Final report

Exploring the ethical dimensions of sequencing newborns' genomes: Rapid literature and evidence review

A Genomics England-commissioned report, delivered by RAND.

Katherine I. Morley, Brandi Leach, Lucy Hocking, Jessica Dawney, Zuzanna Marciniak-Nuqui, Stephanie Stockwell, Dominic Yiangou

August 2022

Table of contents

1. Introduction 4

1.1. Research context and purpose 4

1.2. Approach to this research 7

1.3. Structure of this report 11

2. Ethical concepts and frameworks used in this research 12

2.1. Ethical concepts and principles 12

2.2. Ethical frameworks 16

3. Overarching contextual factors 20

3.1. Public health considerations 23

3.2. Resource allocations 24

3.3. Regulation 24

3.4. Summary and implications for the Newborn Genomes Programme 29

4. Direct contextual factors 32

4.1. The public acceptability of, and trust in, health care and research 32

4.2. Equity in representation, access and use for the Newborn Genomes Programme 37

4.3. Implications for the Newborn Genomes Programme 43

5. Consent and decision making 47

5.1. Reliance on proxy consent from parents/carers on behalf of newborns 48

5.2. Genetic data also relates to other family members: Relational autonomy 51

5.3. Deciding if, how and at what point children should be brought into discussions around the use of their genetic data 52

5.4. Implications for the Newborn Genomes Programme 60

6. Interpreting, communicating and acting on findings 66

6.1. Determining which findings to return and when to share them 67

6.2. Managing uncertainty 72

6.3. Communicating findings 74

6.4. Acting on findings 77
6.5. Implications for the Newborn Genomes Programme 81

7. Governance and the involvement of commercial organisations 85
7.1. Governance and data use 85
7.2. Public–private partnerships and the public good 89
7.3. Implications for the Newborn Genomes Programme 91

8. Summary and areas for further investigation and consultation 94
8.2. Summary of key issues for the Newborn Genomes Programme to consider 95
8.3. Areas for further research and public consultation 102

9. References 106

10. Appendix A – Approach and methodology 121
10.1. Stage 1 – Initial literature search and screening 121
10.2. Stage 2 – Expert workshop #1 125
10.3. Stage 3 – Initial extraction and synthesis 126
10.4. Stage 4 – Thematic analysis 128
10.5. Stage 5 – Expert workshop #2 129
10.6. Stage 6 – Follow-up literature searches and synthesis 129

11. Appendix B – Examples of other potentially relevant initiatives 129

1. Introduction

1.1 Research context and purpose

1.1.1 Broad context for this research

Interest in genetic testing has significantly increased since the mapping of the human genome in 2003, offering great insight into disease risk. National Health Service (NHS) Genomic Medicine Centres have now been rolled out across England and offer tests from the NHS National Genomic Test Directory, with partner organisations in Wales, Scotland and Northern Ireland.[94] This has increased the range of tests available and made genetic tests more accessible. The current focus of these tests, and the 100,000 Genomes Project led by Genomics England, is rare diseases and cancer, and the primary objective is to reduce diagnosis time and inform treatment decisions and estimates of prognosis.[252] As part of this investment in incorporating genomics into clinical practice, Genomics England, in partnership with NHS England and NHS Improvement (NHSE/I), are conducting a research programme to investigate the use of whole genome sequencing (WGS) within a newborn screening context, as well as for wider genomics research to support new diagnostics and treatment for rare genetic conditions.

1.1.2 The Genomics England Newborn Genomes Programme

Newborn screening programmes are designed to identify babies with rare disorders that have severe consequences that can be averted or ameliorated via rapid clinical interventions.[106] In the United Kingdom, such screening is currently performed using biomarker tests, with genetic tests only used to identify specific genetic variants as part of follow-up diagnosis.[260] In contrast, WGS makes it possible to examine all the variants in an individual's genome.[106,222]

The Newborn Genomes Programme (NGP), developed by Genomics England in partnership with NHSE/I, is designed to explore through a research study whether and how WGS should be offered as part of the national newborn screening programme in the hope of accelerating diagnoses and broadening access to treatments for rare genetic conditions. If the research study is successful in generating the evidence required, it could ultimately lead to the widespread implementation of WGS for the screening of newborns in the NHS. The NGP has three interrelated aims:

1. Evaluate the scientific validity, clinical utility, feasibility of and impact on the NHS of offering WGS as a screening test for newborns soon after birth.
2. Understand how genomic and other health data of newborns generated by WGS could be used for research purposes to improve knowledge about diagnostic discovery and facilitate the development of treatments.
3. Explore the clinical utility of newborns' genome data throughout their lifetime and the implications, including risks and benefits, of the long-term storage of an individual's genome.

The NGP is a research study involving multiple stages, which started with the development of a vision for the programme that involved public and expert dialogues.[102] A co-design, planning and feasibility phase began in September 2021 and will continue through to the launch of the study, currently planned for 2023. The research study will be implemented in the NHS, and a subsequent evaluation will be carried out to inform any future decisions regarding the possible implementation of WGS in newborn screening as part of routine care in the NHS. The NGP is being designed and implemented according to a set of foundational principles and commitments, shown in Box 1.1.

Box 1.1 NGP foundational principles and commitments

1. **Patient benefit:** This not-for-profit programme will focus exclusively on delivering healthcare benefits, either directly to those who participate or indirectly to current and future patients and the NHS. The programme will drive the development of knowledge and be a resource for improved diagnosis and care within the NHS.
2. **Research ethics approval:** The programme will be designed and implemented within the NHS as an ethically robust research study with research protocol and consent documentation approved by a Research Ethics Committee.
3. **Parental choice at the initial recruitment stage:** Parents will have the choice to consent for their babies to take part in the programme and will have the option to withdraw from the study at any point. A well-resourced and best practice consent model should be developed and put in place to ensure that participants understand the implications of participation for their babies and families, and of this programme more broadly.
4. **Individual choice as babies grow up:** Participants whose parents choose to enroll them in the study at birth can withdraw at the age of 16, or earlier if they are deemed to have reached so-called "Gillick competence".
5. **Life sciences partnerships:** Collaboration is expected with both academic researchers and biotech and life sciences companies on the development of new treatments for babies whose conditions are currently untreatable. These collaborations would involve access to (not sale of) de-identified data in a Trusted Research Environment, controlled by patient representatives along the lines of the model developed for the 100,000 Genome Project.
6. **Co-designed with stakeholders:** The research study will be co-designed and supported through well-designed and comprehensive public and stakeholder engagement, ensuring transparency and openness.
7. **Evaluation and learning:** The research study should be an opportunity to learn about, identify, consider and address the ethical and social questions that arise during implementation, with the aim of informing future decisions after the research study. Learning and evaluation will take place throughout the research study and be consolidated in a dedicated phase once the pilot study is complete. This will include testing the scientific, ethical, practical and social dimensions before, during and after the pilot study, such as scientific research questions about the clinical validity and utility of WGS for newborns, research questions about the ethical and social aspects of the programme, and questions concerning the economic and practical impact of the programme on the NHS and its workforce.
8. **Without prejudice to future commissioning:** Future decisions concerning a possible nation-wide screening service offering WGS to newborns in the NHS are open and undecided, and will be informed and determined by the evidence generated by the research study.
9. **Diverse by design:** The research study design and implementation will reflect on, take into account and proactively prioritise values such as equity, diversity and inclusion, and non-discrimination, and will make efforts to ensure that the programme does not lead to any harm or potentially negative impacts on participants or the wider population.
10. **Data privacy and security:** Decisions about newborn genomic and associated health data storage, as well as who has access to it and for what purposes, should be subject to careful scrutiny by an appropriately constituted and accountable governance process, and made in the public interest.
11. **Independent ethics advisory group:** A newborn ethics advisory group with broad membership will be established to support the development of an ethical governance framework for the programme, help identify and address key ethical questions, feed into the programme design, and provide ethical oversight of the research study during the implementation phase. The programme will be designed with mechanisms in place to identify ethical challenges and considerations arising during the course of the research study, which will be reviewed and addressed by the ethics advisory group and newborns programme team in a timely way.

Initially, the NGP is envisaged as a research programme through which findings from the sequencing panel may be fed back to the NHS to inform the clinical care of babies through further confirmatory testing. Where consent is granted, newborn WGS data, in combination with other medical record data, will be stored in a repository for research uses and to explore potential future clinical uses of the genome. The research would strengthen the NGP over time by identifying additional variants and conditions that could be included as part of sequencing, and potentially facilitating the development of new treatments to allow the NGP to evolve into a hybrid clinical-research programme.[102,106,155] Hybrid clinical-research programmes focused on genomics have been implemented in multiple countries, including the United Kingdom, often under the label of "precision medicine" initiatives.[173] The programmes have sought to use genomics to improve the provision of healthcare, while using data collected from healthcare system users to support research that will lead to ongoing improvements in care. This approach is often framed as a "Learning Healthcare System" (LHS).[173] The concept of a healthcare system that integrates clinical care and clinical research is neither new nor restricted to genomics: an aspirational LHS model was originally discussed in the United States in 2007 as an approach to integrating quality improvement in routine care.[179,180] An LHS is conceptualised as having five core components[180]:

1. An embedded bidirectional feedback loop by which data collected via clinical practice are used to generate evidence that in turn improves clinical practice.
2. Integrated research and clinical practice underpinned by a commitment to using scientific evidence to improve care.
3. Infrastructure that supports the robust and efficient collection of data throughout care provision.
4. The analytical capability to use routinely collected data to address key clinical research questions.
5. A strategy for incorporating new knowledge and evidence into care provision in an efficient and timely manner.

While an LHS can be implemented by an individual care provider, it can deliver the greatest potential benefit to society through national initiatives due to the number and diversity of participants who can be recruited.[274] However, implementing a national hybrid clinical-research programme for newborn WGS screening would not be straightforward, and requires consideration of the ethical, legal, social and practical issues.[173]

1.1.3 Purpose of this research

The purpose of this research is to explore and summarise the literature regarding the ethical, legal and social issues raised by collecting WGS data from newborns for use in a research programme. This research also addresses considerations for WGS if in the future it were to be added as a screening test to the national newborn screening programme.

This research was commissioned early in the development of the NGP (January 2022). Therefore, it is not intended to provide a critique of the NGP specifically, as at the time of writing many aspects of the programme are still under development. This report provides an overview of different perspectives on the ethical, legal and social issues relating to WGS screening of newborns for research and/or clinical purposes, and identifies gaps in the literature that are potentially relevant to the NGP. It is intended to support the deliberations the Genomics England team will undertake, in conjunction with stakeholders, as the design and implementation of the NGP develops.

In this report, we have drawn out areas that may be particularly relevant to the NGP based on the current, early design of the project. This is to help support the work of Genomics England and is not intended to dictate their areas of focus. As the NGP progresses, some of these areas may become less relevant. For example, Genomics England has already taken some decisions at the early design phase of the project that circumscribe debate in some areas, such as the decision to only provide results for actionable childhood-onset conditions as part of the screening programme. Where this is the case, we have still briefly summarised the literature if it is an area of substantial debate (e.g. the types of conditions to screen for, how consent is managed).

1.2 Approach to this research

1.2.1 Aims

The findings from this work will support the development and delivery of subsequent stages of NGP design, implementation and evaluation. To this end, the research aimed to:

1. Identify values and principles relevant to genomics research and healthcare, especially in the context of newborns and newborn screening.

2. Review and discuss the role of key ethical frameworks that have been proposed or utilised in the context of newborn screening, and their possible limitations.

3. Synthesise and summarise the evidence and key arguments.

In achieving these aims we also sought to:

- Identify and share any models or proposals for adopting ethically robust approaches to key challenges identified in the conceptual framework.

- Provide an analysis and commentary of the ethical issues and their implications for those involved in designing and delivering the NGP.

This report aims to present a neutral, balanced summary of the literature to provide a basis for further deliberation and research by the Genomics England NGP team. As such, it does not aim to critique the literature in order to determine a "correct" approach to any ethical issue, nor does it indicate what Genomics England should or should not do in relation to these issues in the context of the NGP.

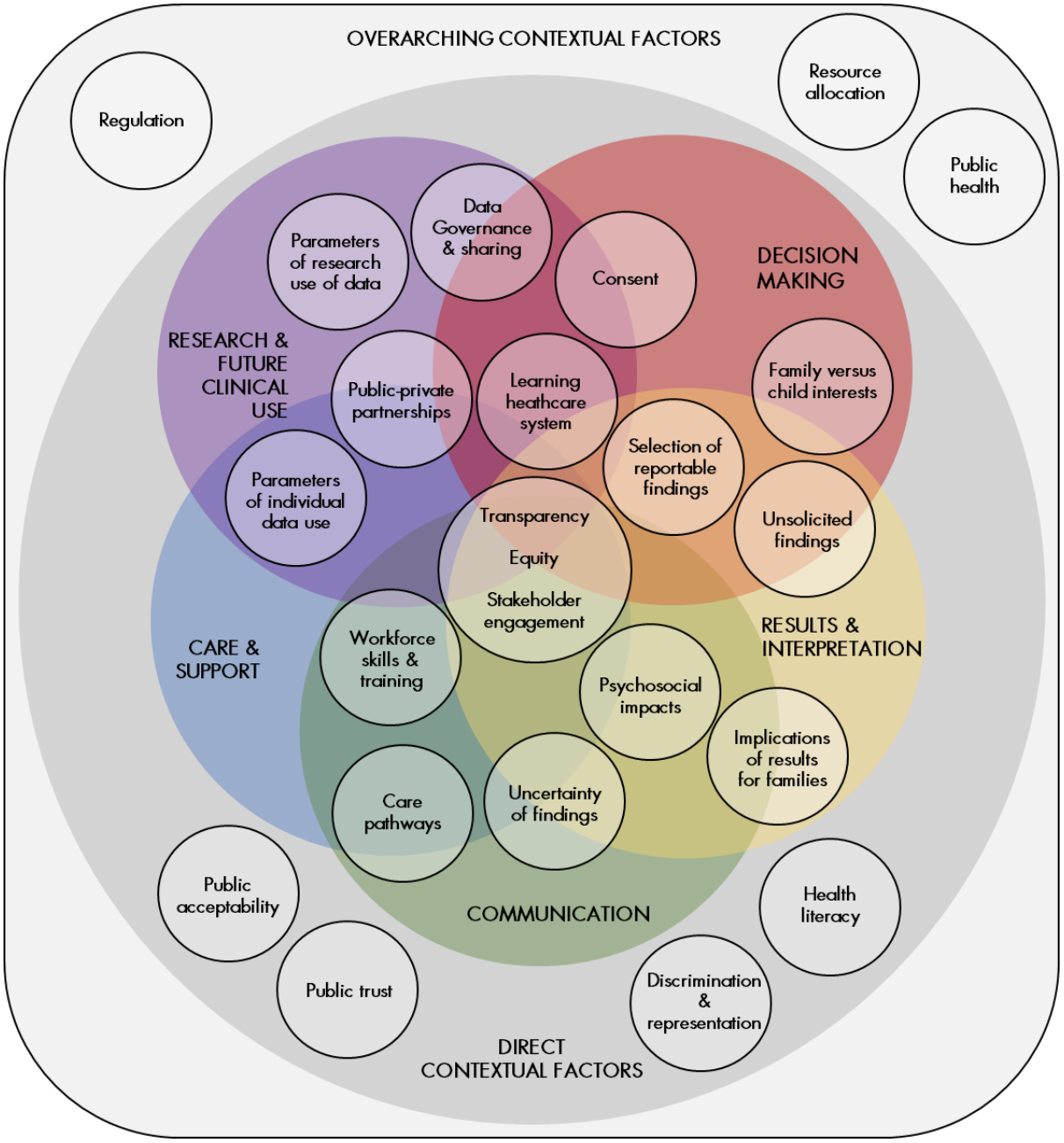
1.2.2. Conceptual framework used for this research

To guide this research, a conceptual framework was developed that maps and describes key ethical, legal and social dimensions/themes that need to be considered for the design and implementation of a programme involving WGS of newborns for research and/or clinical practice. These were grouped into seven broad but interrelated aspects, starting from the decision-making processes of potential participants (or their parents/guardians), through to the future use of the data such a programme would generate, and the broader societal context in which it would operate. This framework is intended to be generic in that it represents considerations likely to be relevant for any programme involving the use of WGS data from newborns. It provides a structure for the conduct of the literature searching and screening, data extraction and synthesis of the findings.[104]

Our conceptual mapping of the issues onto these areas was revisited and refined throughout the project, with the final version shown in **Figure 1.1**. The five coloured circles in the diagram relate to

how a newborn WGS clinical and/or research programme is developed, implemented and managed. Transparency, equity and stakeholder engagement are encompassed by all five circles as these are cross-cutting issues that need to be considered in all aspects of such a programme. More details regarding the diagram components are provided below the figure.

Figure 1.1 Mapping ethical, legal and social issues onto the seven key aspects of newborn WGS screening/research programmes



The five coloured circles in the diagram represent different groups of issues that relate to the following aspects:

- **Decision making** by parents or guardians in terms of conceptualisation of consent (including information and educational resources provided to support understanding of the programme

and manage expectations about what information it will provide), how parent/guardian interests are balanced against those of the child in this process, and management of secondary or unsolicited findings.

- **Interpreting WGS data,** including which findings are reported (and the determining criteria), and how unsolicited findings and the inherent uncertainty of some results are managed.

- **Communicating findings** not only to parents or guardians, but also to health and social care providers where needed, and in the future to the child themselves. This incorporates how the uncertainty inherent in many results is explained, how privacy and confidentiality are managed where results may be relevant for other family members, and ensuring sufficient access to clinical and counselling support to help patients' families understand the findings.

- **Provision of support and care** relates not only to the care pathways for newborns identified as having a variant/alteration associated with a condition, but also to how the NHS workforce is supported to understand and interpret WGS findings and provide appropriate care. It also includes consideration of the potential for underdiagnosis, overdiagnosis and over-treatment.

- **Future use of WGS data** includes consideration of how WGS data stored in a repository might be accessed for use in the future – who will have access, for what purposes and under what conditions.

The five overlapping aspects of a newborn WGS screening programme sit within a **broader societal context** that encompasses two sets of factors that will affect the implementation of a newborn WGS clinical and/or research programme. This report aggregates these into **overarching and direct factors** based on the degree to which the design and implementation of a programme might interact with, influence or be influenced by them. Overarching factors include public health and economic considerations, and regulations and policies that impact different aspects of the programme. Direct factors include health (and genomic) literacy, trust in researchers and clinical services regarding use of personal data, public acceptability of using genomic data for newborn screening, the potential for discrimination, and the lack of representation of minority ethnic groups in genomic research.

1.2.3. Research methods

We conducted a multi-stage review of the literature on the ethical, legal and social issues raised by the use of WGS from newborn screening in a research and/or clinical context, incorporating expert input at key stages. Full details are provided in Appendix A, with a brief summary provided below. A narrative review informed by an initial rapid evidence assessment (REA) was undertaken that provided an overview of the breadth and depth of the literature. This entailed the following components:

1. **Initial literature search and screening:** The academic literature was searched via PubMed and Scopus, and grey literature was searched via Google. Results were screened based on inclusion/exclusion criteria (Appendix A) and were mapped back to different areas of the conceptual framework for the study (see Section 1.3.2 above). Three members of the research team (KM, BL, LH) independently prioritised articles as high, medium or low priority for full text extraction based on a set of defined criteria (see Appendix A).

