Genomic Analysis in Children Task and Finish Group

2019 summary of recommendations

Explanatory note March 2022

In July 2017, then Chief Medical Officer Dame Sally Davies published her eighth report to government. Generation Genome looked at how genomics can improve health and prevent ill-health.

Following this, Dame Sally asked Sir Mark Caulfield, then Chief Scientist at Genomics England, to convene a group to examine in further detail the ethical and societal questions around using genomic analysis in children, and to begin to quantify the benefits and risks.

This summary provides an overview of the group's findings and recommendations which were agreed by the group over a series of meetings and subgroup meetings during 2018 and 2019. This summary document was finalised and agreed in 2019 and provides an overview of the group's work at that time. Appendix 1 of this document lists members of the group.

Genomics England published this summary in March 2022 to provide background, context and transparency to the current programme of work it is carrying out on developing a pilot research programme to explore how, and whether, to offer whole genome sequencing (WGS) to all newborns to accelerate diagnosis and access to treatments for rare genetic conditions. Further information on this programme can be found at www.genomicsengland.co.uk/newborns

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Genomic Analysis in Children Task and Finish Group

Summary and recommendations
September 2019

The Genomic Analysis in Children Task and Finish Group comprised national and international expertise in the acutely ill child and in newborn screening, ethical advisors, representation from the 100,000 Genomes Project Participants, members of learned societies and charities supporting the acutely ill children, co-authors of Generation Genome, NHS England and policymakers (membership in Appendix 1). They met on the 24th May 2018, the 13th June 2018 and subsequently, as two subgroups, focused on quantifying benefits and risks of newborn screening and examining the ethics and societal questions. This was followed by a teleconference in October 2018 and substantial further work during 2019. This summary is a result of the multiple strands of work around genomic analysis in children.

Summary recommendations

1. We strongly support whole genome sequencing in the acutely ill child

- The UK is uniquely well-placed to undertake health implementation research around whole genome sequencing (WGS) in acutely ill infants and children in the NHS and its acceptability to patients and families, which is likely to provide opportunities to inform care of the seriously ill child. We note that whole genomes are in the NHS National Test Directory for appropriate neonatal and paediatric intensive care patients and up to 20% of children may benefit from genomic analysis. As part of the Towards 5 Million Genome analysis strategy propose to reserve whole genomes for unexplained serious illness where a child is in need of intensive care and a genomic basis is possible.
- The members were clear that this health implementation research would be best done in the UK by using a similar approach to the 100,000 Genomes Project in a Research Ethics Committee approved framework, in order to maximise the number of available patients as well as build on a rapid pipeline for translation and adoption.

2. The UK is the place to evaluate whole genome sequencing in the newborn child.

- The group supports a high quality, large-scale prospective and retrospective research to create a major NHS transformation programme using whole genome sequencing for screening in newborns. Now is the moment to investigate the value of this approach given the government priority on genomics and prevention.
- The UK is uniquely placed to drive this transformation now and much of the infrastructure is in place to develop a world-leading programme. This has the potential to deliver benefit to thousands of individuals by preventing or reducing harm and we strongly support developing the evidence necessary to determine whether and how this should be introduced into clinical practice.
- An initial conservative analysis of rare inherited diseases suggested that 1 in 260 live births (2,612 children in 2017) will be affected before their fifth birthday with a condition for which WGS may have the potential to reduce or avoid harm in early life or in some cases avoid death. This could also detect a proportion of rare disease diagnosis. In some cases these children will be pre-symptomatic and may permit trials of therapeutic intervention to prevent or diminish disability. This could enable a paradigm shift to genomic prevention by deploying therapies to modify the disease before fixed disability has occurred. With the addition of adult-onset heritable conditions this would increase to 1 in 55 live births. This is without the impact of polygenic risk scores although we summarise their potential in the detailed report.

- An appropriately powered prospective study in newborns would be required to establish the effectiveness compared to screening offered as usual care (the Guthrie spot) as well as to establish its feasibility and acceptability. Our power calculations indicate that the cohort size should be 150,000-300,000.
- Sequencing of existing older cohorts including the ~28,000 individuals in the Born in Bradford and ALSPAC cohorts would also be required to explore the considerable potential to impact at later points in the life course decades. They would also assist in the modelling of different analytical approaches ad estimation of false positive rates of diagnosis.

3. The societal and ethical impact of newborn screening

- The group strongly recommend detailed further consideration, public dialogue and research into the practicalities, societal and ethical consequences of newborn screening through WGS. This will be based on patient and public engagement, building on the approaches set out in Generation Genome and the public dialogue on genomic medicine and supported by appropriate academic expertise. Drawing upon your CMO Report this could use similar approaches to the successful "Genomics Conversation".

4. The views of those affected by rare disease and their family members

- Representatives of the 100,000 Genomes Project Participant Panel strongly supported a programme in the acutely ill child, and supported initiation of a UK research programme into potential suitability of genome sequencing for newborn screening. They identified a number of important research questions they would recommend to be included.

5. The healthcare professional implications to deliver this programme.

- We did not consider in detail the implications in terms of training and education needs. We noted that much of the infrastructure and pipelines to do this at scale exist but would need some adaptation and enhancements to turnaround. We noted this programme will involve new healthcare professionals involved in antenatal and postnatal care or intensive care as well as professionals in the Genomic Medicine Service and educational programmes, workforce development and some impact assessments will be required.

