), for which early treatment can help to prevent brain damage. About 1 in 10,000 babies born in the UK has PKU or another condition included in the screening programme known as MCADD. PKU and MCADD are examples of rare genetic disorders known as Inborn Errors of Metabolism (IEMs) in which the body cannot properly turn food into energy. The other conditions in the screening programme are rarer, occurring in 1 in 100,000 to 150,000 babies. Four are IEMs and the other is Severe Combined Immunodeficiency (SCID), which causes severe problems with the baby's immune system. This screening programme uses a method known as 'tandem mass spectrometry' (MS/MS), not genetic tests.[38] This method looks for the expected chemical changes caused by the genetic variant, not for the genetic variant in the DNA itself. In some cases (children who test positive for cystic fibrosis) a genetic test is used to confirm the diagnosis. In other cases, further biochemical tests of blood and urine samples are made to confirm the diagnosis.

The existing method used in the UK newborn screening programme (tandem mass spectrometry) could be expanded to identify up to 50 conditions, although it is not suitable for all conditions.[39,40] The reason this has not been done relates to doubts about the benefits versus harms of screening for a large number of rare conditions.[41] This is because all types of tests can give rise to false positives and false negatives, and thus cause more harm than benefit, as described in Section 2. The established way to try to minimise this harm is to allow the National Screening Committee (NSC) to use screening criteria and evidence about each test to weigh up the benefits and harm for each condition. This means potentially expanding the newborn screening programme to include more genetic disorders at birth, if and when evidence becomes available that the benefits outweigh the risks and that this will be cost-effective. This also requires considering what treatments are available and whether they provide benefits from birth. All these aspects need to be carefully considered, specific to each condition, using existing methods (e.g., tandem mass spectrometry), or perhaps new ones. Tests can then be added to identify specific disorders, in cases where this type of screening is assessed as doing more good overall than harm. There is a particular focus on Inborn Errors of Metabolism (IEMs) because the harm caused by these conditions can often be prevented by starting a special diet as soon as possible. However, many IEMs are very rare. Recently a very rare genetic condition, which affects approximately seven babies per year in the UK, has been approved for adding to the newborn screening programme (using tandem mass spectrometry). By doing this, the NSC expects find an additional three babies a year who can be offered drug treatment and a special diet before they become symptomatic, reducing the chance of liver disease and the need for liver transplantation.[42]

Tandem mass spectrometry, like any screening test, can still lead to some false positive and false negative results. However, there are generally far fewer of these problems than if whole genome sequencing (WGS) is used.[43,44] This is not surprising because biochemical tests, such as tandem mass spectrometry, try to measure early signs of symptoms, whereas genomic tests try to perform the much more difficult task of predicting the consequences of a change in a person's DNA. In addition, tandem mass spectrometry is considerably cheaper than using whole genome sequencing, as discussed below. In general, it makes sense to use cheaper and better performing tests for screening, with more expensive tests used to

confirm a diagnosis if needed (in the much smaller number of children suspected to have a genetic disorder).

The cost of using whole genome sequencing (WGS) in a newborn screening programme is currently uncertain. However, costs have been analysed for the use of WGS to diagnose rare disease cases in a smaller group of children with symptoms. One study of such testing in Oxford (NHS England) found that each rare disease case cost £7050 per trio (child and their parents) or £2350 per genome. [45] The key cost drivers were sequencing (£4659 per case) and bioinformatics and reporting (£677). The costs might be reduced by economies of scale and bulk buying the chemicals needed, if lots of genomes were sequenced. On the other hand, costs would be increased by researching unknown variants to try to reach a diagnosis in more children. Another study by NHS Scotland has also estimated the costs of using WGS in people referred for a genetic diagnosis because they have symptoms of disease.[46] In this study, the total cost of WGS was £6625 per trio. In both these studies, money might be saved by avoiding the costs of multiple tests and perhaps missed diagnoses in children with symptoms of genetic disorders (although a recent paper does not find these expected cost savings[47]). However, in a screening programme, costs would be dominated by the costs of testing babies who do not have a genetic disorder and would not have had other unnecessary tests (more than 99% of babies tested). In 2022, there were 605,479 live births in England and Wales[48], 46,959 in Scotland[49] and 20,837 in Northern Ireland[50], making 673,275 births in the UK. Assuming a cost of £2350 per genome, sequencing every baby at birth would cost £1.58 billion a year. Additional sequencing (for example, of both a baby's parents), as well as other tests, would then be needed for those babies identified as having a potential genetic disorder.[51] This sequencing would likely still not lead to diagnoses for all children with genetic disorders and, at the same time, would leave many children diagnosed with a suspected genetic disorder who don't really have one (this is the problem with 'false negatives' and 'false positives' discussed in Section 2).