2. **Expert workshop #1:** Presentation to a panel of experts and members of the Genomics England team of the areas of research identified in the literature mapped to the conceptual

framework (see Appendix A). This was followed by a discussion and identification of gaps and key issues for the literature review to focus on.

3. **Initial extraction and synthesis:** Extraction of articles selected for REA was conducted by six members of the team (KM, LH, JD, ZMN, SS, DY) using a structured Excel template based on the conceptual framework. Initial review and synthesis of papers identified for the narrative review was conducted by four team members (KM, BL, LH, SS) using a software programme for qualitative text coding and analysis (MAXQDA). An initial code list for the narrative review was created based on the conceptual framework, and developed further as more documents were reviewed.
4. **Thematic analysis**: The team reviewed findings from the REA and an initial narrative review synthesis as a whole to identify key themes and areas for further research and synthesis.
5. **Expert workshop #2**: Key themes and questions identified from the thematic analysis were presented to the expert panel (as in workshop #1) and members of the Genomics England team for discussion. Findings from the workshop were summarised and used to further develop the final themes.
6. **Follow-up literature searches and synthesis:** Following the development of the key themes for the research, results from the REA and narrative review synthesis were supplemented with targeted follow-up searches (using Google Scholar and PubMed, and via snowballing).

A total of 4,960 documents were identified using a series of targeted searches of the academic and grey literature. This initial search was limited to documents published from 2017 onwards due to time constraints on the project, although no date-range restrictions were applied to additional targeted searches or snowballing. Of these, 425 documents were identified as potentially suitable for the initial REA extraction stage based on title and abstract screening. Due to the large number of documents, 115 were initially prioritised to be taken forward to full-text extraction (although the full list of articles was revisited multiple times during the research to identify additional documents on key topics). Combining the articles from the initial systematic searches and the follow-up targeted searches, 572 relevant articles were identified (although note that not all of these were ultimately directly cited in this report). The full bibliographic details of relevant articles from the systematic and targeted searches were provided to Genomics England in a separate Repository Annex.

1.2.4. Strengths and limitations of the review

The breadth of this research is both a key strength and a key limitation, with a wide range of ethical, legal and social issues relevant to the use of newborn WGS for screening and research programmes covered. However, due to the breadth of issues covered, it was not possible to explore each issue to such depth as would be needed to ensure that all possible perspectives were captured. The most prominent or commonly acceptable perspectives have been captured, but less popular or minority perspectives on some issues may have been missed by taking this broad approach.

Similarly, we restricted our initial systematic searches to documents published in the past five years. This was a pragmatic decision made to manage the large volume of literature that needed to be reviewed and the time constraints present for this project from the outset. However, many relevant documents have been published earlier and therefore not captured by our systematic search. For this reason, we did not apply date-related exclusion criteria to targeted follow-up searches and

snowballing. This approach will have partially mitigated the issue, but it is still possible that not all older, relevant documents will have been identified and included.

Finally, ensuring that narrative reviews, particularly on ethical, legal and social issues, remain objective can be challenging as they are less structured than a systematic review. To address this, we incorporated discussion and debate of our findings with experts at key points in the research process. Although this cannot completely remove the potential for bias (such a group may come to a consensus perspective that is still biased), external review and challenge can help to ensure balance in the final synthesis.

1.3 Structure of this report

This report summarises the findings from all stages of the research outlined in the previous section. The structure of the report broadly follows the conceptual framework described in Section 1.3.2, and is as follows:

- Chapter 2 provides a high-level overview of key ethical principles and values, followed by a discussion of recent frameworks proposed for exploring issues raised by precision medicine, newborn screening programmes, biobanking and learning healthcare systems.
- Chapter 3 focuses on overarching contextual factors (i.e. those unlikely to be directly influenced by an individual biobank), including public health requirements, resource allocation considerations and regulation.
- Chapter 4 focuses on direct contextual factors (i.e. those that may be directly influenced by a biobank), including public acceptability, public trust, and equity in representation, access and use.
- Chapter 5 discusses issues relating to consent and decision making.
- Chapter 6 explores the interpretation and communication of results from genomic screening and subsequent biobank-supported research, as well as how such results may be acted on.
- Chapter 7 includes a discussion of governance frameworks for genomic research and biobanking, and the involvement of commercial partners in data use via public–private partnerships.
- Chapter 8 summarises the findings from the previous chapters and outlines suggestions for further research and public consultation.

In each of Chapters 3 to 7, which address specific aspects of the use of WGS in a hybrid clinical-research programme, a final section describes the implications of the research summarised for the NGP and provides examples of approaches used in other initiatives, where relevant. These sections from each chapter are brought together in Chapter 8 so that all the findings most pertinent to the NGP are easily available.

2. Ethical concepts and frameworks used in this research

Hybrid clinical-research programmes "blur" the conventional distinction between clinical care and research, and thus raise novel ethical, legal and social challenges.[12,66,124,173,179,180,208,274] This section explores the ethical principles and frameworks that have been invoked in discussions of genomics, biobanking and LHS, and then outlines the conceptual framework for a hybrid clinical-research newborn screening programme, such as the NGP, that has informed the research presented in this report.

2.1 Ethical concepts and principles

Knoppers and Chadwick have mapped trends in ethical and legal norms relating to genetic research and clinical practice from the early days of the Human Genome Project to the current era of precision medicine.[130] In the early 1990s, areas of focus were autonomy, privacy, justice, equity and equality. Following the publication of the human genome, these somewhat individual-focused concepts were supplemented by the addition of principles with a more communal focus, including reciprocity, mutuality, solidarity, citizenry and universality. More recently, Knoppers and Chadwick have added another six principles: governance, security, empowerment, transparency, the right not to know and globalisation.[130] These concepts focus more on the operation of the system within which genomic research and clinical practice operate. These sets of principles are discussed below, with those identified by Knoppers and Chadwick supplemented with concepts that have come to the fore more recently. The shift to a more communal focus also raises issues of bias or diversity, inclusion/exclusion, or one group bearing risks while others benefit – these are not specifically referenced here as they are discussed in more detail in subsequent chapters.

2.1.1. Individual-focused principles and values

Autonomy

Autonomy is the right for individuals to make decisions for themselves, intentionally, with full understanding and without undue external influence.[59] With genetic research and testing, considerations of autonomy may be especially important given the potentially sensitive and identifiable nature of genetic information.[132] Parents typically have the authority to make decisions for their children; therefore, both the parents' autonomy to make decisions for their child and the child's autonomy, at the present time and in the future, should be considered in the context of autonomy in genomics.[59]

Respect for persons

The principle of respect for persons is closely related to the principle of autonomy, in that enabling individuals to make autonomous choices, including about research participation, is one expression of this respect.[39,138,158] However, some authors have argued that the concept of respect for persons is much broader than autonomy as it encompasses respect for a person's needs or desires, including access to their own research data.[39,138,158] It is also recognised as an essential aspect of building trust between researchers and research participants, and this broader understanding of respect for persons has influenced the development of more expansive and involved public engagement strategies.[39,138]

Privacy and confidentiality

Privacy can be conceptualised in different ways; this research defines privacy and confidentiality within the context of genomic medicine and research following Anderlik and Rothstein (2001) as they make the important distinction between privacy and confidentiality. Privacy relates to the individual and their

control over their own information and environment, whereas confidentiality relates to the duties and obligations conferred on a third party when they are entrusted with an individual's private information.[4] In genomic medicine and research, considerations of privacy and confidentiality are focused on the information contained within an individual's genome sequence. The meaningful interpretation of genomic data also requires access to information about an individual's broader health state and medical history, and thus other clinical data, either drawn from medical records or collected by researchers, also needs to be considered.[141] However, genetic information contains sensitive medical information about an individual and their family members, therefore in this context privacy concerns may include those of the individual and of their associated family members.[71,132]

Justice

Justice as a governing principle recognises the need to protect, but not exclude, vulnerable populations from genetic research and testing.[132] Its use as a governing principle implies that vulnerable populations should be included in decision making where possible. Part of protecting vulnerable groups who are not fully able to consent to participation in research or testing (e.g. newborns), is putting in place practices that prioritise their interests, such as considerations of beneficence and non-maleficence (discussed below).

Equity

The principle of equity is concerned with ensuring fair access to and use of genetic research, testing and information.[132] This includes ensuring equitable resource use and costs across population groups, and that genomic research and testing does not lead to further inequalities. For example, genetic conditions are not equally distributed across ethnic groups, and there is the potential for research programmes to place unequal burdens on ethnic groups in which certain conditions are more common.[132] There is also the potential for the stigmatisation and/or discrimination (e.g. for insurance, employment, promotion or loans) of individuals who contribute genetic data.[96,115]

Beneficence

Beneficence is the idea that people should act in the best interests of others.[59] Beneficence is an *active* obligation; in the context of research it obligates researchers to not expose participants to a greater risk than warranted given the benefits of the research, particularly for vulnerable groups such as children.[14] The duty for researchers to act in a beneficent manner is argued to derive from a moral obligation of reciprocity to give something back to the society from which one benefits.[66] Under this principle, there is a moral duty for researchers to act in a beneficent manner when individuals donate genetic samples for research purposes.[146]

Non-maleficence

The principle of non-maleficence is often summed up as "do no harm".[77,145] In clinical practice, it requires medical personnel to balance the risks and potential negative consequences of their actions or intended course of treatment against any potential benefits. Non-maleficence may indicate non-intervention as the most appropriate option.[77] In a research or hybrid clinical-research context, non-maleficence could inform decisions about who should participate, data sharing and privacy protections, and how consent is managed.[68]

Duty to warn

Within medical contexts, the "duty to warn" is the principle that there is a duty to warn patients and research participants if they are at risk of a disease.[243] Although this principle is argued to also extend to potential genetic risks for relatives,[243] the identification of risks through genetic testing places the

duty to warn in tension with other ethical principles such as privacy.[265] It has been argued that the complementary "duty to rescue" strengthens an individual's obligation to warn relatives about any shared genetic risks because the cost to that individual is likely to be less than the benefit a relative will obtain from the knowledge.[128] However, this also shifts the duty to warn or rescue from those for whom this is part of their professional duty (e.g. a doctor) to their patient, which may not be feasible or appropriate.[228] In the context of newborn genetic screening, the identification of adult onset conditions places the duty to warn in tension with the child's right to an open future and principles of autonomy and non-maleficence.[265] These issues are explored further in Chapter 5.

Right to an open future

The right to an open future is the principle that children have the right to make decisions for themselves in the future.[59,249,261] This right is derived from the principle of respect for individual autonomy, and requires withholding information about adult onset conditions to preserve individual future decision making.[59,181,249,261]

2.1.2 Community-focused principles and values

Reciprocity

The principle of reciprocity is a moral obligation to "return benefit with proportional benefit".[66] When used within a social contract framework, adherence to this principle creates the obligation for members of society to give back to their society, for example.[66] Reciprocity can also be considered in relation to a community or the population, such as when undertaking research on genetic variation on a specific sub-population.[131]

Mutuality

Mutuality is the idea that families are a distinct social unit important for ethical consideration.[131] In the case of genetic research, the concept of mutuality is useful for understanding issues around the duty to warn family members if they are at risk of developing a disease.[131] By viewing genetic information as familial information rather than individual, the principle of mutuality would grant some access to genetic information to family members for their own need.[131]

Communitarian or relational autonomy

A communitarian approach argues for a relational understanding of autonomy that recognises how a person's social context and relationships are integral to their capacity for self-determination.[55] Communitarian ethics sees individuals as embedded within social networks, where relationships with family, community and society are critical for the development of autonomy.[55] One implication of conceptualising autonomy in a relational manner is that it then encourages embracing values of mutual responsibility, cooperation and care towards others.[55] A relational autonomy approach can be helpful for resolving ethical tensions around privacy and decision making in newborn genetic testing and research by recognising that individual family members do not make decisions by themselves or in isolation, but instead often do so in consultation with trusted friends, family and healthcare professionals, all of whom could be considered to have a role in decision making.[55]

Public good

A public good approach argues that members of society have a common interest in supporting a healthcare system that provides quality health care while being compatible with competing goals of individual and economic well-being.[66] Within this perspective, it has been argued that members of society have a duty to participate in research that supports the health system, thereby contributing to

the common good, which also confers social value.[66] However, others challenge the idea that genomic research currently operates in the public interest, and therefore question whether a duty to participate in genomic research exists.[71,155,185]

Solidarity

Solidarity is a central principle of many publicly funded healthcare systems, drawing upon the idea that members of society have a responsibility to support the common good.[71] Solidarity may be invoked when describing a social contract between healthcare systems and society, and feelings of solidarity are argued to underly public trust.[71] This concept has also been used to invoke an obligation for individuals to participate in genomic research, although acting in solidarity may require more than simply supporting the common good.[185] It is only by taking the perspective of another, and through a position of sympathy and understanding to proactively "stand up beside them", that solidarity is expressed.[185,186] This latter understanding of solidarity may be especially relevant when considering ethical issues related to hybrid clinical-research systems involving newborns as it encourages solidarity with and "standing up for" those who cannot speak for themselves, such as newborns.[186]

Universality

The shift from an individual to societal or communal focus on the ethical issues surrounding genomics has brought forward the concept of the human genome as a public good.[134] This perspective of the human genome as something to be shared by all creates a principle of universality in relation to genomic research.[131] This understanding presents obligations to share the benefits of research widely, including with future generations, and embrace the view of the genome as a global public good by supporting the creation of international resources, such as publicly available databases.[131,134]

2.1.3 System-focused principles and values

Governance

Governance in health research is perceived in multiple ways, but generally refers to processes and structures implemented by actors such as researchers or funding bodies rather than the state. It relies on principles rather than law for authority to inform decisions, and encompass a broad range of actors.[143] In the United Kingdom there is no clear distinction from the state, as a substantial proportion of research involving human subjects requires approval by the Human Research Ethics Committees and Health Research Authority, which are part of the NHS.[269] Additionally, some aspects of governance, such as data protection and data sharing, are determined by government regulations.[183] However, as Hilgartner et al. (2016) argue, research and debate on the ethical, legal and social aspects of a clinical or research initiative can act as a supplement or even an alternative to regulations, and can help navigate controversies relating to governance.[98,130] Governance in the context of the use of newborn WGS in research and/or clinical practice is discussed in Chapter 0.

Security

Security in the context of genetic research relates to data security and the ethical principle of the right to be free from danger or threat.[130] Knoppers and Chadwick (2015) highlight how security issues encompass more than individual privacy concerns, and include a public interest in maintaining data security. There should also be mechanisms of accountability and procedures in place for appropriate prosecution or penalties if privacy is breached.[155]

Empowerment

Empowerment as a process or an ethical aim is about recognising people's capacity to control their quality of life and creating systems that enable people to engage, such as through greater patient and public involvement in research or patient networks that take an active role in shaping research questions and processes.[130,186] WGS of newborns may empower parents to have greater control over their child's quality of life, or empower a child to have greater control over their own health as they grow up with the additional knowledge afforded by knowing information from their genetic sequence.[186] Beyond the family unit, strategies that support members of a community to make changes with regard to the community's health and/or health care can create empowerment at a community level.[89]

Transparency and openness

The principle of transparency refers to clinical or research activities being carried out in an open manner; it is both an ethical principle and a regulatory requirement (as specified in the General Data Protection Regulation 2016/679, GDPR).[130,174] Transparency has been argued to help build the trustworthiness of institutions, especially amongst population groups that may be perceived as vulnerable, and support communities to become active participants in maintaining or improving their health.[120,137] Transparency can also refer to the principles of open science and the desirability of making research data publicly accessible, with proper controls in place to protect the privacy and autonomy rights of individuals.[130] Transparency is discussed further in Chapter 4, Section 4.1.3.

Right not to know

Under this principle, individuals have the right not to know how their genetics may influence their health. The right not to know can be considered from an individual (liberty, privacy or clinical ethics model) perspective in terms of being compelled to participate in genetic research and be informed of the results, as well as a public health perspective as an authority's right not to disclose.[181,222] This interpretation could be used to argue that children should be protected from their genetic information, particularly if not immediately actionable, until they are old enough to assert their right not to know – otherwise they cannot exercise this right.[181,186] This is one of the rights held in trust (along with the right to an open future), which are rights that should be saved for maturity but can be violated in advance, before the child can exercise them,[181] for example where sharing information will enable treatment of a serious health condition in the child or their parent, and is thus in the best interests of the child. [106]

2.2 Ethical frameworks

2.2.1 Distinguishing between research and clinical practice

A LHS formalises the increasingly blurred distinction between health care and research that is occurring across all areas of medicine as improvement and innovation increasingly become part of clinical practice.[52,105,125,155,208] Conventionally, a distinction is made between research ethics and clinical ethics – research ethics is focused on the generation of new knowledge using aggregate data from many patients and does not promise any direct benefit to participants, while clinical ethics focuses on achieving the best outcome for each patient.[179,208,274] Piasecki and Dranseika conceptualise this ethically as the "segregation model" in which researchers and clinical staff have different moral obligations toward patients, and research participation is informed and voluntary.[208] This conventional clinical ethics approach is centred on individual-focused concepts such as autonomy, privacy and liberty, with individual autonomy taking priority over other ethical principles such as social justice and collective/public benefit.[186,208]

As clinical practice and research become ever more integrated, the use of these conventional ethical frameworks becomes inadequate for the challenges raised by individuals involved in providing care also conducting clinically relevant research.[52,125,155,180,208] Piasecki and Dranseika conceptualise this as an "integration model", in which beneficence at the individual level takes priority over other ethical values, assuming that the research conducted is directly related to the treatment of the patients involved (e.g. determining which available treatment option has a better therapeutic outcome).[208] Under such a model, participant information and consent requirements are the same for research and clinical practice, although integration of research and clinical practice represents an extreme.[208] Some researchers have suggested that in practice the ethical framework required to navigate the ethical questions raised by hybrid clinical-research programmes or LHS is likely to sit somewhere between the "segregation" and "integration" models described above,[208] others have argued that it requires a completely different approach framed by beneficence at the community or population level.[7]

2.2.2. The shift from an individual to a societal focus for ethical frameworks

As discussed above, and by Knoppers & Chadwick (2015), ethical thinking around the challenges raised by genomic medicine and research has developed over the past 30 years from a focus on the individual to a focus on society.[130-132] This has occurred in parallel with applications of genomics moving from individual clinical care to biobanks and public health applications.[186] This shift has ramifications for the prioritisation of different ethical principles and values when considering the challenges presented by genomic medicine and research, and for the ethical and moral obligations placed on actors within this context. Multiple researchers have argued that focusing primarily on the individual and the primacy of autonomy and empowerment in the context of genetic medicine and research has distracted from the consideration of communities and the role of justice, equity, solidarity and public good.[13,146,186,208] There are different perspectives on how communal or societal approaches can guide thinking around the issues raised by genomics, with some of the most prominent approaches outlined below.