6. The Health Economics and Cost Effectiveness of the newborn programme

We did work alongside the Task and Finish Group using conservative estimates for disorders where a treatment impacts substantially on mortality or morbidity within the first five years of life. The **estimated benefits are between £360,323 and £1,441,292, with impressive quality adjusted life year (QALY) gains of between 16.8 and 40.3** for each child diagnosed yielding an incremental cost effectiveness ratio (ICER) of less than £50,000, which would be considered as cost-effective. Across the proposed newborn WGS cohort conservatively **estimated cost benefit of £0.1B over ten years based on the assumption of a modest 0.24% diagnostic improvement of WGS over the current 'heel prick'**, and using £360,232 as the projected lifetime cost benefit (the bottom of the range of medical and social care costs avoided per treated child).

The following detail underpins these recommendations:

Detailed recommendations of the group

Distinguishing diagnostic from screening tests

The group emphasised the important distinction between a diagnostic test to influence the immediate healthcare of an individual who is ill and a screening test, which might warn of future risk and diagnoses, enabling a preventive strategy. It was noted that current screening programmes are approved if they lead to finding conditions that present in childhood and benefit from early interventions. Genomic screening could extend the number of such conditions tested for. If considered acceptable and desirable, it might also predict (far off) future conditions, as well as, identify familial consequences.

The group emphasised that there are important distinctions when considering the value (utility) of any test including genomics

- production of the raw sequence and the genetic variants (the **assay**)
- its analysis in a given clinical context (the **analysis** which might be for diagnostic or predictive purposes)
- the return of results (the **output**)

These elements may be temporally separated and any implementation of a genomic test needs to address the longitudinal life course implications for an individual. As new knowledge accrues, the comprehensive content of a whole genome may be revisited and interrogated for new insights into risk or disease and the healthcare consequences in terms of implementation and economics would need consideration.

Whole genome sequencing for diagnosis in the acutely ill child

The Group were strongly supportive of NHS England's Genomic Medicine Service plan to implement whole genome sequencing for diagnosis in the NHS from 2019. This will be done in a staged manner with a planned turnaround time of under 21 days aiming for ten days expected via the new Genomics England pipeline, pending contractual agreements. Opportunities for further research that could valuably draw upon the NHS England service in this area were identified, as discussed below.

The status and unmet need in the acutely ill child

There were 96,556 admissions to neonatal units in the UK in 2016, not all of which needed neonatal intensive care (NICU) and 26,500 (2015) admitted to paediatric intensive care units (PICU) in England. In the UK 2.8 neonates per 1000 live births die per year, which is the second highest mortality rate in Europe. Of those admitted to neonatal or paediatric intensive care between 5-20% are estimated to have an underlying genetic condition and a greater proportion may merit genomic testing to inform diagnosis and/or management of a possible underlying genomic disorder.

The evidence base for genomic testing in the acutely ill child

The Group heard from experts in the US and UK who summarised the evidence using a range of genomic sequencing approaches, and demonstrated that a high diagnostic yield is possible in selected populations (30-57%). A recent NHS-based study indicated that 20% of NICU and PICU patients had a serious genetic disorder that could be diagnosed by a 14-21-day turnaround whole genome trio analysis that informed clinical management (French, 2019). We evaluated the worldwide literature where some of the studies provide data to quantify the clinical impact and cost savings (Stark et al. 2018, Farnaes et al. 2018, Boukhibar et al. 2018, van Diemen et al. 2017, Meng et al. 2017, Willig et al. 2015, Soden et al. 2014).

The Group observed that these studies have been small and leave a substantial number of unanswered questions regarding the best ways to implement testing across a national health system to maximise the pace of clinical benefit and outcomes for very sick children. In spite of the limitations of study size there was early evidence of cost-effectiveness and it was clear that these programmes can be undertaken within

an ethical framework with parental or guardian support and engagement (Kingsmore et al. 2015, Perkin et al. 2015, Stark et al. 2018, Clark et al. 2018, French et al. 2019). There are a small number of UK and international studies that aim to address some of these questions but there is nowhere where this is being done across an entire health system. Investigators from most of these studies are members of the Group.

Recommendations on whole genome sequencing in the acutely ill child

There is consensus in the Group that there is a substantial and unique opportunity to address outstanding questions through a healthcare implementation research framework by augmentation of the planned NHS England service. This might be through a phased implementation focused initially on specialist NICU and PICU centres. NHS England and Genomics England can capitalise upon their proposed hybrid NHS formal documented patient choice for a genomic test alongside a Research Ethics Committee approved research opportunity. This offers the ability to longitudinally life course follow participants using electronic health data, recall participants for further research opportunities and allow access for international researchers and industry. We recommend that this offers the vital roadmap for achieving this through the planned service by NHS England and Genomics England with the NHS and appropriate academic research groups. Research opportunities identified by the group include:

- examination of the benefits of a rapid whole genome sequencing pipeline (for example circa 7-10-day turnaround or less versus 14-21 days) in both the Neonatal (NICU) and Paediatric (PICU) Intensive Care setting, especially where there is an urgency in making the diagnosis and selecting a care pathway.
- that the research programme should explore the best means of implementing such a service safely and ethically in the NHS, which could provide opportunities to inform holisticl care of the seriously ill child. This would include the identification of patients most likely to benefit from WGS and match the expectations and needs of families, particularly with regard to communicating the complexity of testing and its results to parents at what is, by its nature, a very challenging time.
- that this programme offers an opportunity for trials of new (for example, gene therapy) or repurposed therapies and offers a unique national platform for research in the seriously ill child.
- that there is a unique opportunity to couple acute genomic diagnosis of high-risk intensively children to long-term outcomes using NHS and other national record linkage in the UK.
- that experience from this programme should inform development of and provide data to inform the research into the use of whole genome sequencing as a screening test in the newborn.