In contrast, the cost of existing newborn screening programmes, mostly based on tandem mass spectrometry, are considerably lower. For example, in Europe, the reported cost in 2011 of newborn screening programmes varied from €0.46 (40 pence) per newborn in Serbia (for two conditions) to € 43.24 per newborn (£36.61) in the Netherlands (for 17 conditions). In the UK, the marginal cost of adding four conditions to the newborn screening programme in 2014 was estimated as 50 pence per baby.[52] Additional costs are involved in delivering the results of any newborn screening programme.[53] It is also important to remember that existing newborn screening programmes cannot be replaced by WGS: this is because the screening programme includes some conditions, such as congenital hypothyroidism, which are not usually genetic and therefore cannot be diagnosed by WGS.[54] This means that the costs of the existing newborn screening programme would not be avoided by using WGS. The Generation Study will rely on a separate (additional) blood sample, taken from the umbilical cord at the baby's birth, and will have a slower turnaround time (initially 8 weeks, reducing to 2 weeks by the end of the study).[55]

In summary, using whole genome sequencing (WGS) as a screening test in healthy newborn babies means spending precious NHS resources on children who aren't sick. Although tandem mass spectrometry is far from perfect, it provides more reliable answers at less than a hundredth of the cost of WGS. Since Genomics England expects less than 1 in 100 babies to be diagnosed with a genetic disorder, more than 99% of the cost might be avoided if only children thought to have symptoms of a genetic disorder were referred for WGS. Costs could be reduced further if more specific genetic tests were used first, and whole genomes only used when existing tests fail to give an answer – this is discussed further in Section 3.2 below.

3.2 Speeding up diagnosis of genetic disorders

Many families with children who have a genetic disorder describe a long journey, often taking years, between finding out that their child as ill and getting a diagnosis. This is sometimes referred to as a 'diagnostic odyssey'. The problem of the 'diagnostic odyssey' could be reduced (but not eliminated) by improving access to better genetic testing for children who are sick.

For children with symptoms or who are at high risk, whole genome sequencing (WGS) might be one type of testing that could be made available, but this depends on what is the most effective and/or cost-effective approach to achieving faster diagnoses. In theory, WGS is already available within the NHS through the National Genomic Medicine Service.[56] However, using WGS might not be the best or most cost-effective approach and there are still practical problems and constraints due to limited resources within the NHS. Whole genome sequencing (WGS) should not be chosen automatically as the best type of test, but the pros and cons of using it should be properly weighed up.

It is important to realise that using WGS more widely would still leave many people without a diagnosis (because the cause of their condition can't be found), but it could still speed up and improve the process for some people with rare conditions.[57] More studies are still needed to work out all the pros and cons, but research – including some research by Genomics England - suggests that whole genome sequencing (WGS) could be part of the answer for children and babies with an unexplained condition, thought to be genetic, or who are in intensive care.[58] This more focused use of testing (based on better testing of children who are sick) can also take place within families, so that children and their parents, and sometimes brothers and sisters, are tested as well. This considerably improves the chance of a correct diagnosis.[59]