Revision of rights-based approaches

Ashcroft (2007) presented a critique of the standard rights-based approach to biobanking research that is focused on guarding against violations of human rights.[9] He suggests that this approach is problematic because it is primarily concerned with avoiding the negative consequences arising from eugenics, unregulated human experimentation, and the misappropriation and commercialisation of individuals' data. While important, making these the primary considerations leads to a "protection-oriented" approach to the regulation of genomic research, which Ashcroft argues is not well-suited to the actual challenges it presents. As an alternative, he promotes a "development-oriented" framework that considers a wider range of human rights, particularly economic and social rights including the *right to benefit from scientific research* and the *right to a high standard of health*. This would situate genomics as a collective endeavour that aims to maximise social benefits.[9]

Similarly, others have emphasised that human rights belong to groups as well as individuals, and can be used to promote positive action by institutions and governments, as well as ensure protection from the potential negative effects of genomic research.[133] Focusing on the *right to benefit from scientific research* and the *right to be recognised for contributing to scientific endeavours*, these researchers view the human genome as a common resource that should be shared.[13,133,134] Public health or biomedical research and the sharing of data needed to support this can thus be viewed as a public good to be prioritised over individual-focused concepts such as autonomy.[13,133]

Morrissey and Walker (2018) consider that the individual's *right not to know* and a *child's right to an open future* have roles in both clinical and public health ethics.[181] Considering these rights in the context of genomic population screening with reference to cultural health capital (see next section), they argue that focusing solely on individual rights may result in overlooking social justice questions such as the resources required for decision making, and the impact of how population screening is offered. They therefore advocate considering a social justice perspective when applying individual rights to ethical challenges raised by precision medicine.

Cultural health capital

Cultural health capital, a framework for understanding how people's cognitive, behavioural, social and cultural resources are leveraged within healthcare contexts, can be used to understand inequities in access and use.[245] It argues that these resources are context specific and that patient benefit will vary across social and organisational settings and historical periods. The concept is rooted in a hierarchical worldview that presumes unequal power between social groups within societies, with cultural health capital one avenue through which the social hierarchy is maintained. This occurs because there are systematic inequalities in the processes of acquiring and using cultural health capital that mirror existing social inequalities, and the healthcare system itself is argued to be shaped by dominant group interests in such a way as to value the cultural health capital resources of already privileged groups.[245] Cultural health capital provides an important lens for understanding disparities in health status and care; however, it has been criticised for focusing excessively on individual and group deficits, and giving insufficient weight to individual preference and autonomy.[1] This is discussed further in relation to genomics in Section 4.4.2 of Chapter 4.

Public health ethics

While multiple public health ethics frameworks exist, they are generally guided by core principles of public benefit, proportionality, equity, trust and accountability.[10,144] Many of these are shared by research ethics and clinical ethics frameworks; the key distinction is in how individual interests are balanced against those of society. The primary focus of public health ethics is promoting population rather than individual health, while ensuring a fair distribution of risks and benefits in order to reduce or remove inequalities.[10,144]

Ballantyne (2019) suggests the use of a public health ethics framework, rather than a research ethics framework, for decisions regarding the secondary use of data for biomedical research.[10] She views this approach as providing greater prominence to important considerations including the distribution of benefits and burdens within a community, power and participation in decision making, and the justification for encroaching on individual liberty for the public good. However, Ballantyne notes that this raises new ethical challenges, including the limit of risks it is acceptable to expose an individual to for the common good.[10]

Newson (2021) also takes a public health ethics approach, focusing on the principle of solidarity (subsumed within equity in Ballantyne's framework).[186] She considers the implications of this for a newborn sequencing programme, using it to highlight the shortcomings of an individual focus led by concepts such as autonomy and empowerment. In particular, she emphasises the responsibilities that

[1] Expert consultation workshop. March 2022.

an individualistic approach places on people may not always be welcome and does not consider differences in people's capacity to manage them. Newson conceives solidarity as a tool for understanding how an intervention will affect key actors and groups, and what support will be needed to implement the intervention without creating or increasing inequalities.

Social obligations and contracts

Lee frames the sharing of personal data as a "gift", and places genomic research within a societal-focus ethics framework.[146] Unlike the altruistic perspective of research participation, the gift framework conceptualises participation not as a one-off event, but as long-term relationship between the participant and the data recipient(s) characterised by mutual obligations, reciprocity and solidarity. This, Lee argues, requires demonstrating the benefits to the most vulnerable groups in society; unjust inequities in precision medicine must be addressed to maintain and increase public trust. This applies to both clinical practice and research, as whether individuals trust the healthcare system influences the degree of trust they place in research.[146] This suggests the need for new approaches to the governance of genomic research that responds to participant values and inequalities.

Winickoff and Neumann (2005) put forward a social contract for biobanks under what they label a "BioTrust Model".[270] They conceive of this as a charitable trust that supports the management of genomic resources and the governance of genomic research, while promoting community participation, representation and trust. Such an approach inherently creates obligations to use genomic resources for the benefit of those who contribute, and in the interests of the public good.[270] Lucassen et al. (2016) discuss reciprocity and the mutual obligations created by the incorporation of genomics into a nationalised healthcare service within a social contract framework.[155] The authors suggest the increasing use of genomics in health care will lead to greater integration of research and clinical practice, which would increase the importance placed on the collection and analysis of data, and lead to a greater degree of uncertainty in genomic medicine. They argue that these changes require a "re-negotiation" of the social contract between the NHS, service users and other stakeholders, particularly regarding consent, confidentiality and supporting family members, obligations of health professionals and researchers, and governance and system responsibilities.[155] Such a re-negotiation would need to be based on a shared, positive relationship, which is not present in the current system, leading to greater transparency and governance to ensure public trust. From a UK public perspective, a social contract is anticipated to be based on reciprocity, altruism and solidarity.[110] Similarly, in recent UK public dialogue on newborn genome screening, the importance of altruism was highlighted, particularly in reference to participants (and their parents) from under-represented groups helping to address existing inequalities in genomic data resources.[102] Using a social contract framework is therefore useful for exploring how society may choose to manage the challenges presented by genomic medicine and research for collective and individual rights and duties.[71]

Related to this is the concept of a "social licence", which describes the moral duty that organisations have to act responsibly, beyond what is required to comply with laws and regulations.[184] It is reliant on reciprocity, lack of exploitation and contributing to the public good, and is the permission or approval given by society for researchers to collect, use and share data.[184] Muller et al. (2021) suggest that a social contract perspective is more applicable to considerations of the state, while the social licence perspective is more useful for the consideration of private involvement in research, particularly as it can address power imbalances between research participants and those who use their data.[184]

A Learning Healthcare System ethics framework

Faden et al. (2013) set out an ethical framework for an LHS that explicitly considers the integration of research ethics and clinical ethics, and its implications from a societal perspective.[66] The foundation of their framework is two key principles: 1) a moral priority on learning; and 2) a responsibility to address unjust healthcare inequalities. These principles place the following novel obligations on all actors in a healthcare system – clinicians, researchers, administrators and patients[66]:

1. Respect the rights and dignity of patients (including family members and guardians).
2. Respect clinician judgements.
3. Provide optimal clinical care to each patient.
4. Avoid imposing non-clinical risks and burdens on patients.
5. Address unjust health inequalities.
6. Conduct continuous learning activities that improve the quality of clinical care and healthcare systems.
7. Contribute to the common purpose of improving the quality and value of clinical care and healthcare systems.

Faden et al. (2013) acknowledge that obligations 5, 6 and 7 differ substantially from traditional research ethics and clinical ethics. The **obligation to address unjust inequalities** is intended to broaden the consideration of justice from a narrow focus on the fair distribution of research benefits and burdens to a proactive consideration of how to eliminate unfair or unacceptable inequalities in the clinical evidence base, the way care is provided, and healthcare outcomes. It explicitly requires researchers, clinicians and administrators to consider whether the risks and burdens of activities will disproportionately affect those already disadvantaged. The **obligation to conduct continuous learning** is envisaged as applying to clinicians and organisations in both the public and private sectors, including private practice and pharmaceutical companies. It creates a requirement that these actors contribute to knowledge and data to support improvement of the overall system. Placing an **obligation on patients to contribute to healthcare improvement** by donating their data for research has not previously been discussed in traditional research and clinical ethics. The authors justify this through appeal to the concept of the *common good* or *common purpose*, which in this context means an obligation to participate in learning activities that can only be achieved as a collective. They differentiate this from the concept of a "duty to serve as a research subject" as it occurs in the context of an individual receiving treatment (i.e. benefit) from the system they are contributing to.

Faden et al. (2013) argue that these changes in the conceptualisation of ethical frameworks for research and clinical practice necessitated by an LHS guided by these principles can be justified based on the societal goals of: 1) creating and maintaining a just healthcare system; 2) providing high-quality health care based on the strongest available evidence; 3) ensuring economic well-being.

However, Wouters et al. (2021) suggest that the LHS ethical framework needs further refinement when applied to genomics,[274] and argue that a "precision medicine" LHS requires additional consideration for multiple reasons:

- The use of WGS means that patients are effectively being tested for more genetic variants than needed to provide high-quality care. This deviates from the LHS principles that research activities should not differ substantially from routine clinical care or present risks to a patient's health or values that exceed those of standard clinical practice.

- Genomic data could be used for research related to race and ethnicity that could lead to discrimination or stigmatisation of certain groups, even if specific individuals are not identified.

- If breaches of confidentiality occur, the familial nature of genomic data means that more individuals than the person from whom the data were derived would be affected.

In light of this, Wouters et al. (2021) put forward three areas in which considerations for precision medicine may differ from other LHS:[274]

1. Consent: A central discussion regarding LHS is whether informed consent is needed for all activities or can be waived in some circumstances. The idea of waiving consent entirely is not defensible in precision medicine LHS as patients will be exposed to an innovation that may present risks beyond standard care, and thus other approaches to managing consent are needed. To do otherwise risks using an LHS to conduct research by stealth without consent or appropriate review.

2. Independent review: Current approaches to ethical review and oversight will need to be rethought in the context of an LHS, and regarding precision medicine approaches may need to include explicit consideration of data protection.

3. Public engagement and accountability: Although consideration of unjust health inequalities is a core element of the LHS ethics framework, the underrepresentation of ethnic minority groups in genomic research needs to be explicitly addressed to avoid reinforcing existing inequities. This will require focused engagement with specific communities, as well as the general public.

Although the LHS concept was developed in the United States, which has a very different healthcare context to countries such as the United Kingdom, the LHS ethics framework potentially provides a way to harmonise the positions taken by others regarding a communal or societal approach to genomic research and medicine. As defined by Faden et al. (2013), the framework has addressing health inequalities at its core, and thus can be argued to support solidarity and reciprocity.[66,274] Barton et al. (2021) argue that an LHS approach can therefore be used to address many of the requirements put forward by Lee's framing of research participation as a "gift".[12,146] It also creates the type of mutuality and reciprocal obligations envisaged by a social contract framework. As part of these obligations are designed to ensure that individuals benefit from research, this also addresses considerations of the right to benefit from and be recognised for participation in research.

However, point 2 of the framework – respecting clinician judgements – puts great emphasis on the perspective of individual clinicians in terms of how care is designed and provided. Further modification of the framework, beyond that suggested by Wouters et al. (2021)[274], is likely to be needed to ensure that it can be used to meet the needs of an initiative such as the NGP, which is undertaken within a socialised medical system and seeks to establish and maintain long-term engagement and trust with participants and their families (see Section 4.1 below for further discussion on engagement and trust).

3. Overarching contextual factors

Chapter summary points:

Any newborn genome screening programme, whether conducted primarily for research objectives, clinical objectives, or both, will require consideration of the overall contextual factors related to public health considerations, resource allocation and regulation.

- For a newborn WGS screening programme to be adopted as a public health initiative, it must **demonstrably serve the interests of the population as a whole** and improve health outcomes. Where the primary objective is research, this is also an important consideration, as such research should contribute to decision making about implementing screening at the population level, while also providing value as a research resource.
- Related to public health requirements, a newborn WGS screening programme should be at least as **cost effective** as any existing newborn screening programme that does not use WGS, particularly if WGS is proposed to replace current practice.
- While there is **limited research on the regulation of genomic medicine** compared to the body of research on ethical issues, several areas have been highlighted that are important for newborn WGS screening research and clinical practice:
    - **Duty of care**: The degree to which all those involved in a newborn WGS screening programme, both clinicians and researchers, have a duty of care to participants/patients is currently an area of discussion. A duty of care could theoretically extend beyond those who may directly interact with a participant to include individuals or organisations who provide services or infrastructure (e.g. testing laboratories, bioinformaticians).
    - **Return of secondary or incidental results**: The principle of returning results to participants from WGS studies, whether focused on clinical practice or research, is generally agreed upon. However, what information should be returned, what constitutes best practice, and the obligations this places upon researchers to search for and share findings is still a subject of debate.
    - **Consent:** There is ongoing discussion in the United Kingdom regarding the need for consent when processing data for health and social care research versus using public interest or legitimate interest as the legal basis. The basis on which data will be used must be determined for any WGS screening programme. However, even if consent is not required for the use of a participant's data, this does not necessarily remove the need to seek ethical approval for data use.
    - **Privacy and data sharing:** Privacy and data sharing in the United Kingdom is currently very closely aligned with the European GDPR, which means that participants in a WGS screening programme have the right to request access to their data. The NHS Constitution for England also specifies that individuals have a right to be informed about how their data will be used and decide whether it is shared for research purposes. What this means in the context of a long-term research programme is open to discussion.

There is currently no definitive guidance on how to manage these issues in the UK. The development of programme-specific policies that set out how these elements will be managed has

been recommended as an interim solution. The recently proposed Learning Health Research Regulation System[23] which emphasizes a values-driven, transparent and inclusive approach, may provide a useful framework.

This section briefly discusses overarching contextual factors that affect the use of WGS of newborns in research or in a clinical or public health screening context. The factors that will have an overall impact, but which any single initiative has limited ability to alter, are public health considerations, resource allocation considerations and regulation. The chapter concludes with a discussion of the implications of the literature in this area for the design and implementation of the NGP.

3.1 Public health considerations

If WGS is implemented as part of a newborn genome screening programme it will need to satisfy the public health considerations that govern most population screening initiatives. Public health is the combination of organised efforts to prolong life expectancy and to improve the health and well-being of whole populations.[16,177] Public health screening of the population also focuses on the prevention of disease and requires wider population participation to succeed.[177] For the use of WGS in population screening to meet public health objectives, such a screening programme must be designed to serve the interests of the population at large,[52,121,182] must be cost-effective[45,211] and must be standardised across the entire population.[186]

The clinical objective of newborn screening is straightforward: identify children with treatable conditions early enough that the impact can be prevented or reduced.[70] However, its implementation is often challenging. To aid the assessment of screening for use as a public health intervention, Wilson and Jungner developed a set of criteria that included the availability of treatment and ability to detect relevant conditions at an early age as core components.[5,70] These criteria have been adapted over time – Andermann et al. (2008) provide a summary of these developments and present a set of criteria that have been updated for genomics.[5] Any assessment of newborn screening programmes, including those using WGS, will use a version of these criteria.

Box 3.1. Amalgamated screening criteria[5]

- The screening programme should respond to a recognised need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- The overall benefits of screening should outweigh the harm.
- There should be quality assurance, with mechanisms to minimise potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset

Many of these criteria are reflected in the recommendations from the Paediatric Task Team of the Global Alliance for Genomics and Health for newborn genomic screening, which focus on equity of access (to both screening and follow-up care and support), clinical actionability in childhood, and not disrupting existing newborn screening programmes.[70]

3.2 Resource allocations

Resource allocation in this context refers to decisions made about how much public money should be spent on different healthcare interventions and providers, including a newborn screening programme. A WGS newborn screening programme would cost significantly more than existing newborn screening programmes.[222,256] Generating and interpreting the data from WGS is currently resource intensive, and some healthcare providers may not have sufficient resources to devote to this activity on a population-level.[49,79,251] This raises concerns that its use will divert scarce resources from existing successful newborn screening programmes without providing equivalent benefit, although most proposals for the use of WGS in newborn screening currently propose supplementing rather than replacing existing programmes.[38,86] Programmes may also have the unintended consequence of increasing pressure in other areas of the healthcare system due to demands for follow-up diagnostics and care.[84,105,117] However, in many cases these resources would always be needed to support children who will develop the condition in question; the screening programme will just lead to earlier identification and treatment,[38,79] which may lead to a reduction in lifetime healthcare resource use.[38,79] This will need to be balanced against the resource usage generated by the diagnostic follow-up of children incorrectly identified as being at high risk of developing a condition (i.e. false positive screening results).[79,106,117] The character of these considerations depends on the specific health system and the financial, technical, human and physical resources available.[84,117]

The cost-effectiveness of conventional newborn bloodspot screening has long been assumed, although cost savings have been queried given that it leads to the need for specialised medical provisions and increased resource allocation.[258] However, any newborn screening programme using WGS is likely to be compared to existing programmes in terms of cost and outcomes to determine whether it warrants long-term investment. Using WGS as part of the diagnostic work-up for infants and children who are unwell is likely to be cost-effective,[195] and preliminary analyses suggest that a WGS newborn programme in England would be cost-effective due to costs saved via a reduction in the time it takes to receive a diagnosis.[73] Assessments of screening for specific childhood-onset illnesses have been optimistic about the cost-effectiveness of this approach, but caution that pre-emptively assessing the cost-effectiveness of a full newborn screening programme is challenging because a large number of conditions are included, the timeliness and reporting of information will vary by healthcare system, and it is difficult to quantify long-term outcomes.[85,139,262] The evaluation of pilot programmes prior to full implementation has been suggested as a route to exploring this further.[85]

3.3 Regulation

The regulation and policies of the country within which a WGS newborn screening and/or research programme takes place may define or restrict some aspects of how a programme is designed and implemented. Literature on the regulation of hybrid clinical-research systems in genomics is currently very limited and predominantly focused on the US context, which is quite different from UK and other European health system contexts. Multiple researchers have noted the lack of research on the legal issues raised by this area compared to ethical issues, particularly in important areas such as consent, duty of care and data access rights.[91,175,272,280] There are substantial differences between countries in

terms of how consent, duty of care and data access rights in the context of genomic medicine are addressed by laws and policies, and the legal questions raised by these areas are still being debated by researchers; a clear consensus has yet to emerge and is likely to be contingent on the specific details of the genomic medicine initiative in question and the country in which it is implemented.[251] This section provides a high-level summary of discussions on the regulatory aspects of key elements of a newborn genome screening programme, which are duties of clinical and non-clinical researchers to patients, return of results, consent and privacy, and data sharing. There is a focus on literature addressing the European and UK contexts where possible, but this should not be considered a conclusive legal assessment of what would be feasible for the NGP under UK law. The ethical aspects of these areas are discussed in detail in later chapters; this section only summarises the legal debate.