Whole Genome Sequencing in the newborn for the purpose of screening

There was agreement that the application of whole genome sequencing as a screening test in every newborn child to detect potential early, middle and later life health risk would need a dedicated research programme to examine the potential scientific, clinical, political, economic, ethical and societal impacts. Implementation of technologies such as whole genome sequencing that focus on prevention and early detection are likely to increase the length of a good quality life and mitigate the potential societal cost of disease.

Recommended societal and ethical framework and public dialogue

Drawing on both Generation Genome and the recent briefing note from the Nuffield Council on Bioethics, the group discussed the societal and ethical framework in which the research would need to be developed and aspects of the public dialogue that would be required to determine the acceptability of whole genome sequencing in the well newborn. The group considered the idea of WGS analysis in newborns in two separate contexts:

1. Use of WGS as a technology in addition to or potentially to replace parts of the current NHS newborn bloodspot, physical examination or hearing screening programmes. What extra health or technical benefit there might be for the current newborn screening programme?
2. Novel uses of whole genome sequencing in newborns not currently related to the newborn screening programme.

In the first case, direct comparison of the yield and cost of the existing and new (genomic) tests would be relatively simple. The mechanisms are in place now.

The second is more complex and a national debate on these issues would be hugely helpful. This could be an extension of the "Genomic Conversation" launched after Generation Genome but focused on the new born. The work will provide valuable data and insights to inform any review of the framework and governance for newborn screening decision-making, which may need to be reassessed in light of specific considerations in implementing WGS if the technology changed (GAUK, 2019 and PHE, 2019).

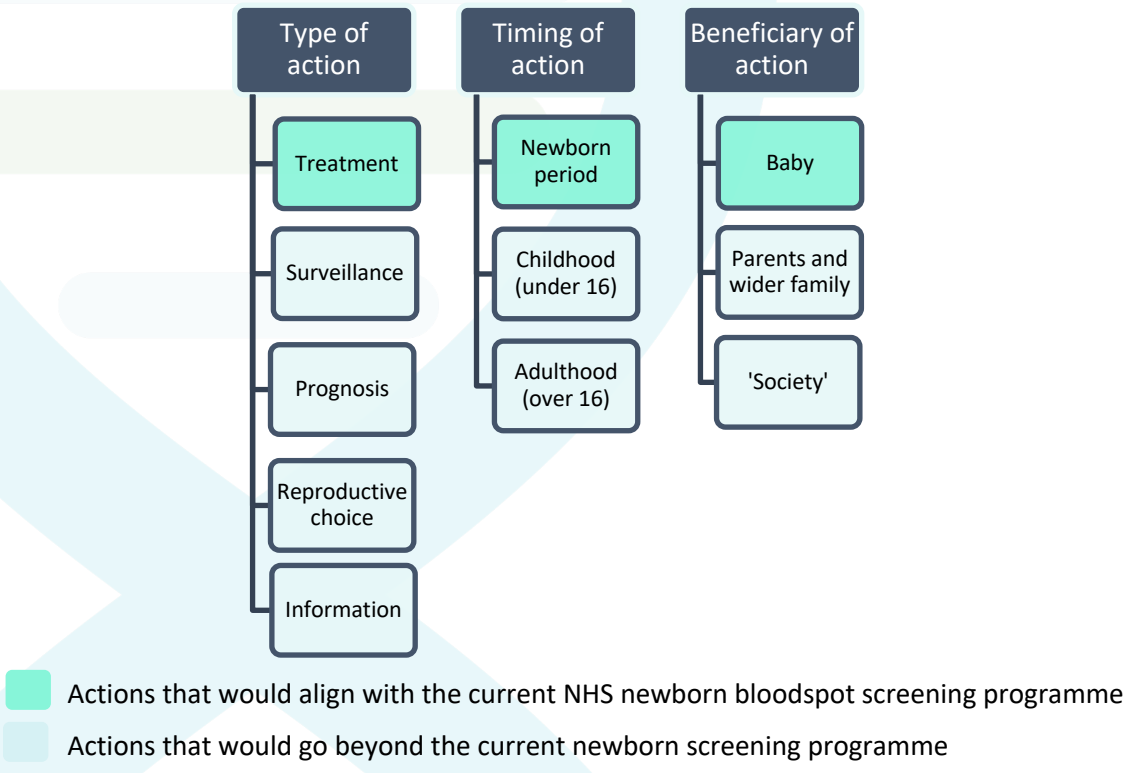
The group set out some key definitions and scenarios aimed to provide a framework for further discussion and exploration of ethical principles and public attitudes, as shown in Box 1 and Figure 1 below.

Box 1. Key definitions

Screening: in this context refers to an offer made to a citizen by the state, rather than being sought by the citizen in response to a specific anxiety or question.

Action / actionable findings: should be considered in terms of the type of action that might result, the timing of the action, and the beneficiary of or person harmed by the action (Figure 1). The extent to which parents are offered a choice in which actions result from the analysis of a sequence being generated remains for further discussion.