Whether WGS is really the best option, even for children who are sick, is yet to be determined. Another option for these children is to use a gene test panel (which only tests for specific genetic variants linked to known genetic diseases), and which could deliver similar information more cost effectively, without the need for sequencing whole genomes. For example, in Sweden, analysis begins with a gene test panel focused on medically relevant genetic variants (mutations and other genetic variants) known to be relevant to the suspected disease of the patient. If a diagnosis is still not obtained, but a rare genetic disease is still suspected, research using whole genome sequencing (WGS) can then be undertaken.[60] Another alternative is to use exome sequencing. Only part of a person's genome, called the exome, is thought to provide the instructions to make proteins, although the rest of the genome plays an important role in which proteins are expressed. In humans, the exome is about 1.5% of the genome.[61] A study by NHS Scotland (using genetic tests to diagnose sick babies, rather than screening healthy ones), found that the cost of whole genome sequencing (WGS) was around three times greater than that for exome sequencing, but using WGS gave very little added benefit in terms of diagnoses, compared to exome sequencing.[62] In all the children in the study (who had symptoms), earlier non-genetic tests had also been conducted, which played a part in finding out their diagnosis.

In the USA, a working group of the Medical Genome Initiative (which includes two employees of Illumina, see Section 7) has recommended that whole genome sequencing is used[63]:

- For babies in intensive care with an unexplained illness that might be genetic (if the test can be done fast enough);
- As an alternative to multiple single gene tests, when a patient's symptoms have a likely genetic cause but no specific disorder has been identified;
- When current gene panel tests (which test specific genes) do not include all the known genetic variants that might lead to a suspected genetic disorder;

- When patients are being treated for a non-genetic condition that might be better explained by a rare genetic diagnosis.

In other cases, the working group recommends more targeted testing of specific genes for a suspected genetic disorder, rather than using WGS. Although these recommendations should be assessed independently of any influence by the company Illumina, they illustrate how WGS might be used in a more targeted way. As well as being more cost-effective, this avoids putting the majority of healthy babies at risk of over-treatment, or creating a DNA database of the whole population, which can be open to misuse (see Sections 6 and 7).

All these approaches have the advantage that they focus the use of WGS on the small number of patients most likely to benefit. This saves precious NHS resources that can then be spent on these children's care, rather than on paying to sequence the genomes of large numbers of healthy babies. In 2023, it was reported that families of children with rare genetic disorders were being made to wait more than a year for genome sequencing results in the NHS.[64] In March 2024, only 12% of complex genetic tests (including gene panels of more than 10 genes, whole exome sequencing and whole genome sequencing) in Cambridge (one of the main centres) were being delivered within the target testing time of 84 days.[65] Yet these children (not healthy babies) are the group most likely to benefit from this type of test. In addition, the NHS Genomics Medicine Service (GMS) has been criticised for focusing too much on WGS, which is not needed by most families. A survey of professionals involved in the GMS found that a common viewpoint was that WGS had been given far too much focus by those designing the service where "*90% of the discussion are around whole genome sequencing and that makes up maybe 5% of all the work that goes on*".[66] This may reflect the role of commercial interests, discussed in Section 7.

4. Won't the study help to find out what works best?

> "*The Generation Study estimates that some 500-800 children will have a positive screening result (less than 1% of participants). For many of the conditions screened for, it is not yet known whether an early genetic diagnosis would ever result in clinically significant disease or lead to the child faring better than if the disease was detected after clinical presentation… The study as currently designed is not set up to answer these questions. It will probably prove the feasibility of detecting health relevant variants through newborn genome screening, but its design does not include a systematic way to learn whether identified babies ultimately benefitted*". Geneticists writing in the British Medical Journal, 2023.[67]

The Generation Study is using a 'technology-led' approach, which focuses on the use of whole genome sequencing (WGS) in a newborn screening programme. This 'technology led' approach has been criticised because its starting point is how to implement a particular technology, not whether this is the best approach to improving outcomes for children with genetic disorders.[68,69] There is a risk that this puts more emphasis on the interests of the company selling the technology (particularly the US company Illumina, see Section 7), than on the interests of the families involved.

The study incorporates an evaluation programme, due to report in late 2025, which will include some important information such as costs.[70] However, there are some major limitations to what this can achieve.

Firstly, the evaluation cannot fully compare the study's findings with the use of different approaches or technologies (see Section 3), since alternatives (except the *status quo*) are not part of the study (although there may be some useful data as a result of using tandem mass spectrometry as a confirmatory test for some diseases). Similarly, although the evaluation says it will follow up 'false positives', it is unlikely be able to resolve the question of whether or not children without symptoms have been wrongly diagnosed (because of the

short-term nature of the evaluation and the possibility that children might develop symptoms later).