3.3.1 Duty of care

WGS programmes, particularly those that sit at the intersection of clinical care and research, raise legal questions regarding the duty of care that non-clinical researchers have to a patient/participant, and the duty of care that clinicians may have to the genetic relatives of a patient/participant. In this context "non-clinical researchers" can encompass not just those directly involved in the research project, but also those who provide services or infrastructure to the project (e.g. testing laboratories, bioinformaticians).[175] While many published guidelines indicate that researchers should offer clinically actionable findings to research participants,[251] some fear that this may lead to misconceptions that confuse research with clinical care.[157]

If researchers also have a therapeutic relationship with research participants, or the research is intended to affect clinical treatment or outcomes, from a legal perspective it is likely that researchers would be perceived as having a duty of care to provide information on clinically actionable genetic variants to participants, even if the variants were not the primary focus of the research study.[157,175,251] In the absence of a therapeutic relationship, whether researchers can be perceived as having a duty of care is less clear. In the United Kingdom this is likely to depend on the perceived "proximity" of the researcher and the patient, and whether such a duty can be considered "fair, just and reasonable", but there is currently no definitive guidance.[175]

It is also possible that researchers, particularly those with a therapeutic relationship with a participant, may be perceived as having a duty of care to warn a participant's relatives of clinically serious genomic variants. The applicability of this duty is currently unclear in England and Wales as the courts have so far appeared disinclined to rule that clinicians have a duty to individuals not technically their patient.[175] However, this may be dependent on the context in which the duty may apply.[175] In the United States, this duty has been found to exist, but only via a clinician advising a patient to discuss their results with their genetic relatives as direct disclosure by the clinician would require patient consent.[157]

Providing participants with results from a research study, rather than from a clinically certified laboratory, could create additional legal challenges. While multiple mechanisms operate to ensure the quality of results from research laboratories, they are not held to the same standard as clinical laboratories and may use newer techniques not yet available for clinical laboratories.[272] The potential for errors in interpreting genomic data could create a liability for clinicians and laboratories, and raises the question of whether it is reasonable to require the same quality standard of a research laboratory for which the primary purpose is not the generation of results for direct clinical use.[157,272]

3.3.2 Return of secondary or incidental results

Where genomic data are collected, stored and analysed over an extended period, the long-term approach to returning results to patients or participants needs to be considered from a legal perspective. Legal analyses of this area have focused on whether there is an expectation to return results not related to the primary purpose a sample was collected for, often called "secondary", "incidental" or "unsolicited" findings. Secondary findings are genetic variants or conditions not related to the main research or testing aims but which are actively searched for during testing, with patient consent.[150] Incidental or unsolicited findings are findings not deliberately sought by researchers, clinicians or patients but which arise unexpectedly during the course of analysis and could include findings not directly related to a health condition, such as non-paternity.[213]

If secondary and/or incidental findings are to be returned, this raises additional questions about what information should be shared, and whether a clinician or researcher can overrule a patient's desire not to receive any results (which relates to their duty of care, see Section 3.3.1 above). While there is a degree of consensus emerging around an obligation to return results, what these results should consist of and the conditions under which they should be returned are less clear. The legal perspectives on these issues are summarised in turn below, with a discussion of the ethical and social issues raised by return of results presented in Chapter 6 below.

There is broad consensus that individuals have a right to know and/or access their own data; the 2003 United Nations Educational, Scientific and Cultural Organization (UNESCO) International Declaration on Human Genetic Data and the most recent European GDPR support this, although this right is distinct from the duty a researcher may have to return results.[248,251] However, how these rights and duties are incorporated into laws and policies varies between countries. While some countries stipulate that results "must" be returned, others specify that researchers "should" or "may" return them, while others prevent any return of results.[251] Rules that specify "should" or "may" generally require results to meet certain conditions relating to whether they are clinically actionable, have analytical validity or clinical validity, and the availability of counselling support.[251] The United Kingdom takes a "should" approach, which is contingent on whether the benefits of returning the results outweigh any harm to the patient or participant.[251]

As discussed further in Chapter 6, there is also a temporal aspect to decisions regarding the return of results to patients and participants in longitudinal studies, including for secondary findings. The ongoing reinterpretation of genomic variants as knowledge evolves does not have a comparable precedent, but could present additional liability.[42,157] Currently, there are no standards regarding the duty of clinicians or researchers to re-analyse the genomes of patients and participants.[157,175] Mitchell et al. (2017) suggest that as WGS becomes a more standard part of clinical care, a duty of care to return secondary findings may become established, which may lead to changes in what is considered the accepted standard of clinical practice.[42,175] Liability could then result from a lack of identifying and sharing secondary findings.[42] Additionally, healthcare systems and organisations could theoretically be found liable if the support and resources they provide are insufficient for individuals to fulfil their duties in returning results to patients or participants.[157]

Even if clinicians and researchers are agreed to have a (potentially lifetime) duty to re-analyse participants' genomes, this does not determine *what* information should be returned to individuals, particularly in a research context. This is especially important in countries such as the United Kingdom, where return of results is predicated on the benefits of receiving the results outweighing any potential harm.[251] Mitchell et al. (2017) suggest that this will be determined by professional expertise but

influenced by the current standard of practice, which will change over time.[175] It is also unclear how the standard of clinical practice would dictate what should be returned from non-clinical research. Thorogood et al. (2019) highlight a move towards focusing on whether results may have "personal utility" to individuals, expanding the types of findings returned beyond those clinically actionable to those that may inform family planning or self-knowledge.[251] There is no single uniformly accepted definition of "personal utility", although a systematic review of the concept found that it encompasses multiple domains including affective, cognitive, behavioural and social outcomes.[135]

Some commentators also suggest that clinicians and researchers could be liable for information they chose not to identify and/or report.[157] It is possible that a "duty to rescue" could be invoked to require the disclosure of immediately actionable findings, although as with duty of care (discussed above), whether this would apply to researchers who have not had any direct interaction with a participant/patient is questionable.[41] Searching for a broad range of secondary genetic variants would be expensive. In the context of a publicly funded screening programme, the cost, and the fact that it could be perceived as screening for variants that do not have adequate public health justification, may be untenable from public health and financial perspectives.[251] There is also the question of whether it is legally permissible for an individual's *right not to know* to be overridden in the case of serious, clinically actionable information. There is currently no consensus on the right approach to this situation, beyond ensuring that rules for returning results are clearly defined from the outset of a study.[157,251]

3.3.3. Consent

Discussions of legal issues relating to consent in genomics research focus on the information that needs to be disclosed to potential participants during the consent process, and the legality of a broad consent approach (i.e. seeking consent from participants for research that is unspecified, except in broad terms, at the time of consent). There is agreement that all "material risks" that a participant could face during a study should be disclosed, including impact on clinical decision making.[175] However, in the United Kingdom it is not clear whether this is also considered to include more indirect harm, such as the psychological impact of the information received.[175] A hybrid clinical-research programme adds an additional element of complexity as participants need to be informed which aspects of the programme are governed by research laws and ethics and which are governed by clinical laws and ethics, potentially with laws relating to clinical care taking precedence where both would apply.[272]

Long-term genomic research appears to be moving towards the increasing use of broad consent, but the legal perspective on this, particularly in the European Union, continues to develop.[91] Sensitive data use in the United Kingdom is currently governed by the Data Protection Act (2018), which implemented EU data protection law, including GDPR, at the time of the United Kingdom leaving the EU (the UK Government has recently consulted on possible changes to data protection law in the UK following its departure from the EU, although specific proposals for change have not yet been made (as of June 2022)). GDPR requires that any use of sensitive personal data is justified; for genomic research, the legitimate reasons include:

- Explicit consent of the data subject – Article 9(2)(a).
- Reasons of substantial public interest – Article 9(2)(g).
- Archiving purposes for public interest, scientific or historical research purposes – Article 9(2)(j).[91,92,241]

However, GDPR requires clarification for data use in specific sectors, as neither the concept of "public interest" nor scientific research in this context are well defined in the legislation, particularly in the context of commercial involvement.[91,240,247] The legislation does not provide clear-cut guidance on the use of broad consent and requires specification of the scope of what an individual is consenting to, making the use of broad consent potentially challenging.[91,92] Although Recital 33 of the GDPR lessens specificity requirements regarding the scope of consent in scientific research, the European Union Data Protection Authorities (European Data Protection Board and European Data Protection Supervisor) have not endorsed the use of broad consent.[91,239,240] EU member states have dealt with this by either requiring consent for all research, or resorting to other legal grounds to provide a basis for research to proceed (e.g. public interest).[239,241] However, whether this is the optimum approach has been questioned, given that removing the need for consent also removes a degree of transparency and participants' right to self-determination.[240,247]

In the UK context, there is uncertainty about whether consent can be used as the justification for processing data for health and social care research; the Health Research Authority and Information Commissioner's Office (ICO) explicitly state that GDPR requirements regarding consent do not apply in this context.[207] Thus public interest is the only legal basis that remains for processing data, although the ICO does note that consent may be considered if no other legal basis applies.[207] However, even if consent is not required, this does not remove the need to seek ethical approval for data use.[207]

A new European Union Data Governance Act (DGA), likely to be adopted in 2022 to facilitate improved data sharing, introduces the concept of "data altruism" consent, through which individuals can give consent to the use of their data for "general interest" (including for scientific research or improving public services), and seeks to introduce a uniform approach to consent throughout the EU.[239,240] The concept of "general interest" or "common good" is central to this approach, but how this is operationalised in practice is unclear, particularly with respect to what information should be taken into account to determine whether data will be used for such a purpose.[240] Recent public dialogue work in the United Kingdom has identified broad principles for defining and assessing "public benefit", but these are yet to be formalised.[103] How the DGA and the concept of data altruism consent will relate to the existing GDPR has yet to be fully elaborated, although it is intended that the regulations will be compatible.[240] Whether the United Kingdom will adopt a similar approach to the DGA remains to be seen.

3.3.4. Privacy and data sharing

Academic legal discussions of issues of privacy and data sharing relating to genomic medicine and research have to date focused on who would have access to an individual's data and under what conditions it may be used and shared. Wolf et al. (2020) take privacy in this context to refer to two related concepts: the ability to limit who has access to data about themselves, and the ability to access data about themselves.[272] As Wolf et al. note, these are necessarily interrelated as a person cannot assess the privacy threat posed by sharing data if they cannot access it. Under current UK legislation, people have a right to access their own health records, which may encompass genomic data.[202] However, an access request may be denied by the request recipient (usually the "data controller" such as a general practitioner or hospital) where release of the information is anticipated to cause serious harm to the data subject or another individual.[202]

In terms of sharing their data with others, the NHS Constitution for England sets out patient rights to privacy and confidentiality, to be informed about how data will be used, and to decide whether their data can be used for research purposes.[202] The British Medical Association guidance suggests that

individuals aged 12 and over are considered capable of determining whether their information should be shared.[202] If the "data altruism" consent model put forward in the European DGA is adopted, it is not clear what privacy rights individuals will retain on providing this type of consent regarding the use of their data, and how those rights will align with existing regulations.[240] However, the Data Governance Act also includes provisions relating to data sharing infrastructure, services and intermediaries that may assist patients and research subjects with sharing their data.[239,240]

3.3.5. A Learning Health Research Regulation System

Laurie (2021) discusses the concept of a "Learning Health Research Regulation System" to address the increased blurring of the distinction between clinical care and research that characterises hybrid clinical-research programmes.[142] The key features of such a system are set out in Box 3.2.

Box 3.2. Key features of a Learning Health Research Regulation System:[142]

- A system that is value-driven, where the foundational values reflect those of the range of stakeholders involved.
- Demonstrable commitment to inclusivity and meaningful participation in regulatory design, assessment and reform, particularly from patients and the public.
- Robust mechanisms for assessment and review of regulatory processes and relevant laws.
- System-level interconnectivity to learn lessons across regulatory siloes, perhaps supported by a robust system of regulatory stewardship.
- Clear lines of responsibility and accountability of actors across the entire trajectory of the research enterprise.
- Coordinated efforts to ensure ethical and regulatory reflexivity, i.e. requiring institutions and actors to look back at their own regulatory practices, successes and failures.
- Existence of, and where appropriate closing of, regulatory feedback loops to deliver authentic learning back to the system and its users.
- Appropriate incentives for actors to contribute to the whole-system approach. Replacing a compliance culture with a system that seeks out and celebrates best practice, while not eschewing errors and lessons from failure.
- Transparency and demonstrated trustworthiness in the integrity of the regulatory system as a whole.
- Regulatory responsiveness to unanticipated events

These features are aligned with the LHS ethics framework discussed in Section 2.2.2, particularly inclusivity and the commitment to continuous learning and improvement.

3.4. Summary and implications for the Newborn Genomes Programme

3.4.1. Summary

The overarching contextual factors considered relate to the expectations against which the NGP would be evaluated, and the potential constraints placed on the design and implementation of the NGP due to regulations and policies (or where the most appropriate approach is unclear due to a lack of clarity). This is a summary of the available literature and does not constitute legal analysis or advice.

As one of the NGP's objectives is to determine whether implementation of newborn screening using WGS is feasible, the research undertaken will need to consider the **public health requirements** of such a screening programme, as well as whether it provides value as a research resource. The original guidance for potential screening tests devised by Wilson and Jungner has been updated to reflect current genomic screening practices and can provide a structure for ensuring public health objectives are met.

In addition to whether WGS screening will serve the interests of the population as a whole, its **cost-effectiveness** must be considered as it entails the use of public funds. The WGS must be at least as cost-effective as the current newborn bloodspot screening programme used in the United Kingdom. While initial modelling estimates suggest that this will be the case, and a WGS approach may in fact prove more cost-effective, substantial uncertainties remain and pilot projects are strongly advocated for in the literature. The NGP will therefore be well positioned to make a valuable contribution to knowledge in this regard.

While there is **limited research on the regulation of genomic medicine** compared to the body of research on ethical issues, several areas have been highlighted that are important for newborn WGS screening research and clinical practice:

- **Duty of care**: The degree to which all those involved in a newborn WGS screening programme, both clinicians and researchers, have a duty of care to participants/patients is currently an area of discussion. A duty of care could theoretically extend beyond those who may directly interact with a participant to include individuals or organisations who provide services or infrastructure (e.g. testing laboratories, bioinformaticians).
- **Return of secondary or incidental results**: The principle of returning results to participants from WGS studies, whether focused on clinical practice or research, is generally agreed upon. However, what information should be returned, what constitutes best practice, and the obligations this places upon researchers to search for and share findings is still a subject of debate.
- **Consent:** There is ongoing discussion in the United Kingdom regarding the need for consent when processing data for health and social care research versus using public interest or legitimate interest as the legal basis. The basis on which data will be used must be determined for any WGS screening programme. However, even if consent is not required for the use of a participant's data, this does not necessarily remove the need to seek ethical approval for data use.
- **Privacy and data sharing**: Privacy and data sharing in the United Kingdom is currently very closely aligned with the EU GDPR. This means that participants in a WGS screening programme have the right to request access to their data. The NHS Constitution for England also specifies that individuals have a right to be informed about how their data will be used and decide whether it is shared for research purposes. What this means in the context of a long-term research programme is open to discussion.

3.4.2. Key areas for further research and consultation for the NGP

The nature of overarching factors means that there are few direct actions that can be taken to resolve issues in this area. However, many researchers suggest that uncertainty around the interpretation of regulation can be managed through the establishment of clear guidance, frameworks or decision tools that set out how issues have been addressed within a specific programme.[157,175,251,272] In particular, they suggest developing such tools in relation to:

- Navigating situations in which both clinical and research regulations apply, particularly to specify which should take precedence.
- Management of incidental or secondary findings, including what information will be offered (and whether it will be verified in a clinically certified laboratory), who will receive it and how it will be provided. If only findings of a certain type will be returned (e.g. those clinically actionable), specify the process by which this will be determined.
- How consent and return of results will be handled for minors.
- How requests from participants for access to their "raw" genomic data, or their medical records, will be managed.

The recently proposed Learning Health Research Regulation System, which emphasises a value-driven, transparent and inclusive approach, may provide a useful a framework for developing the necessary tools and guidance. Even if a completely integrated learning health system is not implemented, Laurie (2021) suggests that this approach can be useful in providing a "Whole System Approach to health research regulation".[142] Key elements of this approach include:

- Taking a multidisciplinary approach to systems design that incorporates bioethics, social sciences and humanities, and meaningful participation from patients and publics.
- Investigating how congruent the central values of healthcare and health research are, and how they can be used to improve regulation.
- The use of self-reflection and feedback loops in system design and delivery to learn from failures early on and avoid them later, potentially supported by additional expertise via regulatory stewardship.

4. Direct contextual factors

Chapter summary points:

- Trust underlies many aspects of genomic research and screening programmes, including public acceptability and decisions to participate.
- Genomic research endeavours need to engage in practices that clearly communicate and demonstrate their trustworthiness. These practices can include transparency, communication supported by genomic health education, and community and stakeholder involvement.
- Equity concerns in genomic screening and research relate to the potential for discrimination and inequities in representation, access and use.
- Unequal representation of ethnic minority and other disadvantaged groups within genomic data creates inequalities in the utility of genomic medicine for underrepresented groups because the poor diversity in existing databases results in treatments and knowledge that are unrepresentative and limited.
- Inequities in access and use are rooted in people's differential resources to manage follow-up care and decision making associated with genomic screening outcomes. They also result from racism and discrimination in the healthcare system, which contributes to different care-seeking preferences and behaviours.
- Although some health inequities will be outside the control of a single programme to address, actions such as community engagement, providing sufficient workforce to support participants with decision making, and follow-up care and dynamic consent[‡‡] tools offer potential approaches to reduce inequities.

This chapter discusses the concepts of public acceptability, trust and trustworthiness, as well as the concepts of discrimination, participation, and equity of access and use of genomic medicine, and explores the importance of these concepts for newborn WGS screening and repository programmes. The chapter highlights key approaches for developing and maintaining public acceptability and public trust, and for enhancing equity of access and use, based on the literature. Unlike those discussed in Chapter 3, the factors discussed in this chapter may be directly influenced by the way a WGS newborn screening initiative for research and/or clinical care is designed and implemented.

4.1. The public acceptability of, and trust in, healthcare and research

4.1.1. Acceptability, trust, and trustworthiness

Acceptability

The public acceptability of healthcare interventions and innovations refers to public attitudes or opinions towards widespread genomic screening. However, the different aspects involved, such as socio-political, community and market acceptability, make it difficult to define and measure.[36,38] One proposed approach to measuring acceptability on an individual level considers: 1) affective attitude (feelings about the intervention); 2) burden (the effort and challenges related to participation in the intervention); 3) ethicality (whether the intervention is consistent with individual values); 4) intervention coherence (the level of participant understanding of the intervention); 5) opportunity costs (costs of the intervention and other ways that resources could have been spent); 6) perceived effectiveness (belief in the effectiveness of the intervention); and 7) self-efficacy (confidence in the ability to participate in the

intervention).[36] In the case of newborn screening, the impacts on both the child and the parent(s)/carer(s) need to be considered when assessing acceptability.[36] Very recently, researchers put forward the idea of using the Delphi method to explore the social acceptability of new health technologies (in this case non-invasive prenatal testing), which may be a useful approach in the context of newborn WGS.[57]

Trust

Although trust is a commonly understood concept, its definition does not necessarily have a consensus, particularly in the context of genomic medicine.[2] Following Adjekum et al. (2017), this report considers trust as a relationship between two actors, whereby one assumes the other will complete a task or fulfil an obligation. Trust can be delineated into affective-based and cognitive-based.[2] Affective-based trust derives from social norms and people's expectations that others will uphold conventional moral and other norms of society. This form of trust undergirds cooperation in well-functioning societies. Cognitive-based trust is a rational behaviour based on assessment of risk, where actors aim to judge the trustworthiness of other actors with whom they are entering a trust relationship. These principles relate not only to genomic testing, but to broader contexts of data storage in biobanks or repositories, data use, healthcare professionals and the healthcare system as a whole.[69,173,199,254]

Trustworthiness

Trust is a relationship of dependency between actors, with trustworthiness being the characteristics and commitments of actors that justify trust.[166] As O'Neill (2015) defines it, the trustworthiness of institutions comprises *honesty* in claims and commitments made by the institution, *competence* in key functions and responsibilities of the institution, and *reliability* in the sense that the institution is consistently honest and competent.[198] She further notes that being trustworthy and having trust are distinct. [166,197] Trust can be misplaced and given to untrustworthy actors, or not given to trustworthy actors.[197] This means that it is insufficient for institutions to enact organisational governance structures or practices worthy of trust if they aim to become trusted – they must also successfully communicate their trustworthiness to the public in a way that resonates.[166]

4.1.2. The importance of acceptability, trust, and trustworthiness

Neither a population-based newborn screening programme nor a biobank can function effectively in the absence of broad public acceptance as they rely on people's willingness to participate. The importance of public acceptability for newborn genetic screening is linked to the nature of genetic data, deemed to be intimate, personal, private, and requiring special treatment and high levels of public trust in the handling institutions.[13,48,99] The importance of public trust is also linked to the wide scope of activities and issues that clinical-research hybrids touch on, including a range of privacy issues (explored in Chapter 5), the potential of exploiting data for financial gain, the potential for group harm, and challenges associated with the commitment to advance health technologies over a long time horizon.[166]

Trust in genomic medicine, healthcare professionals and institutions affects people's willingness to participate in genomic research,[11,69,170,211] and this trust varies across countries.[169,171] For example, cross-country research on trust in genomic medicine finds that measures intended to promote openness, such as the ability for individuals to access their own genomic data, are not given equal weight across different countries.[171] Similarly, a cross-national survey found that although people are generally most willing to donate genetic data to medical doctors and least willing to donate to for-profit researchers, this distinction mattered most to people from Poland, Portugal and Germany, and

least to people from Egypt, India and Pakistan.[169] Respondents from the United Kingdom fit the overall pattern of reporting greater willingness to donate genetic data to medical doctors and non-profit researchers than to for-profit researchers.