Figure 1. Types, timing and potential beneficiaries / persons harmed



Scenarios and additional areas of consideration

To help frame such discussions, the group also set out scenarios in terms of the pattern of analysis and reporting of findings following sampling in the newborn period (Appendix 2). It is assumed that in all scenarios, if this is a research programme, the choice for participants includes consent to data/samples being accessed for research use.

There are a wide range of questions that would need to be considered in relation to the ethical acceptability of WGS in the well newborn. These relate to the clinical utility of expanding screening, the potential impact on the child, family and wider society, and resource implications for the health and social care system. For example:

- The tension between the benefits of early and high uptake and the fact that sampling is in the newborn period, where the context would be parents of a new, assumed to be healthy baby.
- The uncertainty of genomic information such as incompletely penetrant variants (i.e. variants that do not always result in disease).
- Wider implications on health and social care system not just resourcing the 'programme'. The genome of a child may reveal things about their parents.
- What information in the genome is made available to citizens and how this is done?
- What information relevant to future health status may be made available as a 'by-product' of the programme?

The current consensus statements on genetic testing in children from the British Society of Genetic Medicine, the American Society of Human Genetics and the European Society of Human Genetics (Lucassen et al 2010, Botkin et al 2017) all emphasise the primacy of the best interests of the child. They also reinforce the importance of considering both the child's medical best interests and their best interests more broadly. As such, these statements support the use of pre-symptomatic genomic testing for conditions relevant in childhood where there is a clinical intervention of utility. Testing for conditions with adult onset remains controversial and, although there is potential for the best interests of a child to be served, much greater caution is required with arguments based upon early intervention to modify lifestyle as evidence is currently lacking in many areas.

The Group also highlighted the importance of working with others exploring the use of WGS in the context of the Newborn Screening Programme, noting the support for such a programme in the Genetic Alliance UK Newborn Screening Patient Charter Project (Genetic Alliance UK, 2019).

Public and Patient Engagement and Involvement will need to be a strong component of the programme, taking into account the findings of the Genomic Dialogue and the principles of a new Social Contract for genomics. This will also need to incorporate engaging with academic expertise in the domains of ethics and social science.

Why this newborn programme is so important for healthcare transformation in the UK.

The NHS Long term Plan and UK strategies for Prevention in the2020s.

This transformation of healthcare is anchored in the strategic priorities of the NHS Long Term Plan on early detection and is aligned with the goals of the recent government consultation paper on Prevention in the 2020s (Department of Health and Social Care, 2019). The Genetic Alliance which unites many patient-facing charities

Newborn screening may detect potential avoidable harm

The principal anticipated benefit of the programme is through the use of WGS in newborn screening to detect the potential for effective interventions. Over a lifetime approximately 6% of people (1 in 17) may

develop one of the 7,000 plus rare inherited diseases meaning that an estimated 39,947 of the 679,106 children born in 2017 (and a similar number each year) will develop a rare disease. One third of the children affected typically die before their 5th birthday.

An expert sub-group of the Genomic Analysis in Children Task and Finish Group conducted an assessment of the potential of WGS as a screening test in the newborn to prevent avoidable harm or identify where an intervention in childhood is likely to reduce disability and improve quality of life. **An initial conservative analysis of rare inherited diseases suggested that 1 in 260 live births (2,612 children in 2017) are affected with a highly penetrant condition for which identification through WGS has the potential to reduce or avoid harm in early life or in some cases avoid death.** This compares to 1 in 704 live births for the disorders included in the current newborn blood spot screening programme. **We noted that the majority of the interventions required were not expensive (e.g. vitamin B6 for syndromic epilepsy) and offered real potential to avoid or reduce expensive societal costs of disease. Only 8% of genes examined had a potentially high cost long term treatment.** The potential for over diagnosis and harm would need to be formally addressed as part of the research (see WGS of retrospective cohorts below).

There may be cost savings and earlier diagnosis in those manifesting with rare disease
Availability of genome data in individuals who have undergone newborn screening would allow its analysis for diagnostic purposes and further targeted analysis at an early stage in those with symptoms suggestive of rare disease. It will also save the wet lab costs of WGS that would otherwise be borne by the NHS (below we include new cost-benefit analysis undertaken on behalf of Genomics England).

If a newborn programme had broad uptake across the population, it would have the potential to support a substantial fraction of genome-based diagnostics in the young. From data derived from the 100,000 Genomes Project and other programmes we estimate that diagnostic whole genome sequencing would currently identify the molecular cause in between 20% (circa 6,962 children and their families per year) and circa 40% (estimated 13,925 children and their families per year) of individuals who develop a rare potentially genetic childhood disease. As a screened cohort ages, the range of uses of these data will expand.

The health economic assessment of the 100,000 Genomes Rare Disease programme will reveal the value of whole genome sequencing, but there are already instances within the programme where the number or nature of hospital outpatient episodes may be substantially reduced by earlier diagnosis.

The potential of pharmacogenomics to detect and avoid harm and reduce ineffective prescribing
Considerable harm and excess cost results from ineffective prescribing. The availability of genome data has potential healthcare **benefits that would be available to the whole screened** population rather than in disparate subgroups. These benefits are relevant from cradle to grave, for example to guide **antibiotic prescribing from the neonatal period** (avoiding aminoglycoside related hearing loss in those at risk) through to later life in those prescribed **multiple drugs in combination**.