Secondly, although the study will examine whether or not parents experience (short-term) regret about the decision they have made to take part in the study, it cannot assess the much longer-term issue of whether the children themselves will later have regrets about the storage and use of their DNA without their own knowledge or consent. These issues are discussed further in the sections below.

5. Does the study need all this genetic information?

The Generation Study is collecting whole genomes from every baby and storing them for life (and maybe longer). Only a tiny proportion of each genome (less than 0.01%, or 1 in 10,000 of the chemical letters in the DNA) will be used to try to identify a genetic disorder in the baby.[71] This means that more than 99.99% of the information that is collected from each baby is only being taken because it might be useful for research. Although the baby's whole genome sequence will be stored, if the child develops possible symptoms of a genetic disorder later on, that require investigation, this will be dealt with by re-testing within the NHS Genomics Medicine Service (GMS), rather than querying the genome that is stored (partly because sequencing technology might have improved by then).[72] Thus, the sequence that is being stored is not expected to be used in the baby's care.

5.1 Will the planned research help other babies in the future, or children growing up?

> "*Little evidence exists supporting the notion that the use of WGS for common complex disorders will result in clinically actionable information other than general health advice urging for a healthy balanced diet, doing physical activity regularly and, in general, abandoning unhealthy behaviour*". Ethicists endorsed by committees of the European Society of Human Genetics, the Human Genome Organisation, the Public Health Genomics (PHS) Foundation and the Public Population Project in Genomics (P^3G), 2015.[73]

Because most of the information is being collected for research, it is important to ask whether this could help these children, growing up, or perhaps other babies in the future. It is impossible to be certain about this, because we don't know for sure how the information might be used, or what future research might find out. However, there are reasons to be sceptical about what might be delivered, and to question why DNA for research can't be collected from adults instead, with their fully informed consent, to answer specific research questions (see Section 5.2).

We do know that research can be useful for those children who have symptoms that might mean they have a rare genetic disorder. In such cases, understanding more about which genetic variants lead to a disease can result in a diagnosis of a previously undiagnosed rare condition, which can be very important to such families.[74] More new genetic variants are expected to be discovered over time, and more will be understood about known variants (including, as described above, evidence that they may be considerably less harmful than at first believed). However, this type of research can be done without a screening programme, by involving children with symptoms of genetic disorders and their families, and, in some cases, comparing them with healthy adults with the same genetic variants.

So, what about the majority of healthy children in the study? In most cases, their genomes are not relevant to the discovery of new diagnoses of genetic disorders in children who are sick, although there may be a few exceptions in the case of children who develop genetic disorders later on (the vast majority will not). Genomics England has provided surprisingly

little information about how these stored genomes from healthy babies are expected to be used. There are three main types of research that could be involved:

- Looking for statistical links between a person's genome and how their body breaks down medicines, in order to develop tests that help to decide a person's risk of side effects or of the medicine not working (known as 'pharmacogenomic' tests).
- Looking for statistical links between numerous genetic variations in a person's genome and their risk of more complex later-onset disorders (such as heart disease, diabetes, cancers and dementia). These conditions involve a person's biology (including their genes), environment (including lifestyle) and an element of chance. This type of study (known as a Genome Wide Association Study, GWAS) might be used to develop computer algorithms to try to predict a person's risk of these conditions (known as 'polygenic risk scores', or 'integrated risk scores'), and/or it might be used as a starting point to try to find clues about what drugs might work as treatments for some of these conditions.
- Looking for statistical links between a person's genome and social and behavioural characteristics, such as intelligence or educational attainment, criminality or homosexuality, with the aim of predicting these characteristics from a person's genes.

Of these potential applications, pharmacogenomics is not controversial in principle, but is not widely used in clinical practice, despite decades of research. This is because, although many genes appear to play a role in how well drugs work, or whether they cause side effects, these differences are generally not large enough to make a noticeable difference to health outcomes or medical decisions.[75,76] In addition, it is questionable whether it is ethical to use DNA from babies to conduct this type of research (see Section 5.2), when, in most cases DNA from fully consenting adults could be used (who generally take more medications). In some cases, DNA for research could be taken (with consent) solely from specific patient groups who might benefit from this type of research (such as children with cancer). However, in the case of cancer, pharmacogenomic studies focus on the genetic changes that occur in the cancer tumour (which aren't there at birth), so a sample must in any case be collected from the tumour, not from a baby at birth.