Current trust behaviours are also rooted in specific historical cultural contexts,[146] and current or historical negative experiences within one facet of a system (e.g. clinical care, research) can lead to distrust of other areas.[11,69,146,211] In this regard, persistent inequities in the healthcare system have contributed to lower levels of trust amongst some racial and ethnic groups, and lower participation in genomic research.[146] This topic is explored more fully in Section 4.2. However, given the many actors involved, research also suggests that there may be limits to what a single institution or actor can do to rectify low levels of trust in the systems associated with genomic medicine and biobanks. For example, although research suggests that people tend to view some actors as less trustworthy than others (e.g. for-profit researchers versus medical professionals),[166,169] or to view some aspects of trust as being beyond the control of biobanks (e.g. the ability to control future data breaches), this lower level of trust does not prevent them from participating in genomic research.[137,166] In the UK context, participants in the 100,000 Genomes Project voiced trust in the NHS as a reason for participation; however, they also expressed doubt about whether they could trust that the biorepository would remain protected in the long-term, suggesting that they had limited trust for some wider system actors, yet still participated.[51]

There are also practical implications of trust and public acceptability for implementing a clinical-research hybrid programme. As explored further below, addressing the challenges of becoming trustworthy could encompass diverse aspects of a programme, including the process of facilitating consent, community engagement and education, and decisions around how best to communicate results. For example, evidence suggests that people with higher levels of trust prefer to receive genetic results directly from healthcare providers, whereas those with lower levels of trust prefer methods that give them greater control, such as electronically-mediated communications.[170]

4.1.3. Developing and maintaining public acceptability and trust

The literature offers various approaches to enhancing trustworthiness and building trust. These include transparency, enhancing genomic health literacy and stakeholder/community engagement.

Transparency

Making transparency a core element of the NGP can contribute to developing and maintaining public trust in the programme by serving as a demonstration of trustworthiness. Multiple authors have emphasised the role of transparent information sharing in the development of trust in newborn screening programmes.[49,69,160,189,199] Sharing information with research participants is argued to demonstrate the trustworthiness of an endeavour through the development of a reciprocal relationship (affective-based trust) and allowing potential participants to make their own risk assessments (cognitive-based trust).[49,69] Cross-national research finds that being transparent about who will benefit from data access, as well as who is using the data and why, are viewed by the public as amongst the most important measures for increasing trust in genomic research across countries.[171] Research further highlights the importance of transparency regarding the purposes of data retention and storage, and subsequent secondary use, for building trust, noting that providing detailed information to parents about subsequent secondary use is seen by the public to be of particular importance.[112,118,162,233,254] Informed consent is viewed as a fundamental method of demonstrating trustworthiness through research transparency.[69,161] Where informed consent is used as the process for facilitating consent, researchers are encouraged to use consent processes to communicate shared values and convey how

their goals align with those of potential participants in order to communicate trustworthiness in the absence of interpersonal trust.[203,56,205,233,253,255] However, there are challenges with relying on informed consent to promote trust. First, people have differential capacities to engage with the information presented,[72,205] and second, approaches to obtaining consent may focus on individual concerns rather than familial or community concerns, or addressing deeper reasons why people might disagree with research agendas.[161] Chapter 5 explores ethical issues related to consent and decision making in detail. Critiques of transparency (which may be enacted through consent processes) and suggestions for how to address these critiques in relation to trust and trustworthiness are discussed here.

From transparency to communication: genomic health literacy

Transparency has been critiqued as being insufficient for trustworthiness because making information available to the public is not the same as actual communication.[198] To support trust, information must be accessible and understandable to the people who need it, including those with less time or knowledge.[198] Genomic health literacy is defined as the ability to understand and use genomic information as part of health-related decision making.[109] Research suggests that if parents have low (genomic) health literacy they may find it challenging to make informed decisions about participation in population screening programmes involving genomics, particularly if they also need to make decisions regarding a long-term biobank research programme at the same time.[72,205§] . Research also shows that enhancing genomic literacy can increase understanding of, and potentially trust in, genomic medicine.[25 278] Therefore, some authors suggest that improving genomic health literacy is central to enhancing communication and transparency.[25,278] It has been argued that the public does not have access to reliable and up-to-date information about genomics.[186] The public's understanding of genomics is strongly influenced by popular culture, whether in the form of movies, television shows and social media, or by medical conditions experienced by high-profile members of the public.[46,109] This results in low genomics literacy or misconceptions, especially with regards to the limitations of genomic testing.[46,186] Authors note that low genomics literacy can lead to the assumption that data derived from genome sequencing is equal to information encoded in genes, fuelling unrealistic expectations about their certainty and definitiveness.[186]

Suggestions have been put forward for educating the public about genomics and screening programmes. For example, some countries, including the United Kingdom, are incorporating genomic education into primary and secondary school.[281] There is evidence that genomic education at the secondary level helps students transfer genomic knowledge to family members, to participate in careers in genomic research and to request genomic research results.[281] Additional public education efforts include introducing education programmes to clinics[189] or to social networking platforms.[210] Individuals are also directly targeted through workshops and outreach programmes, or through the development and activities of patient and public involvement networks, such as that created by Genomics England, where patients co-create and review educational and consent materials.[281] However, due to the complexity of genomic testing methods, the uncertain nature of the results and the wide variety of potential research uses of the data, authors have also highlighted the need to design pilot studies evaluating different education content and communication methods to establish best practices in educating the public.[64,79]

Healthcare practitioners facilitate recruitment into genomic research and provide information about potential research studies and eligibility to patients, and are frequently consulted by patients to help interpret genomic results.[206] As trusted sources of information, healthcare practitioners also play a key role in genomic education and people's willingness to participate in hybrid clinical-research programmes, with evidence that the perceived trustworthiness of healthcare practitioners affects

people's willingness to participate in genomic research.[206] It is therefore important to recognise that some patients are more likely to trust their physician than others, with historically marginalised communities such as ethnic minorities or immigrant communities less likely to view healthcare professionals as trustworthy.[206] Furthermore, some authors caution that physicians may have limited genomic knowledge, suggesting a need to prepare them to play the role of primary educators of the public in relation to newborn genetic screening.[64,206,255] Some countries, including the United Kingdom, have adopted formal genomic education of healthcare professionals, with examples including graduate and post-graduate training programmes in genomic medicine, and continuing professional development for doctors, nurses and non-medical healthcare workers such as analysts, laboratory workers and pharmacists.[281]

In addition to supporting genomic literacy, O'Neill argues that organisations need to develop effective organisational cultures to support engagement and communication. She argues that transparency is valued in part because it creates incentives for organisations to act in a trustworthy manner, and with honesty and reliability.[198] However, to realise this aim O'Neill argues that organisations need to do more than operate in a transparent manner. They also need to develop effective organisational cultures that prioritise positive engagement with legal and institutional standards, rather than mere compliance with law and regulation.[198] She suggests that by doing this, organisations can better equip themselves to communicate consistently and authentically with the public.

Stakeholder and community involvement

Stakeholder and community involvement can help to build trust and public acceptability, assist with understanding public perspectives on ethical questions such as what information should be returned to parents and how best to communicate that information, and contribute to genomic health education efforts.[212] Research indicates that the early involvement of relevant stakeholders is important to support people's trust in both healthcare interventions and in the research and clinical bodies carrying it out,[79,210,219] and that community involvement may be especially important for developing trust amongst marginalised groups.[28,161]

Community and stakeholder involvement can be defined as the role that various individuals, social groups and institutions play before, during and after the implementation of a healthcare intervention. This includes direct stakeholder involvement activities such as public consultations, expert advisory committees, research projects, patient and public involvement panels, and lobbying activities.[48,112,162,204,210,219,238] Meaningful engagement is an active, empowering and collaborative process where stakeholders' knowledge, experience and judgement informs healthcare and/or research decision making.[212] These relationships are argued to be built on a foundation of honesty, transparency and trust.[212]

The stakeholders involved in newborn genome screening programmes include professionals (e.g. clinicians, nurses, midwives, clinical scientists, IT specialists, genetic counsellors, public health officials, policy makers, regulators) and members of the public (e.g. parents, caregivers, children, community leaders).[112,150,153,204,212,279] The need for discussion and collaboration between all stakeholders is an important theme in the literature, both with regards to discussing broader social and ethical issues, as well as the more practical aspects of planning and implementing a complex healthcare programme, such as newborn genetic screening.[111,112,162,210,219] Issues requiring public and stakeholder involvement include:

- Which conditions should be screened for[79,150,162,204]
- The screening and return of actionable and non-actionable secondary findings[150**]

- The return of incidental findings (e.g. clinically actionable adult-onset conditions)[213++]
- Data sharing practices (e.g. the return of raw data)[219]
- The use of genomic data in research[48,210]
- Data storage and data security standards[48,279]
- Deciding on the model of informed consent[210]
- The development of educational materials for both parents and the wider public[64,79,279]
- Establishing reliable and feasible follow-up systems [279]
- The increase in workload of the professionals responsible for rolling the programme out.[150]

It has been suggested that arranging targeted stakeholder involvement sessions is particularly important for groups at higher risk of false positive screens, as well as those who have traditionally had less trust towards existing newborn screening programmes.[79]

Community involvement can take various forms, although examples in the literature often involve the creation of a board or panel comprising members of the public.[212,238] For example, Genomics England uses a panel of people from various backgrounds who have contributed data to Genomics England research and who advise on aspects of programme design and sit on programme committees.[238] Other examples include the Community Research Board (CRB), which is a long-term initiative developed to support paediatric genomic screening and research in North Carolina, with a specific aim of increasing ethnic and racial diversity amongst research participants.[212] In its early stages, the CRB included a focus on trust building and bidirectional capacity development that covered foundational concepts and identified issues of importance to participants in order to support researchers and community members with effective engagement.[212] Community engagement can also entail building community networks with a focus on community empowerment, as is the case with the Genetic Alliance.[238] Through their work using genetic sequencing to identify rare diseases in low- and middle-income countries, the Genetic Alliance aims to empower communities by providing an ownership stake in the company running the biobank. Every person who contributes data will be given shares in the company, thereby giving them control over how their data are used.[238]

4.2 Equity in representation, access and use for the Newborn Genomes Programme

4.2.1. Discrimination, and equity in representation, access and use

Health inequities

Health inequities are avoidable differences in health experiences and outcomes between population groups.[28] They may be caused by factors such as differences in social and economic conditions, and are associated with individual-level characteristics such as ethnicity and gender.[28]

Discrimination

Discrimination within genomic screening and research programmes relates to the possibility that biases in the research and healthcare settings of the intervention will exacerbate existing health disparities of patients who are socially and economically disadvantaged.[46,52,63,64,165] For example, unequal health outcomes by ethnicity in health systems, including in the United Kingdom, are well documented, and evidence suggests that structural, institutional and interpersonal racism contribute to the issue.[122]

Specific experiences of interpersonal, structural and institutional racism in the NHS include lack of access to interpretation services, poor quality or discriminatory treatment by healthcare professionals, failure to collect adequate ethnicity data in order to provide effective monitoring, and avoidance of help-seeking due to fear of racist treatment.[122] To the extent that the NGP relies on existing NHS infrastructure or workforce, for example in recruitment or interpretation of results, it risks reproducing previously documented discriminatory experiences.

Discrimination can also stem from future re-analysis of data and disclosure,[38,48,205] although this is highly dependent on who stores the data, how, and who comes into possession of the data later – parents, the state, various institutions, insurance companies, employers, etc.[61,256] Potential discrimination related to the reidentification and disclosure of genomic data includes insurance discrimination, [59,156,205,250,256] restricted access to education or employment, [116,205] social stigmatisation, [167,250,256] and culturally specific consequences such as potential negative impact on family social standing and marriage prospects.[99,167105,137,227]

Equity in representation

Groups noted to be at higher risk of exclusion from genomics research are those of non-white backgrounds,[140,156] people with intellectual disabilities who might have difficulties with informed consent,[136] people with a family history of mental health issues,[156] groups with higher levels of distrust towards healthcare institutions,[46] people with low genomic and health literacy,[46] socio-economically disadvantaged groups and those living in low socio-economic areas,[46,99,156] and (in English-speaking systems) non-native English speakers.[99] The literature highlighted the underrepresentation of ethnic minority groups in genomic databases as being a particular challenge for equitable representation.[185,229] One article defined criteria for equitable representation as including whether the samples in genomic biobanks are representative of the population by race, ethnicity, gender and disease risk, with sufficient numbers of ethnic minorities in the sample to conduct subgroup analyses.[88] There is evidence that people from ethnic minority groups are less likely to participate in genomic research, resulting in unrepresentative repositories.[105,137,227] There is specific evidence from the UK's 100,000 Genomes Project that Black Caribbean and Black African people are hesitant to contribute to genetic research due to historical experiences of racism.[105,122] The long-standing issue of underrepresentation of ethnic minority groups in genomic medicine creates inequalities in the utility of genomic medicine for these groups because the poor ethnic diversity in existing databases results in treatments and knowledge that are unrepresentative and limited.[20,87,105,122,140,165,186,222β]

Equity of access and use

Universal access to genomic screening does not equate to equity of access and use. Potential inequities arise from unequal resources to manage follow-up care and decision making associated with genomic screening outcomes. This includes costs of participating in newborn screening programmes, such as transportation costs and the time taken to attend information sessions with healthcare professionals,[117] and the capacity and social capital to follow up on genetic results with additional screening and treatments. These factors are likely to map onto existing health disparities.[46,99] Hybrid clinical-research programmes also have the potential to contribute to inequities in outcomes if uptake is greater amongst populations with already higher quality health outcomes.[28]

4.2.2. Implications of equity for genomic hybrid clinical-research programmes

Considerations of discrimination, representation and equity within hybrid clinical-research programmes, population screening programmes or genomics research tend to draw on ideas from

public health ethics frameworks that include social justice, solidarity, cultural health capital and trust. These concepts situate individuals within their communities, emphasising the relational nature of rights and clinical-research interactions, and ask researchers to consider about whom and for what purpose they are collecting data.[146,46,99,136,140,156]

Representation

Much of the literature on ethical issues related to representation within genomic research focuses on ethnic minority groups,[105,137,185,227,229] although some articles consider representation of other groups such as those with intellectual disabilities.[136] The lack of representation of ethnic minority groups in genomic research to date raises issues related to people's trust in healthcare systems and willingness to support hybrid clinical-research initiatives. Trust in research is closely linked with people's experiences of clinical care, and studies suggest that decisions to participate in research are closely linked with people's experiences in the health system.[146] When the health system is perceived as untrustworthy due to persistent racial or ethnic inequities, ethnic minority groups are less likely to participate in research. Historical examples of racism in research can also influence the perceived trustworthiness of genomics research, with, for example, members of ethnic minority groups in the United States citing the Tuskegee Syphilis Study and the treatment of Henrietta Lacks as a reason for lower trust in research.[137] The underrepresentation of ethnic minorities in genomic databases reinforces existing inequities, contributing to distrust amongst ethnic minority groups and further disincentivising research participation. In the case of long-term research programmes, where data storage, research and its benefits occur over many years, the need for research institutions to be viewed as trustworthy is argued to be even greater than with shorter-term research.[137]

However, trust in this context should not simply be considered at the individual level. When making decisions about whether to participate in research, members of ethnic minority groups are likely to consider benefits and harms to their *community* in addition to potential individual benefits or harm.[229] For hybrid clinical-research programmes, a community-centred approach would suggest the need to first recognise whether and how structural inequalities might limit the ability of some communities to benefit from research, and the potential for group harm if the data were to be used against them.[274] For example, Lee (2021) cites the continued misuse of genetic data, including by White nationalists using genetic ancestry data to make claims of racial superiority, as a group harm. Other authors highlight the risk of group harm if people associate research findings with negative group stereotypes (e.g. higher rates of mental health disorders).[137] Lee suggests that new approaches to consent, which recognise the potential for research on groups to harm individuals *and* groups, might be needed for genomics research.[145]

When considering other underrepresented groups, people with mental disorders or intellectual disabilities may be excluded from genomic research through the application of the safeguarding ethos embedded in some informed consent approaches.[136] This safeguarding ethos adopts the premise that individuals must demonstrate decisional capacity in order to give informed consent to participate in research. According to Kong et al. (2020), tests of decisional capacity as a pre-condition for genomic research participation ignore the ethical principle of autonomy that allows individuals to make decisions about their own healthcare, even at some risk to themselves. Kong et al (2020) argue instead for adopting a human rights perspective on disability, which suggests that physical or mental disabilities require positive accommodation from institutions to support people to participate fully, rather than excluding people or asking them to change. A human rights perspective also recognises that appropriate support facilitates autonomy and capacity, empowering people to make decisions and act for themselves.

For a hybrid clinical-research programme, adopting a human rights framework on disability would mean considering approaches to consent that support people in their decision making and facilitate their participation in genomic research.[136] Supported decision making provides people with tools, opportunities for dialogue or education, or other forms of support to help them express their views.[80] From an ethical perspective, supported decision making incorporates the principle of relational autonomy, which recognises that people make decisions as actors embedded in social-relational contexts.[136]

Equity of access and use

Related to the issue of representation are concerns about equity of access. Genomic data and the benefits it brings are currently limited to a subset of the population. Universal screening programmes, have the potential to bring more equitable access to the benefits of genomic data.[8,93] However, universal access to genomic screening does not equate to universal access to the benefits of genomics research. Potential inequities arise from unequal resources to manage follow-up care and decision making associated with genomic screening outcomes.