Integration with research and clinical trials
Such a research programme would in effect become a major international resource as personal and societal impacts, outcomes, cost-effectiveness, psychological aspects and utility could be examined through the life-course as the children grow older. If the Genomics England and NHS Genomic Medicine Service consent model was utilised this would enable recall for research from a prospective database that would create opportunities for clinical research harnessing extant NIHR Infrastructure e.g. the Clinical Research Network and the BioResource.

This programme could offer a unique trial platform for testing new targeted therapies to rare diseases by identifying potential patients at an early stage of disease or before symptoms arise. The rare disease therapy market is growing and innovative therapies that prevent truncation of proteins, or modify function of a key pathway or channel e.g. treatments for cystic fibrosis are becoming a reality. This research

programme could allow us to form an Industry Rare Disease Platform for early trials of new therapies and prevention. We recommend that this be linked to discussions around subsequent access to the NHS through the Accelerated Access Collaborative.

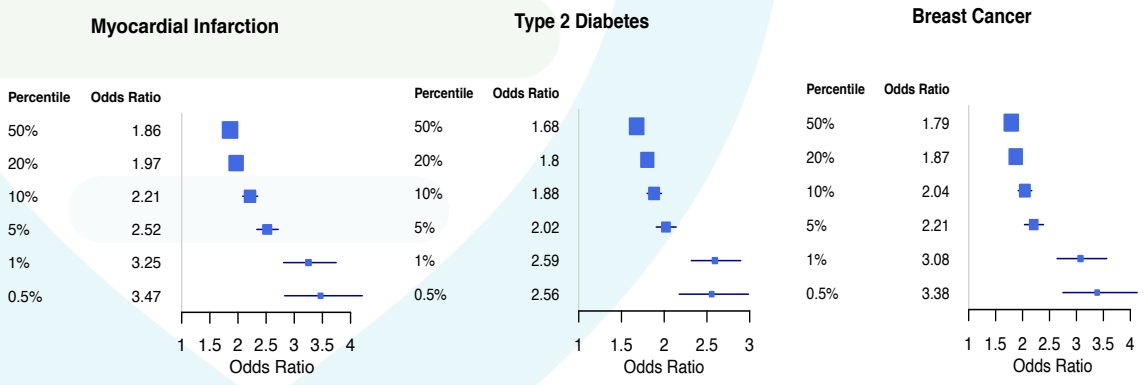
Investigation of the potential benefits and risks of polygenic risk scores in middle and later life

In later life at least 4 in 10 of us will develop cancer (365,000-400,000 incident cancers in the UK per year), 7 million people in the UK are suffering from heart disease and 850,000 are living with dementia. In some cases early knowledge of potential disease risk may enable preventive measures in some of the more common diseases. These are conditions that usually have a multifactorial origin involving multiple genes and lifestyle factors and there is growing evidence that polygenic risk scores (PRS), which aggregate the impact of many hundreds of variants associated with a specific disorder into a single score, may be becoming valuable.

Polygenic risk scores are becoming better at predicting common complex disease risk. The ability to apply such a risk score might present the opportunity to offer targeted information about choices that would impact on a healthier lifestyle in early life (teenage or earlier) that could reduce risk of these diseases at older ages. Although we do not have randomised trials of lifestyle interventions in early life we do have middle and later life assessments and in public health data the secular fall in cardiovascular disease rates with dietary change and reduced incidence of dementia with smoking cessation are evident. Longitudinal follow-up of individuals who have undergone WGS and impacts on their lifestyle choices and health would be valuable to assess evidence of impact.

To evaluate the potential of polygenic risk scores Genomics PLC curated and integrated data from multiple genome-wide association studies (GWAS) allowing generation and assessment of PRSs for 50 diseases and traits. To validate the PRS for a particular disease it was then assessed in the subset of UK Biobank of European ancestry (~340,000 individuals, referred to as the "test individuals"). Figure 1 provides results of the PRS for three common diseases: myocardial infarction; breast cancer; and type 2 diabetes. A high-level summary is that individuals with PRS scores at the top of the range across a population (in the UK, this will be a large number) can be at substantially increased risk of disease.

Figure 1. Polygenic risk scores for three common diseases (breast cancer is women only)



The application of PRS in risk prediction for common diseases will be further tested and refined in the Accelerated Detection of Disease (ADD) Cohort and other research. There will need to be consideration of these estimates and timing of description of risk but this could be an important component of the newborn screening research programme. The timing of the sharing of an individual's PRS needs careful consideration especially if the impact will be in adulthood. The complexity of the probabilistic nature of the information is well recognised. However, the opportunity to mitigate the risk of type 2 diabetes and

obesity or avoid heart attack could be a substantial contribution to public health, and could be leveraged as a collateral benefit from existing WGS data. In essence even if a different technology to WGS was eventually implemented, the principle and feasibility could be tested out in a newborn cohort with real world data.

Sequencing of a prospective newborn cohort

The proposed prospective newborn research cohort aims to establish the effectiveness compared to usual care as well as to establish its feasibility and the personal and societal impacts and to provide evidence to inform decisions about the adoption of such an approach in clinical care. The primary outcome is the number of individuals detected by the programme over and above usual care who undergo an intervention that is lifesaving or substantially impacts on morbidity (for good or bad) within the first five years of life compared to the expected natural history of their disease.