Polygenic Risk Scores (PRSs) are computer algorithms which attempt to predict the risks of common diseases from millions of small differences in a person's DNA. They are highly controversial because of their poor predictive value and unreliability, and also because their use wrongly implies that only a subset of people (those at supposedly high genetic risk, according to the algorithm) should eat healthily, quit smoking, or avoid polluted environments.[77,78] Major improvements in public health don't need this type of research, because tackling unhealthy products, poverty and pollution does not require individual risk assessments. In fact, there is extensive evidence that the tobacco, food and other (polluting) industries promoted the shift towards genetic research and the idea of individual 'prediction and prevention' of disease, as a means to prevent controls on their products and pollution.[79,80] Integrated Risk Scores (IRSs) try to combine PGSs with other non-genetic risk factors – to decide who might be offered statins, for example - but they are also controversial because they add a lot to costs without improving health outcomes.[81]

Developing genetic risk scores to attempt to predict other characteristics such as intelligence or educational attainment, criminality or homosexuality, is highly controversial. However, there is no guarantee that such studies won't take place. For example, UK Biobank, which contains DNA from half a million adults, collected for "health-related research", has allowed studies to take place on the genetics of educational attainment and homosexuality. [82,83,84] If PRSs are used widely in medicine, it is highly likely that PRSs will also be developed for such traits, potentially leading to controversial applications outside of medicine. Many conclusions drawn from developing PRSs for complex social traits are likely to be misleading, but this doesn't mean that they won't be used.[85] There is a long history of

attempts to use claims about genetic differences to advance unjust social policies.[86] In all such cases, there is a risk that policies and resources could ultimately be decided based on genetic categories, rather than on a person's own achievements or behaviour. This problem is exacerbated because GWAS and PRSs can wrongly attribute social causes to genetic differences.[87]

Less controversially, identifying genetic variants that play a role in common diseases could identify information, such as a new drug target, that could lead to a new treatment for disease. However, despite high expectations, the number of new drugs based on new drug targets has not increased in the years since the collection of genomic data has become commonplace, suggesting this approach has not been productive, despite a few limited successes.[88] Whilst genetic information can sometimes provide clues in drug discovery, it plays a relatively small part in drug development.[89] In the field of drug discovery, "*genetics provides hints not answers*", according to one industry executive.[90] Millions of potential genetic variants have already been identified in studies using DNA from adults: the main bottleneck in delivering new treatments is understanding what these findings really mean, which requires a lot of painstaking detective work, including related laboratory work (known as 'functional genomics'), and perhaps new computational methods of analysis.[91,92] Because millions of genetic clues have already been identified in adults, but not properly investigated, this type of work does not require a new database of DNA to be collected from babies at birth, who will have no say in how their DNA is used.

All of these types of research commonly involve categorising people according to their ethnic group or into a selected number of 'genetic ancestry' groups, which is also controversial. [93,94] This is because this type of study tends to conflate race, which is a social construct, and ancestry, the genomic variation between populations, which cannot in reality be separated into distinct categories. In doing so, differences in health outcomes that may be explained by environmental or socio-economic factors (including racism) may be wrongly attributed to genetic differences.[95,96]

5.2 Is the study ethical?

"*An absolutely trivial amount of good, in terms of clinical pick-up that you can potentially do something about, will come from this programme…We already have mechanisms in place for genetic testing on babies and children who have unexplained symptoms. What the new programme is proposing is wholesale genetic sequencing of individuals who do not have anything wrong with them, and are unlikely to develop a genetic disease, and then keeping hold of their data. I am not sure how ethical all this is. We are talking about parents giving permission for researchers to take DNA from a baby where there is no pressing medical need to do so*." Geneticist Professor David Curtis, quoted in the Lancet medical journal.[97]