One framework for understanding inequities in access and use is cultural health capital. Cultural health capital is a framework for understanding how people's cognitive, behavioural, social and cultural resources are leveraged within healthcare contexts.[245] It argues that these resources are context specific, in that what will benefit a patient will vary across social and organisational settings and historical periods. The concept is rooted in a hierarchical worldview that presumes unequal power between social groups within societies, with cultural health capital one avenue through which the social hierarchy is maintained. This occurs because there are systematic inequalities in the processes of acquiring and using cultural health capital that mirror existing social inequalities, and the healthcare system itself is argued to be shaped by dominant group interests in such a way as to value the cultural health capital resources of already privileged groups.[245] Cultural health capital provides an important lens for understanding disparities in health status and care; however, it has been criticised for focusing excessively on individual and group deficits and giving insufficient weight to individual preference and autonomy, as discussed at the March 2022 expert consultation workshop.

Cultural health capital suggests that universal access is not necessarily equitable. Many individual rights (e.g. the right not to know, autonomy) are not universally accessible, but context dependent.[181] They will be exercised differentially by different patient groups dependent on their available cultural health resources. For example, those with lower cultural capital may be less likely to resist normative pressures to consent, or less likely to assert a right to receive (or not) information on unintentional findings. A cultural health capital approach would suggest that the social-relational nature of research and clinical encounters needs to be considered when designing consent and communication processes.

Inequities also exist in people's resources to manage life-long or rare conditions once identified through screening.[126] This is true even in systems with publicly funded healthcare such as the United Kingdom because of the non-clinical burdens of care, including costs associated with travel to medical appointments, time off from work for caring responsibilities, or the cost of special diets that may not be covered by health systems.[126,224] Research suggests that some people may decline to receive results from genetic testing when they do not think they will have access to the necessary resources for follow-up care.[229] As some authors have argued, equitable programme delivery will pose

an additional challenge for the NHS, which will have to roll out the intervention across NHS trusts, which vary with regards to funding and resourcing capabilities.[52,140]

4.2.3. Overcoming inequities and discrimination

How can ethical values and frameworks help overcome the challenges of representation and equity?

When considering issues of representation and equity, the first ethical question raised by the literature is whether people, or groups of people, have a duty to participate in genomic research, and the implications of this for research programme recruitment and engagement strategies. On the one hand, research programmes could be argued to have an ethical duty to increase the participation of underrepresented groups in genomic research to improve the utility of these data for everyone, including underrepresented groups,[88] and to avoid exacerbating existing disparities.[28] On the other hand, why should people from underrepresented groups participate in genomic research, particularly if it means being exposed to potential risks before an intervention is available for the rest of the population?

The ethical principles of *solidarity* and *justice* consider whether members of underrepresented groups have a duty or responsibility to contribute to genomic research. A justice approach posits that those who benefit from a collective good, such as knowledge or treatments derived from research, should share in the burdens by contributing to research.[115] In this formulation, there is a "free-rider" problem when some members of society do not contribute to the creation or maintenance of the collective good. Similarly, the idea of solidarity has been used to argue that there is a social duty to support the health-based common good through participation in genomics research – a duty based on the social contract that exists in societies with publicly funded health systems.[66,185] Appeals to the common good are seen in recruitment materials for genomic research programmes, such as the All of Us programme in the United States, which aims to sequence one million genomes and is making a concerted effort to increase the diversity of its sample.[185]

Set against this is the argument that the distribution of benefits in healthcare systems is historically unequal, and therefore collective goods are unequally distributed. This means that ethical approaches assuming a common duty to contribute to research, but that fail to recognise the uneven distribution of benefits, are inaccurately accounting for risks and benefits when considering the participation of ethnic minority groups and other vulnerable populations.[145] Furthermore, the ethical concept of solidarity includes a reciprocal obligation for health system actors to "stand beside" ethnic minority groups and other vulnerable populations by affirmatively addressing existing health inequities.[185,186] This suggests that genomic medicine must demonstrate how participation in research will lead to more just outcomes for disadvantaged groups, and includes a duty for research programmes to act affirmatively to mitigate health inequities.[146] Therefore, a solidarity approach would suggest that unless and until meaningful action to address health inequities is taken, there is no *duty* for members of disadvantaged groups to participate in genomics research.

Communitarian ethics can be helpful for thinking about the participation of ethnic minority groups and people with disabilities in genomic research. Communitarian ethics sees individuals as embedded within social networks, where relationships with family, community and society are critical for the development of autonomy.[55] A communitarian approach recognises that people do not make decisions by themselves, but often in consultation with trusted friends, family and healthcare professionals, all of whom could be considered to have a role in decision making.[55] This approach would argue for consent and decision-making models that go beyond the individual, such as supported decision-making approaches to consent (as discussed in Section 4.2.2).[136]

Lee (2021) argues that from a practical perspective, healthcare institutions can enhance the participation of ethnic minority groups in research by becoming more trustworthy, as negative experiences of healthcare provision colour perspectives on healthcare research. This means being transparent with individuals and communities about the policies and practices that determine how both clinical and research data are collected, used and stored.[26,124,180] The policies should be developed with engagement and input from specific communities of interest by working with community leaders and the general public.[146,274]

The LHS framework also suggests that overcoming historical distrust involves community engagement focused on equity.[28,66] The authors suggest that health equity should be a core mission of an organisation, demonstrated by it being a strategic priority embedded across all initiatives and with sufficient supporting resources.[28] The authors also highlight the importance of setting up mechanisms for getting feedback from the community about the process of engagement, although do not specify what these mechanisms should be.[28]

Recruitment and consent models may also be employed to enhance the recruitment of underrepresented communities. For example, targeted approaches that take a dual approach to recruitment by embedding focussed work with minority populations alongside a general population approach have been shown to be effective at reducing disparities in the uptake of childhood vaccines.[28] Moving recruitment to more diverse settings where members of minority communities are already engaged, such as primary care, can also increase recruitment and representation.[88]

Dynamic consent models (discussed in detail in Chapter 5) are suggested as another method of addressing equity concerns in genomic research and potentially increasing the representation of currently underrepresented groups.[214] Dynamic consent involves leveraging digital tools to allow participants to access and review their consent choices throughout the duration of a research study, and has the potential to allow participants to revisit consent decisions, make decisions about how their data are used, and communicate with the research team.[214] Prictor et al (2018) argue that dynamic consent provides several equity benefits, including accessibility options, real-time translation, the ability to embed animations or other tools to support those with limited health literacy, and the ability for people to view the consent at a time and place of their choosing so they can include others in their consent decision if they choose. This could support, in a limited way, ideas of communitarian ethics and relational autonomy by allowing potential participants flexibility in who they include in their consent decision making. However, the authors note the potential for dynamic consent to create new inequalities between those with access to digital resources and those without.[214]

How can ethical values and frameworks help overcome the challenges of equity of access and use?

As discussed, challenges around inequity in access and use stem from people's differing resources to benefit from and use the results of genomic research.[245] They also result from racism and discrimination in the healthcare system, which contribute to different care-seeking preferences and behaviours.[122] Different ethical frameworks attribute varying weights to these considerations and suggest multiple approaches to addressing inequity in access and use.

A public health ethics framework would suggest a need to account for people's differential resources when designing hybrid clinical-research programmes. Newson (2021) highlights how the act of giving parents (and potentially later their adult child) genomic information about their newborn creates new responsibilities for them in having to understand, manage and make decisions based on that information, and that this new responsibility may not be welcomed.[186] She argues that this shifting of

responsibility from health system actors to individuals reflects a shift towards greater individualism in healthcare, where individuals are the "primary responsible actors for their own health and that of their children".[186,] This shift towards individualism ignores how broader, social factors such as socio-economic, cultural and geographic factors affect people's choices, preferences and capacities in healthcare decisions. Furthermore, a public health ethical framework argues that any new hybrid clinical-research programme should avoid creating new healthcare needs that cannot be supported, thereby not exacerbating existing health inequities.[186] This includes providing for any additional workforce that might be needed to support parents with the new responsibilities shifted to them, including understanding the results of genetic screening and managing follow-up care.
Solidarity and social justice approaches would suggest that health system actors have a duty to use resources to take meaningful steps to address existing health inequities before or in addition to introducing new technologies.[181,185] This is taken further by the ethical framework for the LHS, which is underpinned by solidarity and reciprocity. It requires prior determination of whether a hybrid clinical-research initiative will reinforce or ameliorate existing unjust inequalities, with steps taken to minimise or remove inequalities in healthcare.[66]

However, just as a solidarity approach places an ethical obligation to address inequities, a human rights approach sees potential harm in *not* introducing new health technologies. This "right to benefit from science"[234] is similar to a social contract approach in that it argues that members of societies have the right to share in its advances and that governments have an obligation to ensure that the benefits of science are well distributed. To withhold these benefits until all health inequalities are resolved (the most extreme interpretation of the solidarity approach) would in practical terms mean never introducing the technology at all, as discussed at the March 2022 expert consultation workshop. Despite the apparent tension between the two approaches, they both recognise the need for a pragmatic approach to the equitable use of and benefits from new technologies.

From a practical perspective, the literature suggests that community engagement can help ensure equity of access and use.[28,88,146] Longer-term community partnerships can support equity in policies, interventions and services resulting from the use of genomic data.[88] As with community engagement to enhance participation, community engagement in this context could be focused on understanding the needs of the target community to support equitable access and use. Similarly, given the potential for genomic health literacy to affect decision making, access and use, genomic education as discussed in Section 4.1 provides a potential way to reduce inequities in access and use.

4.3. Implications for the Newborn Genomes Programme

4.3.1. Summary

Acceptability, trust and trustworthiness

Public acceptability, trust and trustworthiness are interrelated yet distinct concepts. The public acceptability of genomic research and screening is influenced by an endeavour's trustworthiness, or its honesty, competence and reliability; however, **trustworthiness alone is insufficient to generate public trust**. To engender public trust, genomic research endeavours need to engage in practices that clearly communicate their trustworthiness. These practices can include transparency, communication supported by genomic health education, and community and stakeholder involvement. Public trust and acceptability are essential for the success of genomic screening and research programmes. Trust underlies people's decisions to participate in screening and research, and is especially important given the highly personal

nature of genomic data and the wide scope of activities that clinical-research hybrid programmes engage in.

The literature suggests several **approaches for engendering trust**. Transparency through information sharing is frequently highlighted as a key method for facilitating trust. This approach often relies on informed consent processes to convey information. However, it has been critiqued for not distinguishing between making information available and actual communication. For the latter, information must be accessible and understandable to those who need it. For actual communication to occur, approaches such as genomic health education of the public, patients and healthcare professionals may be needed. This education can happen through a variety of avenues, such as formal educational programmes, workshops, clinical interactions or the informed consent process. Community and stakeholder involvement can help to build trust and public acceptability, assist with understanding public perspectives on ethical questions such as what information should be returned to parents, and contribute to genomic health education efforts. Community involvement can take various forms, although examples in the literature often involve the creation of a board or panel comprising members of the public. Whatever form it takes, the engagement should strive to be meaningful and bidirectional, and to empower the community to contribute to decision making in the research or screening programme.

Equity in representation, access and use

Equity concerns in genomic screening and research relate to the **potential for discrimination, and inequities in representation, access and use**. Discrimination within genomic screening and research programmes relates to the possibility that biases in the research and healthcare settings of the intervention will exacerbate existing health disparities, or the potential for participants to face direct discrimination stemming from the future re-analysis of data and disclosure (e.g. restricted access to education or employment). The unequal representation of population groups within genomic datasets, including ethnic minority groups, creates inequalities in the utility of genomic medicine for these groups because the poor ethnic diversity in existing databases results in unrepresentative and limited treatment and knowledge. There is also evidence of inequitable access to and use of genomic research, with potential inequities arising from unequal resources to manage follow-up care and decision making associated with genomic screening outcomes.

The lack of representation of ethnic minority groups in genomic research to date raises issues related to people's trust in healthcare systems and their prior experiences of care. Evidence suggests that persistent racial and ethnic inequalities and past experiences of racism contribute to lower levels of participation by some ethnic minority communities in genomic research. **Ethical frameworks are divided about whether ethnic minority communities have a duty to participate** in genomic research based on the idea that everyone should contribute to the collective good, or whether given the unequal distribution of benefits in society and persistent ethnic inequalities there is instead an obligation for genomic medicine to address inequities first. This debate is further complicated by the ethical imperative to make datasets representative to avoid exacerbating existing inequities and creating potential further disincentive to participate.

Inequities in access and use are rooted in people's differential capacities and resources. Ethical frameworks situate people within their social and relational contexts, recognising the importance of social, cultural, economic, geographic, historic and other factors in shaping people's experiences with health and research systems. They argue that individual-oriented versions of ethical principles ignore these important contextual factors that contribute to differential and inequitable outcomes.

While noting that some health inequities will be outside the control of a single genomic screening or research programme to address, the literature offers **potential ways to reduce inequities** in representation, access and use. Most frequently, and to address all of these issues, authors suggest engaging with communities to understand their needs and concerns. Genomic education or other capacity building efforts might also encourage participation and equitable access and use, as could providing sufficient workforce to support participants with decision making and follow-up care. Tools such as dynamic consent processes may also help overcome barriers to participation by allowing for the incorporation of accessibility support (e.g. translations, health literacy education).

4.3.2. Examples from other projects

The following are examples of specific projects from this chapter that relate to community engagement:

- As noted in Section 4.1.3, Genomics England uses a panel of people from various backgrounds who have contributed data to Genomics England research and who advise on aspects of programme design and sit on programme committees.[238]
- The Community Research Board (CRB) is a long-term initiative developed to support paediatric genomic screening and research in North Carolina, with a specific aim of increasing ethnic and racial diversity amongst research participants.[212] In its early stages, the CRB included a focus on trust building and bidirectional capacity development that covered foundational concepts and identified issues of importance to participants in order to support researchers and community members with effective engagement.[212]
- Community engagement can also entail building community networks with a focus on community empowerment, as is the case with the Genetic Alliance.[238] Through their work using genetic sequencing to identify rare diseases in low- and middle-income countries, the Genetic Alliance aims to empower communities through giving them an ownership stake in the company running the biobank. Every person who contributes data will be given shares in the company, thereby giving them control over how their data are used.[238]

4.3.3. Key areas for further research and consultation

In contrast to the factors discussed in Chapter 3, direct contextual factors can potentially be influenced by how a programme is designed and implemented. Based on the literature, there are several areas that are important to consider as part of the NGP, but may require further research and/or consultation:

- Community engagement is frequently suggested as a key method of engendering trust with the public in general, and with marginalised and underrepresented communities specifically; however, there are few examples in the literature of what this looks like in practice for genomic research. Furthermore, the persistent underrepresentation of ethnic minority groups in biorepositories suggests that issues of trust and access have yet to be overcome. Further research or consultation is needed on how to meaningfully engage with communities and on what "successful" community engagement in a genomic research context looks like will strengthen NGP design and implementation.
- Relatedly, the literature reviewed did not address how to balance different and potentially competing views from different stakeholder groups. If a broad range of stakeholders is consulted, as much of the literature suggests, it is possible that tensions will arise over suggested courses of action. Further research into how best to manage these tensions could facilitate more effective stakeholder engagement.

- Further research could also explore public perceptions of public- and government-backed genomic research endeavours, and how these impact perceptions of trustworthiness. Large-scale public–private partnerships during the response to the Covid-19 pandemic, and the various messaging around and coverage of these efforts, may have shifted public attitudes towards government or commercial involvement in research.
- Transparency is seen as a key method of demonstrating trustworthiness; however, when research is uncertain, people may perceive it as less trustworthy.[58] This presents challenges for researchers working in areas of rapid change or uncertainty about how to achieve transparency in a manner that demonstrates trustworthiness, rather than undermining transparency by contributing to confusion and uncertainty. Further research or consultation is needed on this topic.
- The relationship between genomic health literacy and decision making and the potential for education to increase the participation of ethnic minority groups could also be usefully explored further. Although current research suggests a relationship between genomic health literacy and decisions to participate in research, it is not clear how this intersects with social and relational factors such as community preferences, or cultural or political beliefs. For example, people may choose to prioritise community concerns or cultural or political beliefs over clinical decision-making strategies. As the programme explores the role of individual autonomy in decision making, it could also investigate both the value and limits of genomics education in supporting this autonomy.

5. Consent and decision making

Chapter summary points:

- Both clinical care and research rely on parents/carers to provide **proxy consent** on behalf of their child. This means a decision must be made on how to balance the autonomy of the child with that of the parent/carer. A pragmatic approach could be taken whereby proxy consent is sought (and results shared) for screening childhood-onset, actionable conditions. However, this issue becomes more complex when considering whether proxy consent is appropriate for the long-term use of the child's data for research that does not have a clear, direct benefit to the child. There is also a related issue of children developing the ability to consent over time and proxy consent no longer being applicable.
- Genetic information has a **relational component**, which means that it also contains data relating to family members. This creates a question about whether there is a duty to warn family members about a higher risk of a condition and leads to the notion of relational autonomy. In the case of a newborn genomic screening programme, a relational autonomy approach would involve discussions with healthcare professionals and wider family members about preferences and potential implications of consenting to newborn screening. Throughout this process, it would be vital to place the best interests of the newborn at the centre of decision making, and any preferences and opinions of others should not be a key decision-making factor.
- Children usually develop the ability to be **involved in decision making over time**, reducing the importance of parental/carer autonomy as they age. Long-term research, such as biobanking, creates questions about when children should be brought into the decision-making process, and if and when consent should be sought from children later in life.
- There are three **different approaches to seeking consent**: informed consent (opt-in), presumed consent (opt-out) and tiered consent (consenting to separate aspects of data usage differently). The choice of which to use depends on what the data are being used for, and each has advantages and disadvantages.
- There is concern that parents/carers are not able to make a **truly "informed" decisions** or provide consent given the many implications of genomic testing/screening, and the ability to provide consent is likely to be subjective. This may mean that there is not a one-size-fits all approach to seeking consent. While the consent process can be tailored to individual participants, this would be challenging for large-scale research initiatives such as a national biobank.
- The **timing of consent** is important when obtaining proxy consent for newborns. Seeking consent soon after birth is unlikely to be the optimal approach as parents/carers will be stressed. It may be preferable to provide information during pregnancy, followed by brief reminders of the information soon after birth (depending on the type of DNA sample used).
- Ideally, **proxy consent will come from both parents/carers**, although this is not possible in all situations and so consent from one parent/carer can be deemed sufficient. If there is disagreement between parents/carers, a consensus should try to be reached; however, if this is not possible, screening may not be able to proceed, or may need to be postponed.

This chapter discusses the concepts of consent and decision making as they relate to newborn WGS for research and/or clinical use, and reflects on the implications and consideration points specifically related to the NGP. The aim of this chapter is to outline the different types and models of consent discussed in the literature that *could* be used for the NGP; it does not recommend a specific approach or discuss which are or are not feasible. While it is recognised that not all models would fit the NGP, all options are included here for completeness.

Consent is the act of providing permission or agreement for something to happen. Usually, a person provides consent to participate in research themselves. However, in the context of newborn research (including screening), parents/carers agree to participate on behalf of their child (termed proxy consent). While the act of giving proxy consent may seem straightforward, a multitude of ethical issues arise when applied to newborn WGS, particularly if data are stored long term for research or clinical purposes. The three main ethical issues are:

1. Parents/carers are providing consent on behalf of their newborns, whose views cannot be known until later in life.
2. Genetic information is not only associated with the newborn, but also their family.
3. If newborn data are retained for long-term research use, their consent may need to be sought in future.