A power calculation for the cohort size required to confidently establish effectiveness was performed based on the work carried out by the Genomic Analysis in Children Task and Finish Group. As set out above, an initial conservative systematic analysis of rare inherited diseases suggested that 1 in 260 live births (2,612 children in 2017) are affected with a condition for which identification through WGS has the potential to reduce or avoid harm in early life. The impact of these interventions varies from relative amelioration of symptoms through to more radical improvements and avoidance of early death.

The power calculation also takes into account the focus on individuals with early and substantial benefit from intervention as well as the trade-off between sensitivity and specificity of what is expected to be a highly automated pipeline analysing the child's DNA alone. Although it is expected that a subset of families will be analysed as mother-father-child trios to examine the relative merits of this approach. Using the parameters set out in Appendix 3, the power calculation indicates that the cohort size should be 150,000-300,000.

Sequencing of retrospective cohorts

The Genomic Analysis in Children Task and Finish Group considered the potential value of whole genome sequencing (or analysis of available WGS data) existing retrospective cohorts (Appendix 4). Analysis these cohorts is recommended as part of the programme as it would provide data regarding the potential impact on medical outcomes later in life. It would also provide early data to model the likely true and false positive yield of different analytical approaches to inform analysis of the prospective cohort, making sequencing early in the programme preferable. Considering the changes in disease incidence over the generations, the Group recommend a focus on programmes established within the last two decades.

- Whole genome sequencing of the existing **Born in Bradford** (13,500 people) and **Avon Longitudinal Study of Parents and Children** (ALSPAC) birth cohorts (14,500 people) could be used to model the true and false positive yield of different analytical approaches and to model the potential impact on medical outcomes in later childhood and early adulthood.
- Analysis of available whole genome data from the **UK Biobank** (500,000 people) and **100,000 Genomes Project** (c.97,000 people) cohorts could be used to model the true and false positive yield of different analytical approaches and to model the potential impact on outcomes in middle and later life.

Potential timelines for the newborn screening research programme

We did not have detailed discussion on the precise timelines as we need to know some of the findings from the modelling and research proposed above. Genomics England estimate that the findings from retrospective resources could be available over the next two to five years. The power calculation for the prospective cohort has been calibrated to detect immediate medical outcomes in a five year window.

The 100,000 Genomes Projects Participants views on genomic analysis in children

At the first meeting we asked the Genomics England Participant Panel to consider the question of whole genome sequencing in the acutely ill child and in the context of research into its use in newborn screening, to give the National Genomics Board an independent view from those who are participants of the 100,000 Genomes Project (those affected and family members). The Participant Panel Chair (Jillian Hastings Ward) shared with the Participant Panel the questions we had been tasked to answer at their teleconference; there was strong support for a programme in the acutely ill child, and the group supported initiation of a UK research programme into potential suitability of genome sequencing for newborn screening. The group identified a number of research questions they would recommend to be included, concerning the health, emotional and social impacts of any change to the newborn screening programme. They have indicated their willingness to continue to provide input into the development of any future research programme. Some expressed uncertainty about whether, as parents of children who already have chronic health problems, they would wish to know about risks of additional future health problems. For similar reasons they would also wish to see the opportunity to opt out of receipt of findings for middle and later life. An additional recommendation was that in parallel with the research programme, a major public engagement programme would be very valuable.

They also supported a carefully designed public and broader participant engagement programme with involvement on an ongoing basis to fully evaluate societal views and to improve the nation's 'genomic literacy' so that future generations of parents have a better baseline understanding of Whole Genome Sequencing.

Genetic Alliance UK Patient Charter on Newborn Screening

Genetic Alliance UK have recently issued a Patient Charter on Newborn Screening in July 2019. This was independently prepared for its membership in parallel to the work of the Task and Finish Group. The charter examined the decision making process for the inclusions of disorders in the UK newborn bloodspot screening. It was also strongly supportive of a research programme to examine the potential of WGS for newborn screening as proposed by the Task and Finish Group.

The Health Economic Case for a Newborn Programme

Genomics England commissioned the Boston Consulting Group to estimate the health and economic benefits of this newborn whole genome programme taking into account the costs of such a programme because there is very limited literature in this area. They concluded that the economic benefits of a newborn programme are driven by a substantial reduction in the long diagnostic odysseys for rare disease patients within the NHS, and early interventions affording greater improvements to outcomes, drastically improving quality of life for individuals and families affected. For disorders where a treatment impacts substantially on mortality or morbidity within the first five years of life, the estimated benefits are between £360,323 and £1,441,292, with impressive quality adjusted life year (QALY) gains of between 16.8 and 40.3 for each child diagnosed. Even at the lower end of the median estimates of the benefits of identification of these disorders, there would be an incremental cost effectiveness ratio (ICER) of less than £50,000, which would be considered as cost-effective.

Across the proposed newborn WGS cohort an estimated cost benefit of £0.1B over ten years based on the assumption of a modest 0.24% diagnostic improvement of WGS over the current 'heel prick', and using £360,232 as the projected lifetime cost benefit (the bottom of the range of medical and social care costs avoided per treated child). In the best case scenario if this was rolled out across the entire UK newborn population by 2027, and a higher (but still conservative) estimate of £540,000 per treated child is applied

then a cost benefit of £0.6B could be achieved over the ten-year period (net of any incremental sequencing costs).