"*Storage of genetic information…raises a host of questions, ranging from governance and privacy protection to ensuring stability and accessibility of the data…Moreover, respect of newborns' right to privacy, right not to know and autonomy to give consent once they are of legal age suggests that storing the whole-genome sequence information for further testing in childhood is premature…*" Ethicists endorsed by committees of the European Society of Human Genetics, the Human Genome Organisation, the Public Health Genomics (PHS) Foundation and the Public Population Project in Genomics (P^3G), 2015.[98]

Researchers consider established principles when they decide whether a study is ethical. Many have doubts about the Generation Study for several different reasons. [99,100]

Standards in medical ethics require that people give "fully informed consent" to this type of study. Although parents can consent on their babies' behalf, this is limited to what is in the best interests of the child. This raises some important questions:

- Should parents really be allowed to decide to hand over their baby's whole genome, when most of this information is not needed for their babies' health?
- Are parents being misled into agreeing to the project, when testing for specific genetic disorders could be done in other, less intrusive ways, that might also give better outcomes for babies' health?
- Should agreeing to the screening tests (which might help find a genetic disorder in some babies) really be linked to agreeing to store the baby's whole genome indefinitely for research?
- Have parents really been given enough information about how their child's DNA might be misused, and who might access it in future?

It is widely agreed amongst professional ethicists that screening babies for adult-onset diseases is unethical because the child should have a choice whether to know or not when they grow up.[101] All medical testing should be done "*in the best interests of the child*", which usually means only doing tests that are needed for the baby's health. In this study, at least 99.99% of the information that is being collected is not relevant to the health of the babies in the study.[102] Although Genomics England does not plan to give predictions about the genetic risk of adult-onset conditions to the families who enrol, it is still collecting all this information. In addition, because of the limitations of whole genome sequencing (WGS) as a screening tool, most of the babies in whom a rare genetic variant is identified will not benefit, and will have the potential to be harmed, by unnecessary tests and treatments, because most rare genetic variants do not lead to symptoms (see Section 2). In cases where rare mutations lead to some mild symptoms, and there is no benefit to treatment, some people may want to know about this, whilst others will not (this is known as the "*right not to know*"). In such cases, it is generally better for the child to wait until they're older, so they can have a say in whether or not to take a genetic test.

Most of the genomic information being collected in the Generation Study is not directly relevant to the baby's health, so the main purpose of storing it is to conduct research. However, as noted in Section 5.1, Genomics England has provided almost no information to participants about what research will be done, who will be undertaking this research, and how it will deal with controversial issues such as race, or controversial topics such as the role of genetics in intelligence. The Helsinki Declaration, which applies to all medical professionals worldwide, requires research subjects to give fully informed consent to any research that they take part in.[103] Although parents can give consent on behalf of their children, this is normally limited to circumstances in which the study is in the best interests of the child. The open-ended nature of the Generation Study means that parents cannot really know how their child's genetic information will be used. This also applies to non-research uses, such as access by the police, and sharing of data with commercial companies, or overseas (see Sections 6 and 7). Data minimisation is an important principle in data protection law: this means that data collection should be limited to what is necessary for the stated purpose.[104] Yet, the Generation Study is collecting data that goes far beyond the main aim of diagnosing genetic disorders in the babies that take part.

Currently, Genomics England plans to give children a say about whether they wish to continue in the study when they reach the age of 16.[105] There is a process for withdrawal, but Genomics England can't destroy all remnants of the sample or remove data from research that has already taken place.[106] There are some serious reasons to doubt whether promises made about limiting access to stored data and samples can or will be kept in the longer term (See Section 6). Thus, parents are making what could be an irrevocable commitment to their child's whole genome sequence being stored, potentially for life. When

invited to join a genetic research project, most adults choose not to do so: for example, of the nine million people invited to take part in the UK Biobank, only 5.5% participated in the study.[107] This suggests that, given the choice, most of the babies being enrolled might not have taken part.