Many different ways of seeking consent have been proposed to address these issues: informed, presumed and tiered consent (each with advantages and disadvantages). Seeking consent with respect to genomics and research is likely to be difficult due to the open-ended nature of research. Genomics research in particular poses challenges due to evolving knowledge. There are also challenges in identifying causal links between genetic variants and health outcomes, which can make it difficult to accurately inform participants of the risk to their health. These challenges are discussed in more detail below, as well as different consent approaches that have been suggested as ways to address them.

5.1 Reliance on proxy consent from parents/carers on behalf of newborns

As newborns are unable to consent to their genetic data being used for research purposes, there has to be a reliance on parents/carers to provide proxy consent on behalf of that child.[16,59,121,162,222,249,255] This requires parents/carers to decide what is in the best interests of their child,[16,182] and highlights issues around autonomy and the extent to which parents/carers have decision-making abilities over their child's life.[15,19] This must balance child and parental (or carer) autonomy, as well as individual autonomy and public health benefit. Each of these aspects will be discussed here.

5.1.1. Autonomy of the child

Discussions around autonomy of the child with regards to genetic screening focus on two key points: 1) consent to participate in the screening study; and 2) if and when to disclose results to the child.

Consent to participate in a genetic screening study

At the heart of any action taken regarding the health of a child should respect for the child and their choice, and upholding up their right to an open future.[13,15,19,30,32,38,52,55,59,66,71,121,145,156,181,182,194,261,265] However, the nature of newborn screening means that the individual (the newborn) cannot share their views and their choices cannot be respected, with the child reliant on parents or carers to determine this. There are multiple ethical angles that can be taken to support child autonomy, such as the best interests of the child and preventing harm.[265]

A key consideration in the approach to take regarding child autonomy for any newborn WGS research or clinical programme is the long-term use of the child's genetic data. Proxy consent is acceptable for delivering clinical care. However, there is less consensus regarding whether parents/carers should be able to consent for their child's data to be used for long-term research (see next section), and at what point as the child ages that proxy consent becomes no longer acceptable (see Section 5.3).

Consent for disclosure of results

Some argue that newborns are entitled to an open future by not being informed of any risk of developing genetic conditions later in life until they are mature enough to decide for themselves if this is something they want to know (the right *not* to know).[181,222,227,249,273] Knowing the child's level of genetic risk can lead to psychosocial impacts (see Section 6.3.2) and limits the possibility of future autonomous decisions for the child.[67,181,227,273] In the case of newborn screening, one argument could be that parents/carers are well placed to make decisions that align with the best interests of their child if they are given the appropriate tools to make an autonomous decision (a liberty focused approach). At the other end of the spectrum, others argue for the right of the child to know their genetic results, noting that the child's autonomy cannot be upheld without full disclosure of results.[67] However, as the NGP will be focused on reporting the risk of childhood onset conditions, this issue is less relevant as the condition would develop early on in life. This is an issue that would need further consideration should adult-onset conditions be included in the NGP.

5.1.2. Parental autonomy

Parental autonomy is the right of parents to have decisions they make about their own child respected (the same can be applied to carers with legal guardianships over a child).[15,19,59,66,71,101,186,265,268] Those discussing parental autonomy raise a range of different viewpoints on its importance in the context of proxy consent, from almost complete reliance on parental autonomy[38,70,96,97,101,119,147,268] to a greater focus on the autonomy of the child over the parents/carers.[101,152]

The argument for giving greater weight to parental autonomy centres around the reasoning that a key part of being a parent/carer is making decisions on behalf of your child. This is something parents/carers do every day based on their own values and what they think is in the best interest of their child.[38,70,96,97,101,119,147,268] While a child may ultimately grow up to disagree with their parents'/carers' decisions, this is something that can occur as part of childhood and is not specific to research or medicine.[96,101] Some go so far as to argue that parents'/carers' wishes for their child should only be overridden if they are likely to place the child in significant harm.[265]

Others take a more pragmatic approach, recognising that allowing proxy consent may not necessarily adhere to the principle of best interests for the child, but is allowable where there is minimal risk and at least some benefit to the child.[96,97,101] Here, it is recognised that parental autonomy should completely overrule individual child autonomy, while acknowledging that children have a right to appropriate guidance from their parents/carers, as long as it is in the child's best interests.[15,66] It would then be assumed that there are some (albeit a small number of) situations whereby parents/carers are not allowed to make a decision not considered in the best interests of their child.[101] In the case of newborn screening, this argument *could* be interpreted as parents/carers being unable to decline clinical screening for childhood-onset, actionable conditions as the principle of best interest overrides parental autonomy.[71,95,97,273] However, for the NGP, this is somewhat more complex, as it is currently a research study and also incorporates aspects of long-term biobanking, which means there is no direct, immediate benefit to the child. The ability to decline participating should therefore not be withheld from parents/carers (see below).

At the other end of the spectrum is the argument that proxy consent on behalf of children should not happen in any circumstance. Some argue that parental decision making could make the child more

vulnerable in terms of their future autonomy than if they were to make their own decisions as adults.[152] Others argue that in the context of research that does not directly benefit the child, and thus cannot be in their best interests, proxy decision makers cannot consent on their behalf.[101] This is a somewhat extreme view, however, and taking this stance would prevent research into newborn health, leading this group to be underserved in terms of medical treatment and create inequalities that would be unacceptable in a socialised medical system.

A somewhat separate but important issue to consider relates to donor-conceived babies and adopted children, and where parental autonomy lies in this regard. For donor-conceived babies, sperm and egg donors have no legal rights over the child,[108,187] and cannot have a say in whether or not the child undergoes genetic screening. Regarding adoption, the biological parents of an adopted child forfeit their parental responsibility.[81,82] However, care needs to be taken here as parental responsibility is not passed onto adoptive parents immediately, and may take place after the decision about whether to participate in genetic screening needs to take place.

5.1.3. Balancing child and parental autonomy

Balancing the autonomy of the child with that of the parent/carer is not straightforward in the case of newborn screening.[19,45,67,152] In part, it depends on what type of genetic information is disclosed (e.g. childhood or adult onset conditions, actionable or non-actionable conditions).[59,152] There is also a recognition that children obtain the ability to consent for themselves over time, as discussed in further detail in Section 5.3.

Healthcare professionals have a role to play in supporting the balance of child and parental autonomy. The right not to know and the child's individual autonomy should not automatically override professional responsibility if the child's health is at risk.[15,19,66] The healthcare professional can help support a decision to be made that is in the best interests of the child and upholds the right to an open future, while also supporting the parents/carers to make the best decisions on behalf of their child and themselves.[59]

While the literature does not come to a final conclusion on how much reliance to place on newborn autonomy over parental autonomy, it does seem to be generally accepted that parents/carers can provide proxy consent for their children for clinical care and where there is benefit for the child (or, at least, limited harm for the child). Where the balance of individuals' and parents'/carers' autonomy becomes more difficult is when adult-onset and/or non-actionable conditions are being screened for, partly because these can apply to other family members (see Section 5.2) and there are limited actions that can be taken to improve the child's health or minimise risk. Another key issue is the use of data for (long-term) research purposes such as a biobank, where the use of proxy consent needs further consideration as the child is not necessarily benefitting directly from any research, which is longitudinal in nature. Different approaches to seeking consent are presented in Section 5.4.

5.1.4. Individual autonomy versus a public health approach

While this section has focused on the balance between newborns and parental autonomy, there is another overarching debate related to autonomy which considers the balance between individual autonomy (which in this case could be the newborn or parents/carers) and a wider public health/societal benefit perspective of conducting research.

In the case of newborn screening and research, some argue that children have a duty to contribute to the social good (in the form of better understanding of genetic conditions), and thus a readiness to participate should not be undermined by overstressing the importance of individual

autonomy.[38,95,147,268] Focusing on public health interests also allows for a discussion of important values such as justice, equity, solidarity and reciprocity.[55,146] Others claim that children do not have social obligations and should not be exposed to research risks for the benefit of others.[147,268] However, this could be interpreted as no research should be conducted on children, which is not feasible in reality and would lead to health inequalities for children.

The balance of individual autonomy and public health benefit may differ depending on the type of activity within a hybrid clinical-research programme. For clinical care, it makes sense to take an individual autonomy approach, as understanding the health risk of a single individual will not influence public health, although for genomic medicine there may be an impact beyond the individual, such as family members. For research, the balance is shifted more towards the public health perspective as it is being conducted to obtain knowledge about genetic conditions to improve the health of the public, rather than providing benefit to the individual.

5.2 Genetic data also relates to other family members: relational autonomy

While genetic data are taken from one individual, the newborn, the data also have a familial aspect as it contains information relating to the biological parents and other biological family members. This means that there is a potential duty to warn relatives who may be at risk of developing certain health conditions.[13,16,59,71,145,167,173,220,230,250,265] However, the implications of consenting to genetic screening or research are often not discussed in consultation with other family members who may be impacted by the results.[55,173,226] Biological parents may also not want to know the implications of screening results for themselves.[237] This can be circumvented by only sharing results relating to childhood-onset, actionable conditions, although there will inevitably be other implications for the family. For example, findings may have implications for biological parents' future reproductive decision making if variants associated with childhood conditions are identified, or for biological family members who are carriers of genetic variants.[33] It is also worth noting that the type of information that parents (and other family members) can access is influenced by national/international laws, which places restrictions on what data family members can access.[15] This report specifically focuses on the relational autonomy perspective with regards to the familial impact of newborn screening.

5.2.1. Relational autonomy

Relational autonomy takes a holistic view of the individual. It focuses on how individuals relate to and interact with other people in their lives, and how this influences their ability to understand and make decisions about participating in genetic research.[123,230] Relational approaches to consent allow discussions with healthcare professionals and families on the implications of agreeing to newborn screening research, and focus is on more than just the documentation of consent.[55] It also allows solidarity, engagement and social embeddedness to be upheld.[167] Despite much discussion in the literature on the principle of relational autonomy, this is not something that has translated into research or clinical practice.[55]

However, taking a relational approach can focus too strongly on the preferences and opinions of family members, leading to a risk of coercion (thus removing autonomous choice of the individual, or parents/carers).[55] Biological parents also have the right not to know genetic information about themselves, which is difficult to achieve as they will receive the results. This connects the principles of the parents' right not to know with child's right to an open future.[181,265] Arguments are made that the benefits to the child in knowing their genetic results should be prioritised over the biological parents' desires not to know the results themselves, particularly in relation to childhood onset conditions.[97,101] Thus, the newborn should be placed at the centre of decision making, and the decision about whether

to participate in newborn screening should be made with the implications and preferences for others in mind, but not as a key decision-making factor.[55,167,230]

An alternative approach for newborn screening could be to take a relational approach to autonomy and confidentiality, in which the genetic results relevant to the family belong to the family as a whole.[55] This familial approach is rooted in the principle of beneficence to the family, fairness and reciprocity.[55] While this approach seems to be acceptable to patients, it seems less favoured by clinicians, who have concerns over confidentiality breaches and legal action.[55] A family member's right not to know should not override professional responsibility when the child's health is at risk (or, indeed, the health of a family member). The responsibility to make the final decision about sharing results with the family is with the healthcare professional to determine if sharing results is in the best interest of child, supports parental autonomy, and maintains the right to the child's open future (see Section 5.1.3).[19]

5.2.2. Donor-conceived and adopted children

As mentioned in Section 5.1.2, there is a specific issue that needs to be considered in relation to donor-conceived and adopted children, whereby the genetic information from the child also relates to the donor or biological parent. However, in these situations there may not be contact between the donor/biological parent and child for various reasons, and so they are unable to be informed about genetics findings relevant to them. This was not an issue discussed explicitly in the reviewed literature.

5.3. Deciding if, how and at what point children should be brought into discussions around the use of their genetic data

5.3.1. Whether children should be involved in decision making and asked to consent

While parents/carers provide proxy consent on behalf of their newborns to participate in research that involves having their genetic data screened, children usually mature over time (and at varying rates), and often gain the ability to be involved in decision making (and thus the importance of parental autonomy reduces) before the age of legal maturity.[29,59,93,95-97,101,106,147,152,220,227,249,268] Ultimately, children/young adults may disagree with their parents'/carers' choice to have their genome screened and/or their data stored in a repository.[29,30,95,97,101,152,194,201,268] This creates challenges in identifying when children (once older) should be brought into the decision making process (if at all), and raises questions about whether individuals can be asked to consent or offered the chance to withdraw from research later in life (e.g. at reaching the age of maturity).[48,163,219,249]

Arguments have been made that individuals should assume decision-making rights once they reach the age of maturity, and consent should be sought for the future use of data for research. This is particularly relevant when proxy consent has been sought, and if there is greater than minimal risk posed to the individual.[29,30,95-97,101,152,201,219,220,227,268] This extends to renewing or withdrawing consent for the storage and use of samples in repositories.[97,101,220,268] Consenting will enable respecting the individual's choice (and the individual will know this choice is valued by others) and autonomy, and ensure that they have the right to an open future.[13,15,19,29,30,32,38,52,55,59,66,71,121,145,156,181,182,261,265] Should a clinician favour the views of the parent/carer over the child when they reach age of maturity, this would foreclose the individual's right to an open future[152,227] and autonomy, and could be deemed unethical. However, there is an open question about whether, once matured, individuals will still feel their choice has value if a decision has been made on their behalf earlier in life. Box 5.1 below outlines one example of how children can be involved in decision making over time.

Box 5.1. Examples of involving children in decision making over time

The paediatric reporting of genomic results study aims to inform the debate around returning genetic results about adult-onset conditions to children and parents. The study will use genome data already collected via another health initiative. Informed consent will be sought from parents to reuse the data, and children aged 7 to 17 will be able to provide assent. Once children reach age 18 they will be able to take part in the informed consent process. In cases where a child is suspected of having a higher risk of an adult-onset condition, but consent/assent is not given to participate in the study, their genetic sample will be stored until the child reaches age 18, when re-consent will be sought. In cases where a child is suspected of having a childhood-onset condition, but consent/assent is not given to participate, further testing will be conducted to confirm the suspicion and the results will be returned to the individuals without further data collection for the study.[232]

There are resource issues associated with obtaining consent from children/young people, which can be burdensome (for participants and researchers) and hamper research, depending on the type of research the data are used for.[96,97,106,145,201,268] There are also logistical challenges with seeking consent due to keeping accurate contact details over prolonged periods of time. The use of stored data via repositories often means no interaction with the individual, and so feasibility of being able to renew consent is viewed as low.[29,93]

Some argue that consent should be sought where practical, but that otherwise it is reasonable to continue analysing the data, as long as contact is attempted should an important genomic result be found.[29] Similarly, others argue that consent at the age of maturity is not required unless later studies require interactions with the future adult or there is greater than minimal risk.[30,268] However, if future studies require continued access to medical records that are constantly being added to then this argument does not hold. Others argue that individuals should at least be kept up to date with what their data are being used for (e.g. which research studies).[96] Alternatively, consent (of the child or parents/carers) could only take place when there is a large divergence from the original protocol.[96,97,145] However, this raises issues if broad consent was sought in the first instance as the child/parents/carers would not know what the original protocol entailed unless they were contacted about that first.

5.3.2. Children mature at different rates

The variation in maturity rate is not currently reflected in laws or practice, where most often a single threshold exists for when a child is and is not competent (e.g. 16 years old).[93] Some have proposed using non-age based competence assessments to determine a child's ability to be involved in decision making, such as individual developmental level, health literacy, reasoning and understanding.[93,123,147] However, should the NGP result in a national WGS programme for newborns, this would potentially be burdensome to implement given the large numbers of participants.

5.3.3. Whether parents/carers opting-out should be a permanent decision

The issue of a permanent opting-out of newborn screening by parents/carers was only discussed by one paper. This study treated the initial opt-out of newborn screening from parents/carers as a permanent decision deemed acceptable as no harm was inflicted.[29] However, it could also be argued that opting-out of screening is not in the best interests of the child (and so the parental decision should be overruled, see Section 5.1). If the data from newborn screening are stored long-term and used for research or clinical care, it may not be reasonable that the opt-out decision made by

parents/carers should remain in force for the child's lifetime. The child may decide for themselves at a later stage that this is something they would like to have been involved with and wish to opt-in. Whether it is feasible for those eligible at birth to opt-in to a programme later in life will depend on the specific objectives and design of an initiative.

5.3.4. Approaches to seeking consent and their benefits and drawbacks

There is not one, correct approach to seeking consent, and the choice of approach depends on what the genetic data are used for (e.g. clinical versus research uses). Three main approaches to consent are discussed in the literature and briefly outlined in Box 5.2. Examples of consent approaches taken in studies reviewed are provided at the end of this chapter, and examples specific to newborn genetic research are briefly reflected on in this section. There is also a key issue about whether parents/carers are able to make a truly "informed" consent decision, which is discussed later in this section.

Box 5.2. Approaches to seeking consent

1. Informed consent approach:

- Can also be described as the voluntary or opt-in approach.
- The parents decide on behalf of their child if they want the child to participate in a research study,[70,255] based on receiving information on the research and how their child's data will be used.
- Informed consent can take a broad approach (i.e. consenting to the use of data for unspecified future research[38,91]) or apply only to specific uses.[60]

2. Presumed consent approach:

- Can also be described as the opt-out approach[65,70,79,112,162,222,255]
- Here, it is assumed that consent is given, rather than asking for parents' explicit informed consent, but there is the option to opt-out if desired. This is a valid approach as long as there is a clear benefit to the child and it is in the best interests of the child. Presumed consent might be applied to some, but not all, aspects of the offer to parents [59,70,79,162,164,222] It is most often used for low risk activities (e.g. voting registers and organ donation),[257] but is increasingly being used for research – see examples later in this section.
- Alternatively, there can be deferred consent, in which consent is initially assumed and then parents can provide full consent when they are in a position to fully understand the information and make an informed decision.[200]
- The use of opt-out consent in particular is influenced by whether the activity being consented for is clinical or research. As clinical care is most often ensuring the health of the individual and implemented across a larger population, opt-out consent may be more acceptable than for (long-term) research use, where informed consent may be more preferable in light of weighing the benefits for a smaller group of people. For genomics research specifically, the large amount of data produced during screening, and the variety of implications, means that opt-out or presumed consent approaches are often not accepted.[33]

3. Tiered consent approach:

- In this approach, parents can consent to separate aspects of data usage differently.
- For example, parents may be offered the opportunity to consent to screening to obtain information about health conditions separate to the use of genetic information for future research studies/long-term storage.[15,16,38,52,59,112,141,162,255,256,261] Alternatively, parents could be offered the choice as to what type of research their child's genetic data can be used for (e.g.

academic and/or commercial research).[52] In some cases, consent could be dynamic, with participants able to change their consent preferences in real-time.[215]
- Tiered consent can be implemented using a combination of informed and presumed consent approaches. For example, an informed consent approach can be taken for the screening aspect, and a presumed consent approach for the research and repository aspect.[16,45,52,59,112,162,176,200,249,255,256,261]

Informed consent

Taking the **informed consent approach** to newborn screening and research supports the principles of individual autonomy.[123,261] It is often the preferred or gold standard approach for research and newborn screening,[279] and has been noted as the preferred approach for healthcare professionals.[56,255] It may also be the preferred model for patients/the public, and therefore may support uptake of newborn screening.[112,210,261,279] Informed consent is used extensively within research (see example relating to genetic screening in the box 5.3 below).