Concluding remarks

We are extremely grateful to Dame Sally Davies for stimulating the work of this Task and Finish Group. As set out in this summary, the group has recommendations in two areas. Firstly, the group sees great value in health implementation research around whole genome sequencing in acutely ill children in the NHS. Secondly, the group supports a high quality, large scale healthcare research programme of whole genome sequencing for screening in healthy newborns. This would be accompanied by an equally important programme of evidence generation concerning the societal and ethical consequences based on patient and public engagement, building on the approaches set out in Generation Genome and the public dialogue on genomic medicine and supported by appropriate academic expertise. Finally, our very conservative simulations on the economics of the proposed newborn programme demonstrate individual cost effectiveness with important gains in quality and life and potential ten year gain to the economy principally from released cost.

May I take the opportunity to thank the Task and Finish Group for their exceptional work, DHSC and OLS, Genomics England and finally Dame Sally Davies for her support in this important work.

Professor Sir Mark Caulfield MD FRCP FMedSci
Chair of the Genomics Analysis in Children Task and Finish Group
September 2019

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Appendix 1

Members of the Task and Finish Group

Name	Institution
Ailsa Wight	Department of Health and Social Care
Anne Mackie	Director of Programmes for the UK National Screening Committee, Public Health England
Anneke Lucassen	President, British Society for Genetic Medicine Advisor, Genomics England Ethics Advisory Committee
Augusto Rendon	Director of Bioinformatics, Genomics England
Bobbie Farsides	Brighton & Sussex Medical School
Caroline Vass	Registrar in Public Health, PHE Screening
Catherine Joynson	Assistant Director, Nuffield Council on Bioethics
Christine Patch	President, European Society of Human Genetics Clinical Lead for Genetic Counselling, Genomics England Reader of Genomic Healthcare, King's College London
David Bick	Chief Medical Officer, Hudson Alpha Institute for Biotechnology
David Dimmock	Senior Medical Director, Rady Children's Institute for Genomics Medicine
David Rowitch	Professor and Head of Paediatrics, University of Cambridge
Ellen Thomas	Clinical Lead for NHS Genomic Medicine, Genomics England
Gil McVean	Director, Oxford Big Data Institute; Founder and Director, Genomics Plc.
Hilary Angwin	National Quality Assurance Lead, Public Health England
Jackie Leach Scully	Professor of Social Ethics & Bioethics, Newcastle University
Jayne Spink	Chief Executive, Genetic Alliance UK
Jean Nicol	Screening Team, Emergency Preparedness and Health Protection Policy Global and Public Health Group, Department of Health and Social Care
Jillian Hastings Ward	Chair, Genomics England Participant Panel
John Marshall	Evidence Lead for the NHS Screening Programmes, Public Health England
Lucy Raymond	Professor of Medical Genetics and Neurodevelopment, Cambridge Institute for Medical Research
Mark Bale	Head of Science Partnerships, Genomics England Deputy Chief Scientific Adviser, Department of Health and Social Care
Mehali Patel	Senior Research Officer, Bliss (charity for babies born premature or sick)
Michael Parker	Director of Ethics and Humanities, Wellcome Centre and Director of the Ethox Centre, University of Oxford

Monika Preuss	Head of Science, Genomics and Emerging Technologies, Department of Health and Social Care
Natasha Alleyne	Department of Health and Social Care
Neena Modi	Professor of Neonatal Medicine, Imperial College London
Phil Beales	Genomics and Systems Medicine Theme Lead, Great Ormond Street Hospital Head of Genetics and Genomic Medicine, University College London
Richard Scott	Clinical Lead for Rare Diseases, Genomics England
Robert Green	Professor of Medicine (Genetics), Harvard Medical School
Ron Zimmern	Chairman, PHG Foundation
Sally Boxall	Consultant Nurse in Prenatal Diagnosis and Family Support, University Hospital Southampton NHS Foundation Trust
Stephen Kingsmore	President and CEO, Rady Children's Institute for Genomic Medicine
Sue Hill	Chief Scientific Officer, NHS England
Tom Fowler	Deputy Chief Scientist and Director of Public Health, Genomics England
Mark Caulfield	Chair, Genomics Analysis in Children Task and Finish Group Chief Scientist, Genomics England

Appendix 2. Scenarios considered by the Ethical and Societal aspects sub-group

Scenario name / summary	Used as a genomic screening test?	Parents receive feedback?	Actionable in early years?	Requires potential longer-term healthcare resources into adulthood?	Data held in perpetuity?
A: Clinical store					
A1(i): assay held in perpetuity, recontact required	-	Possibly	Possibly	No^	Yes
A1(ii): assay held in perpetuity, consent already given if clinical need arises	-	No	Possibly	No^	Yes
A2(i): assay held for limited time, recontact required	-	Possibly	Possibly	No	No
A2(ii): assay held for limited time, consent already given if clinical need arises	-	No	Possibly	No	No
B: Analyse and test for conditions*					
B1(i): conditions that fulfil criteria for 'screening' with immediately actionable results-report	Yes	Yes	Yes	Possibly	Possibly
B1(ii): conditions that fulfil criteria for 'screening' with immediately actionable results- no report	Yes	No	No	No	Possibly
C Analyse and test for 'other' information**					
C1: wider group of 'actionable' conditions; Analyse and test for 'other' no results reported	Yes	No	No	No	Possibly
C2: parents choose which results to receive	Yes	No	No	Possibly	Possibly
C3: test provider sends all results to parents	Yes	Yes	Possibly	Possibly	Possibly
C4: Analysis continues throughout life course	Yes	Yes	Possibly	Probably	Yes
D: Research only					
	No	No	No	No	Possibly
E: Current practice					
	No	No	No	No	No

*Scenario B is Use of WGS as a technology in addition to/to replace the current NHS newborn bloodspot screening programme; **Scenario C is broadly the novel uses of WGS where the issues of actionability, timing need careful consideration.