Because a whole genome sequence acts like a 'genetic fingerprint', it can also be used to track individuals and identify members of their family (including non-paternity). In addition, groups of people could suffer stigma or discrimination, as a result of identifying genetic differences that may or may not lead to a disease or a supposed association with, e.g., low intelligence, poor behaviour, or a particular ethnic group. Genetic information could also be misused by commercial companies: for example, for misleading marketing. These issues are discussed further below in Sections 6 and 7. There is no information about these issues on the website provided for participants, so it can be questioned whether parents are really 'fully informed' about the risks posed to future generations of collecting everybody's DNA at birth.[108]

6. Is the stored genetic information safe and could it be misused?

"*Someday we'll have a complete pedigree of the entire human population, and everybody will be connected to everybody on a huge family tree that looks like Google Maps*". Professor George Church, co-founder of the Human Genome Project, 2009.[109]

There will be no secrets about paternity anymore". Professor Sir John Sulston, 2008.[110]

"*People have to recognise that this horse is out of the barn, and that your genome probably can't be protected, because everywhere you go you leave your genome behind*." Dr Jay Flatley, CEO, Illumina, 2009.[111]

"*In the wrong hands, US genomic data poses serious risks not only to the privacy of Americans, but also to US economic and national security*". Michael J. Orlando, Director, National Counterintelligence and Security Center, 2023.[112]

Genomics England states that phase 6 of the project is, "*If the pilot is successful, implementation into NHS routine care*".[113] This would potentially mean every baby born in England having its whole genome sequenced at birth and stored in a vast database. Once started, this database would grow indefinitely, to eventually include the whole population.

A person's genome acts like a 'genetic fingerprint', also known as a biometric. A biometric is physical information (such as a fingerprint, iris scan, or DNA) that can be used to identify an individual. Because genetic information is a biometric, it can be used as an identifier, and unlike non-biometric information (such as an NHS number or password), it can't be changed if it is compromised. In addition, genetic information can identify a person's children and grandchildren, as well as non-paternity - hence security is important over the very long term. Although Genomics England says the information will be kept secure, there are several reasons to be doubtful:

- Firstly, data security may be difficult to maintain in the context of new technologies (such as quantum computing, which some believe may compromise encryption, and Artificial Intelligence, which may make it easier to deduce a person's identity from their DNA and other information). [114,115]
- Secondly, the risks of identification grow as databases grow larger, data is shared more widely (e.g., with commercial companies to do research), or genetic information is stored in medical records or returned to individuals, as might happen in the longer term.[116,117,118,119, 120,121]

- Thirdly, promises to keep the data safe can prove meaningless if the law is changed, which can happen very easily. For example, in 2024 a new Data Protection and Digital Information Bill developed by the Conservative Government was dropped because of the July election. This draft law would have ripped up current safeguards and allowed widespread sharing of genetic information – with police and commercial companies, including overseas - without people's knowledge or consent.[122] In 2009, the New Labour government tried to introduce a similar data-sharing law that was quickly dropped due to public outcry.[123]

Governments, security services and police will be able to access genetic information, although currently they will need an order from a court.[124, 125] However, as noted above, the law could easily be changed by future governments to allow police and security service access to become routine.

There is particular concern about how genetic data might be shared with foreign countries. In the USA, concerns have been raised about potential Chinese state access to the genomes of American citizens.[126] At the same time, privacy groups have warned that the US Government itself has the powers to access data on foreign citizens (including British citizens) held by US companies.[127] The risks of 'genomic surveillance' are relevant not only under foreign or authoritarian regimes but also under democracies.[128] Since genomic data is expected to be shared internationally, individuals (including political dissidents, for example) could be tracked down wherever they are, and their relatives could also be identified and targeted. This is because people leave their DNA wherever they go – for example, on a coffee cup at a meeting – and this can be used to find other information about them by matching this DNA with genetic information stored on a database (just as the police do when they use DNA databases to track criminals, using DNA left at crime scenes). In many countries, women could be in danger if non-paternity is exposed, families could be broken up, vulnerable people (such as people on witness protection schemes or fleeing domestic violence) could have their identities exposed, or powerful people could be blackmailed if children born outside marriage can be identified.[129,130] In addition, categories derived from statistical analysis of genetic data (such as 'genetic ancestry', predicted health risks, or claimed genetic propensities to certain behaviours) can lead to stigma and discrimination (see Section 4).

7. Commercial interests

There are concerns that plans to use whole genome sequencing (WGS) in screening programmes are 'technology led', i.e., this is happening just because WGS is a new technology, with powerful advocates, rather than decisions being made in the best interests of the babies involved.[131,132] An important question is: why is WGS being rolled out as a screening tool in newborn babies, when it performs less well, and is much more expensive, than alternatives (see Section 3)? A particular concern is the role that is being played by commercial interests.

Companies that sequence genomes have a vested interest in convincing politicians and investors that their technology will one day be used to sequence every individual on the planet. Genomics England has previously partnered with US company Illumina, which sells the machines and chemicals needed to produce whole genome sequences.[133] Illumina is an American company, but the sequencing for Genomics England is performed by Illumina Laboratory Services (ILS) in Cambridge, UK. The high costs of WGS described in Section 3 above are largely due to the costs of Illumina's sequencing machines and the reagents (chemicals) used to do this sequencing. Illumina has a long history of claiming that whole populations – including every baby - will inevitably have their genomes sequenced, and that this will bring great benefits to health: including dubious claims that common diseases such as diabetes and heart disease will be predicted and prevented using genetic tests.[134,135]

Illumina is one of several companies that are heavily involved in numerous studies of newborn screening using whole genome sequencing worldwide.[136] Illumina's share price has been falling (losing nearly 4/5 of its value since 2021) and the company has a clear interest in convincing its investors that the market for whole genome sequencing is whole populations, not just a subset of babies with rare genetic disorders.

In December 2022, the UK Government awarded £105 million to kickstart the Generation Study.[137] However, as shown in Section 3, at least £1.5 billion every year would be needed to sequence the genome of every baby at birth, not including the costs of feedback of results or of future research projects. It is likely this could only be delivered as a Public-Private Partnership, with commercial companies. Although some of these companies may be interested in drug discovery, others may want to control the algorithms that diagnose or predict disease, because this would give them unprecedented control over the healthcare market. Access to genomes could allow companies to identify individuals and their relatives, and perhaps to use predicted health risks as a tool for direct marketing. For example, Polygenic Risk Scores (see Section 4) could be used as a marketing tool to expand the drug market for healthy, wealthy people, rather than focusing on treating poorer people who are more likely to be sick.[138] Commercial algorithms, unlike NHS doctors, are likely to be biased towards recommending over-treatment because this is likely to be more profitable.

Other companies with a commercial interest are big data and computing companies (such as Google, Microsoft and Amazon) that are paid to store vast quantities of data in the cloud and are interested in using new computing methods (sometimes known as Artificial Intelligence, or AI) to analyse vast databases.

There is significant potential for commercial exploitation and misuse of genetic data. Because there is no public information about how data stored in the proposed database of DNA collected from babies at birth is intended to be shared and used, there is no way for parents to make informed decisions about the potential for abuse.

Conclusions

Whole genome sequencing (WGS) appears to be being rolled out to healthy babies because the technology exists – and because some hope to profit from it – rather than because it's in the best interest of these babies. Many children are likely to be harmed by the return of 'false positive' results and by the diversion of resources - from more cost-effective approaches, and from children who are sick. Alternative approaches, including much more targeted use of WGS in a small number of children, are likely to deliver greater benefits to children with genetic disorders, at lower cost, and with far fewer harms to healthy babies.

More than 99.99% of the genetic information being collected in the Generation Study is not relevant to diagnosing rare disorders but is going to be stored indefinitely for research. Although children will be asked to re-consent when they are 16, babies at birth have no say in how their genetic information is going to be used. It is unethical to take the DNA of healthy babies – who cannot give their own consent - knowing that most people would not give their DNA to such research when invited to as adults. In addition, parents have not been fully informed of the potential harms that could result, including the potential misuse of DNA to track individuals and their relatives, identify non-paternity, lead to stigma and discrimination, or be commercially exploited for misleading marketing.

GeneWatch UK
53, Milton Road, Cambridge, CB4 1XA, UK
Phone: +44 (0)330 0010507
Email: mail@genewatch.org Website: www.genewatch.org
Registered in England and Wales Company Number 03556885

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