Appendix 3: Data to support power calculation for the prospective newborn cohort

- **Frequency of affected births.** The group estimates that between 1 in 410 and 1 in 617 would be affected by a disorder not part of current newborn screening for which there is a treatment that impacts substantially on mortality or morbidity within the first five years of life.
- **Sensitivity and positive predictive value of the test.** The ratio of positive predictive value to sensitivity for 10 exemplar genes was modelled using data from 55,000 non-Finnish Europeans in the gnomAD WGS data set (Table 2). This took autosomal recessive genes for which there are reliable estimates of birth prevalence in Europeans from which it is possible to infer the expected carrier frequency across all disease causing alleles for the gene. For each gene, an automated curation-driven variant prioritisation algorithm was simulated, which detected protein truncating alleles or alleles that are classified as pathogenic in ClinVar. The specificity to sensitivity ratio was then calculated for each gene by comparing the expected pathogenic allele frequency and number of candidate variants observed in the gnomAD cohort. The median ratio of expected to observed alleles, which provides a proxy of the sensitivity to positive predictive value ratio was 1.01 (range 0.59 to 1.28). The power calculation was performed using a range of ratios from 0.9 to 1.1 and positive predictive values of 0.7 to 0.9, giving sensitivities in the range of 0.57 to 0.93.

Table 2. Expected and observed allele frequency in exemplar genes used to assess the expected sensitivity to specificity ratio of an automated curation-driven variant prioritisation approach

Gene	Disease	Expected pathogenic alleles	Observed candidate alleles	Ratio of expected to observed alleles
ACADM	MCAD deficiency	1064	1352	1.271
ATP7B	Wilson disease	1024	1040	1.016
C2	C2 deficiency	778	799	1.027
CBS	CBS-related homocystinuria	191	191	1.000
CFTR	Cystic fibrosis	2200	2776	1.262
GALT	Galactosaemia	524	410	0.782
GCDH	Glutaric acidaemia	358	211	0.589
IDUA	Hurler syndrome/MPS 1	258	176	0.682
IVD	Isovaleric acidaemia	220	194	0.882
PAH	Phenylketonuria	1004	1280	1.275

- **Health and social care cost savings and QALY gains for children identified through the programme.** The group used existing health economic literature on eight exemplar disorders with an estimated combined birth incidence of 1 in 1,000 to estimate the likely health and social care cost savings and QALY gains for children identified with a severe early onset disease. The range of

estimated costs saved was £360,323 to £1,441,292 per child identified with such a disease through newborn screening by WGS. The range of estimated QALY gains was 16.8 to 40.3 per child identified with disease.

- **Costs of delivering the programme.** The cost of delivering the programme in clinical practice from 2025 was estimated using the approaches used elsewhere in the programme. These gave a range of estimated costs of £170 to £795 per child tested from sampling through to confirmation of the diagnosis (or exclusion, in the case of false positive screens).

Required sample size. Using the lower end estimates for the input parameters above, a power of 0.99 and an alpha of 0.05 the required sample size was calculated to determine with confidence whether the programme would deliver an incremental cost effectiveness ratio (ICER) of <50,000 (Ref). This gave a required sample size of 182,521.

Appendix 4: Characteristics and research questions that could be addressed using different patient cohorts

Cohort characteristics	Born in Bradford	ALSPAC	Millennium	UK Biobank	100,000 Genomes Project	National Neonatal Research Database	Prospective cohort
Description	Birth cohort	Birth cohort	Birth cohort	Age group cohort	Cancer and rare disease patients and parents	Neonatal unit cohort (ongoing)	
No. patients	13,500	14,500	19,000	500,000	70,000	1 million	
Age	Born in 2007-2010	Born in 1990s	Born in 2000-2001	40-69y in 2006-2010	All ages	Born in 2007-present	
Linked health records	Yes	Yes	Some	Yes	Yes	Regulatory approval to link	
Suitable samples and consent	Yes	Yes	Some	Yes	Yes	No	
Consent for return of results	No	No	No	No	Some ('additional findings' framework)	No	
WGS currently planned	No	No	No	Yes	Yes	No	
Suitability to model							
True and false positive yield different approaches	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcomes – early child	Yes	Yes	Yes		Some	Yes	No
Outcomes – older child	No	Yes	Yes		Some	No	No
Outcomes – middle life	No	No	No	Yes	Some	No	No
Outcomes – later life	No	No	No	Yes	Some	No	No
Feasibility – consent	No	No	No	No	No	Prospective cases	Yes
Feasibility – sampling	No	No	No	No	No	Prospective cases	Yes
Feasibility – return results	No	No	No	No	No	Prospective cases	Yes
Ability to confidently establish impact on outcomes	No	No	No	No	No	Prospective cases	Yes

- ALSPAC: Avon Longitudinal Study of Parents and Children; WGS: whole genome sequencing