Box 5.3. Example of using informed consent in practice

A study using genetic data collected for the Genomes for Kids study took a two-step approach to consent. Trained nurses first provided information to parents about the study, and a second appointment was held to seek informed consent.[107]

Using informed consent links to trust and transparency, as providing sufficient information and decision-making time can demonstrate to parents/carers the trustworthiness of the researchers and healthcare system.[226,261] However, providing enough information in an easy to understand format to support parents/carers to make a truly "informed" decision is difficult (see Section 5.4), and can actually result in the lower uptake of newborn screening (e.g. due to a lack of or misunderstanding about the purpose of genetic screening).[19,70,86,162,222]

While informed consent can help to support autonomy, the conditions needed to preserve autonomy are not always clear,[123] and there is a need to balance autonomy with the public benefit that could be provided by all newborns participating in a screening programme (should a programme have that objective), and then creating a repository from these data for research use (see Section 5.1.4).[165] There are also challenges because informed consent should ideally also cover future potential secondary uses of data; however, new methods could emerge which could be difficult to foresee at the point at which consent is sought.[52,55,93,95,101,123,155,219] This is an issue particularly relevant to genomics, where knowledge is progressing rapidly. However, broad informed consent allows the use of data for unspecified future research; this supports informed consent while optimising research practice, and does not require multiple interactions between parents/carers and researchers.[91] Informed consent is also resource intensive (e.g. time taken to provide understandable information, following up with each family to seek consent, following up with families if there are any errors in their consent forms).[61]

Tiered consent

Some argue that current informed practice standards are inadequate, and a **tiered consent** approach may be optimal. This approach allows individuals to manage their own preferences, and children can consent/withdraw as they get older.[7,52,96,145,176,186,200,261,267,273] Some examples of where tiered consent has been used in practice are in Box 5.4 below.

Box 5.4. Examples of using tiered consent in practice

- The BabySeq project took a two stage approach to consent. Initial consent was sought from parents to only provide results of childhood-onset conditions. However, as the sequencing methods also identified a mutation related to breast cancer, parents were re-contacted and asked for their consent to confirm whether they wanted to receive information about adult-onset conditions.[225]
- For current newborn bloodspot screening in England, information about screening is provided to parents at or before antenatal appointments. Verbal consent is sought postnatally, and at this point parents are also asked if they would like to be contacted in the future about research linked to the screening programme. Parents are able to have some choice in which conditions are screened for, being able to decline screening for sickle cell disease, cystic fibrosis and congenital hypothyroidism individually.[217]

Dynamic consent is a form of tiered consent that allows participants to view and change their consent preferences in real-time. It can provide participants with greater control over their preferences and can support engagement between researchers and participants.[105,215]

A tiered approach to consent can help improve the uptake of newborn screening and does not seem to impact participant understanding of what they are consenting to.[267] Tiered consent also supports parental autonomy, as any opt-in options will include greater detail on what parents/carers are consenting to on behalf of their child, and could give parents/carers more control over what genetic information to know about.[79,162,261]

Tiered consent can also help balance the individual versus parental autonomy issue, as parents/carers could, for example, consent for the health screening on behalf of their child, with consent to participate in longitudinal research postponed until the child is old enough to consent for themselves.[261] Alternatively, participants could consent for each type of organisation that can use the data for research (e.g. academic and/or commercial use). However, it may not always be simple to distinguish the different tiers of consent – for example, what is considered academic and commercial research is not always clear cut.[52]

Presumed consent

Those in favour of use of **presumed consent/opt-out approaches** highlight that it can be easier for parents/carers than opting-in, thus motivating involvement in newborn screening.[112] Parents/carers may also prefer this approach as the knowledge and understanding they have is, in some cases, deemed more valuable than being offered a choice about whether or not to participate.[255] Some examples of where presumed consent has been used in practice are outlined in Box 5.5 below.

Box 5.5. Examples of using presumed consent in practice

- NHS Digital has recently introduced the national data opt-out. This process means that patients need to opt-out if they do not want their confidential data used for research or healthcare services planning.[188]
- The Icelandic Healthcare Database (a population biobank used for research and commercial purposes) has an opt-out approach to consent. This approach was decided on after extensive consultation with the public. Citizens were able to opt-out of the biobank using a form available in all healthcare organisations. While this approach had public support, many

experts argued against it on legal bases, stating that it did not meet ethical research standards. Only 7% of citizens opted out.[164]

- Vanderbilt University in the United States runs a DNA repository in which blood from all Vanderbilt patients is collected if they have not opted-out – these genetic data are then linked to electronic health records, de-identified and made available for future research. Patients can opt-out of this process via the routine hospital consent forms. Fewer than 3% of patients opted out.[164]

The use of deferred consent specifically could be justified in cases where it is difficult to get prospective consent from parents/carers, or parents/carers cannot receive or understand the information at the time. This would uphold the principles of equity and justice by allowing all newborns to be screened in the first instance.[200] However, this argument is weaker when applied to newborn screening as parents are very likely to have been in contact with the healthcare system at some point during pregnancy.

Presumed consent approaches may also be favoured when taking a public health perspective over individual autonomy, as some argue the use of genomic data should be permitted without explicit and specific consent to maximise the benefit the data can provide for society (meaning society's obligation to promote child health supersedes parental autonomy to decline newborn screening).[115,121,261] This could present as, for example, biological samples from a biobank being exempt from needing parental consent.[249] However, some argue that presuming consent for newborn screening creates a paternalistic state, which takes away individual autonomy at the expense of protecting the health of others through research.[165,261] Other arguments against presumed consent approaches suggest that it is too simplistic.[162]

5.3.5. Ensuring a truly informed decision

While healthcare providers and researchers can go through the appropriate informed consent processes (e.g. offer information about the study and any risks, obtain completed consent forms), this does not necessarily mean consent has been sought, or that an informed decision has been made. For example, the individual may have received information about a study, but this does not necessarily mean they are able to understand it. While this issue is discussed in many of the articles included in this review, there is no clear definition of what constitutes a truly informed decision when it comes to consent or a method for assessing whether a participant's consent is indeed informed. It is likely that what constitutes a truly informed decision will differ on both an individual basis and a contextual basis. This section summarises the literature in this area, with the caveat that much of the literature assumes that a consensus regarding what makes a truly informed decisions is yet to be achieved.

There are several factors that influence the ability to provide consent:

1. Having enough information at the appropriate health literacy level and in an optimal format (i.e. comprehension).
2. Power dynamics (e.g. feeling unable to decline/opt-out).
3. Interaction and influence from social circles (e.g. family preferences or pressures).
4. Resources available to researchers to develop informed consent processes and resources.[36,69,90,194]

In the context of a complex newborn screening and biobanking programme, parents/carers may not be able to make a truly informed decision about the use of their child's data without appropriate support. For example, they may not realise they have a genuine choice about whether or not to participate, may not remember they have been informed about it, or may not have a full understanding of what they are consenting to.[6,11,18,22,52,56,60,65,70,72,86,112,123,148,162,178,189-191,201,230,233,236,237,244,253,255,261] Informed consent also raises questions about what should be discussed during pre-test counselling.[59]

While it may seem that providing more information can overcome the difficulties of seeking "genuine" consent, allowing choices to be made using more complex information may undermine comprehension and compromise informed decision making.[56,123] This links to the issue of trust and transparency (discussed in Section 2.1.3), as complex information may lead parents/carers to worry that the decision they need to make is more difficult than it actually is.[255] In addition, parents/carers may become suspicious of healthcare providers if they have not had the opportunity to review and understand this type of complex information about a medical decision before, leading to mistrust.[255] This issue is influenced by whether the genetic data are used for clinical and/or research purposes, as parents/carers may trust clinicians to have considered their best interest for getting clinical consent. Research, on the other hand, places higher burden on parents/carers to understand complex issues, and relationships may not be present with researchers to support trust.[52]

The right not to know requires sufficient access and understanding of information about the implications of a decision to participate and the interpersonal or societal authority to implement this right – and not everyone has these resources (linking to the issue of equity discussed in Section 2.1.1).[181] Relatedly, concerns about being provided with genetic information may not be seen as a priority for some, with other health and well-being issues considered more important.[181]

While simplifying the nature of the risk can support understanding for parents/carers, it can be argued that this undermines autonomy as people can simplify information in a way that is incorrect or that does not align with the level of risk of what they are consenting to.[123] However, others argue that simplifying risk communication increases autonomy.[69,123,255] Simplified risk description may be best when identifiable risks are low (such as biobanking).[123]

Together, these issues may mean that there is not a one-size-fits all approach to seeking consent, as it can be interpreted subjectively, with different parents/carers having different preferences or needs for the amount, type and format of information they receive to consider themselves able to provide "genuine" informed consent.[90] It is possible to tailor the consent process to each individual, taking each person's preferences and comprehension into account.[90] Alternatively, others argue that the aim of medical treatment, in this case genetic testing, can be decided on in consultation with the individual, and the clinician/researcher can then decide the technical details of how to approach this on behalf of the individual.[90] However, both of these approaches may be difficult for large-scale research programmes (or the national screening programmes they may lead onto) compared to small clinical research projects. Tailoring the consent process or determining what to consent to on behalf of each individual is likely to be too great a burden in this case. It may also create opportunities for discrimination or lead to inequalities.

5.3.6. Engagement of families during the consent process

Engagement of children and families in genomic research through information and informed consent can support the principle of respect for persons, as participants feel included in the research, which

can increase willingness to provide data, improving relationships between researchers and communities.[30] Increasingly, parents/carers also want to be informed in greater detail than in the past about how data will be used and want to be actively involved in decision making.[69,123,255] However, this type of engagement is not essential to hold up respect for persons, and is resource intensive to implement.[30] Box 5.6 below provides an example of how one study used an online platform to communicate with participants.

Box 5.6. Example of engagement between researchers and participants: dynamic consent

Dynamic consent is a tool that allows participants to view and change their consent preferences in real-time.[216] It is also a platform used for communication between researchers and participants, for example to keep participants up-to-date with research findings. This tool can support engagement between researchers and participants, and allows researchers to better manage and record communication with participants. However, there are concerns that the use of online platforms could exclude those without access to the necessary technology.[216]

See Section 5.3.4 for further detail on the different types of consent.

5.3.7. Determining when to seek consent

As well as the issue of determining what type of consent approach to take, there are also challenges with determining at which time point(s) to ask for consent (e.g. antenatally and/or postnatally); however, this was not discussed in great detail in the literature.[72,86,112,255] The point at which consent is sought is partly constrained by the type of DNA sample needed for the screening test (e.g. if umbilical cord blood is used, consent would need to be sought more in advance than a blood sample from the newborn).

Consent taken soon after birth may not be optimal as parents/carers may have many competing demands to manage (especially if there have been birth complications), and may not be able to fully comprehend what they are consenting to.[62,178] The timing of consent can also have implications on parents'/carers' willingness to engage, with them being more likely to decline if approached during stressful periods.[72] One study found that it may be more beneficial to provide information during pregnancy, followed by brief refreshers on the information soon after birth and before the test is conducted.[62,178] Taking a tiered or deferred approach to consent can mitigate the issue of asking for consent during stressful periods. For example, oral consent can be asked of parents during the antenatal period, followed by written consent to confirm participation (and/or for participation in research) at a later date.[176,267]

5.3.8. Seeking consent from both parents and dealing with conflict

Ideally, consent will come from both parents (or carers if applicable) due to the familial nature of genetic data – some argue that this should be best practice, while acknowledging that it is not possible in all situations.[95,96] Current guidance from the British Medical Association (BMA) highlights that, legally, consent from only one parent/carer is needed to provide medical treatment of any kind (including, but not exclusive to, newborn screening).[27] In the March 2022 expert workshop, participants discussed that consent from one person should be deemed enough to go ahead with WGS, and if two parents/carers are present, both should provide consent for newborn screening to take place.

Potential conflicts can occur between parental opinions for whether screening should go ahead.[59] The BMA guidelines recommend attempting to reach an amicable consensus, but if this is not possible, clinicians can be reluctant to override strong parental/carer opinions (where there is no clearly strong benefit either way).[27] Expert workshop participants noted that as a general rule, WGS should not take place where there is disagreement between parents/carers. However, this links to the issue discussed earlier around what is in the child's best interests. Where consent relates to clinical care (i.e. screening), it may be considered in the best interests of the child, and so questions arise as to whether parents/carers should be able to decline. However, for research that does not necessarily offer direct benefit to the child, it may be more acceptable to not enrol a child as a participant if there is parental disagreement.

5.4 Implications for the Newborn Genomes Programme

5.4.1. Summary

There is a range of ethical issues in relation to seeking consent for a newborn genome screening and research programme, these include reliance on proxy consent from parents/carers, genetic data relating to other family members, deciding if/how children should be involved in decision making, and determining which type of consent to use (and ensuring decisions are truly informed).

Reliance on proxy consent

There must be a reliance on parents/carers to provide **proxy consent** on behalf of their child to take part in the NGP. This creates a need to **balance the autonomy of the child with that of the parents/carers**. At the heart of any action taken regarding the health of the child should be respect for the child and support for their best interests, while also upholding their rights to an open future and their right not to know. However, parents/carers also have autonomy over their child, and there is a need to respect the decisions that parents/carers make for their child.

Some argue that parents'/carers' wishes for their child should only be overridden when they are likely to place the child in significant harm. Others argue that proxy consent from parents/carers on behalf of children should not happen in any circumstance (although this is not feasible in practice and would lead to a lack of research conducted on newborns and create subsequent health inequalities). Others take a more pragmatic approach, recognising that parental autonomy should not be given undue importance in relation to individual child autonomy, while acknowledging that children have a right to appropriate guidance from their parents/carers, as long as it is in the child's best interests.

The balance between parental and child autonomy varies depending on the type of activity being conducted (clinical or research, and the type of research). As the NGP is a research study, parents/carers should be able to decline participating. This becomes more complex, however, when considering the national (clinical and research) screening programme the NGP could lead onto. Here, the pragmatic approach could be taken in that information on childhood-onset, actionable conditions is shared as it is in the best interests of the child's health, and it could be argued that parents/carers should not be able to decline as this could cause harm. However, this is more challenging when considering whether proxy consent is appropriate for the long-term storage and use of screening data for research (as would possibly be the case for the potential future screening programme). This may not have a clear, direct benefit to the child, and leads to the necessary consideration of children developing the ability to consent over time. Further issues would arise should the newborn screening include adult-onset and/or non-actionable conditions.

Navigating these issues requires striking a balance between individual autonomy and wider public health interest. While taking an individual autonomy approach can uphold choice and liberty, it can be argued that children have a duty to contribute to the social good. For the NGP, this would be the contribution that genetic data could make to research and ultimately improving health outcomes. Others argue that children do not have social obligations and should not be exposed to research risks for the benefit of others. Taking an individual approach to autonomy does not allow recognition of relational autonomy (see below), and how this influences autonomy.

Genetic data are familial in nature

Genetic information has a **relational component**, as while it is unique to one individual, any information about health risks is also relevant for family members. This creates the question of **whether there is a duty to warn family members** about a higher risk of a condition, and leads to the notion of relational autonomy. In the case of the NGP, this would involve conversations with healthcare professionals and wider family members to discuss the preferences and potential implications of consenting to newborn WGS screening. Throughout this process, it would be vital to place the newborn at the centre of decision making, and any preferences and opinions of others should guide decisions, but not be a key decision-making factor. Instead of taking an individual autonomy approach to consent for the NGP, a relational approach could be taken, which would mean the genetic results belong to the newborn and family (although there are concerns about maintaining confidentiality).

Children gain the ability to be involved in decision making over time

While newborns are unable to consent for themselves to participate in the NGP, they gain the ability to be involved in decision making over time, reducing the importance of parental autonomy. Because of the long-term research aspect of the NGP, this creates questions about **when children should be brought into the decision-making process,** and if consent should be sought for the NGP later in life.

Some argue that children should be offered full autonomy once they reach the age of maturity, and consent should be sought for the future use of data for research (or to withdraw from the study). Some argue that consent is not needed as long as re-contact is attempted if a significant finding is uncovered, because there is minimal risk for the child and/or there is not a significant divergence in the research from what was originally consented to. Seeking consent has implications for increasing burden (on both researchers and the child), and there are challenges with keeping contact details up to date. However, if the NGP has ongoing access to participant medical records then this burden would be lessened, and the justification for not seeking consent would be harder to support.

There are different approaches to seeking consent, and challenges in ensuring that parents/carers can make truly informed decisions

There are three different approaches to seeking consent: informed consent (opt-in), presumed consent (opt-out) and tiered consent (consenting to separate aspects of data usage differently, which can consist of both opt-in and opt-out aspects). The choice of which to use depends on what the data are being used for; each approach has advantages and disadvantages.

Informed consent is often the gold standard approach in research as it upholds autonomy and supports trust. However, providing enough information that is understandable to participants is a challenge, especially in the case of complex genetic topics. It is also resource intensive.

Presumed consent approaches may be easier and acceptable for parents/carers, and may be the preferred approach if a public health perspective is taken and newborn WGS is implemented as part of

a national screening programme. However, presumed consent reduces individual autonomy and is not usually compatible with research programmes.

With a tiered approach, participants can manage their own preferences (supporting autonomy), and children can consent or withdraw when they get older. In the case of the NGP, tiered consent could take the form of, for example, consent for the health screening on behalf of their child, and postponing consent to participate in research until the child is old enough to consent themselves. However, it may not always be simple to distinguish the different activities being consented to.

There is concern that **parents/carers are not able to make truly informed decisions about the use of their child's data**. There are questions around whether more or less information, and how complex this information is, supports or hinders the ability to provide a truly informed decision. This is particularly important to address if consent is being sought for long-term access to and use of genomic or medical record data. Simplifying risk can support participant understanding, and there are arguments on both sides for whether this supports or undermines autonomy. These issues may mean that there is not a one-size-fits all approach to seeking consent, as it is a subjective notion for each parent/carer. While the consent process can be tailored to individual participants, this may be challenging to implement for a large-scale research programme such as the NGP, or newborn screening on a national scale.

The **timing of consent and what to do about parental disagreement** are also important, but not discussed in detail in the literature. Seeking consent soon after birth is unlikely to be the optimal approach as parents/carers may be stressed and will have other higher priorities. This may mean any consent provided may not be truly informed or consent may not be given at all. Taking a tiered approach to consent can mitigate this issue. It may be preferable to provide information during pregnancy, followed by brief reminders of the information soon after birth. The timing of consent is also influenced by the type of DNA sample being taken (e.g. cord, heel prick blood). Ideally, consent will come from both parents (or carers if applicable), although it is acknowledged that this is not possible in all situations. If there is disagreement between parents/carers, a consensus should be reached, but if this is not possible it may be detrimental to override one parent's/carer's strong views.

5.4.2. Examples from other projects

Informed consent

- A study using genetic data collected for the Genomes for Kids study took a two-step approach to consent. Trained nurses first provided information to parents about the study, and a second appointment was held to seek informed consent.[107]
- The Paediatric Reporting of Genomic Results Study aims to inform the debate around returning genetic results on adult-onset conditions to children and parents. The study will use genome data already collected via the MyCode Community Health Initiative. Informed consent will be sought from parents, and children aged 7 to 17 will be able to provide assent (agreement, or not, to participate). Once children reach age 18 they will be able to take part in the informed consent process. In cases where a child is suspected of having a higher risk of an adult-onset condition, but consent/assent is not given to participate in the study, their genetic sample will be stored until they reach age 18, when consent will be sought. In cases where a child is suspected of having a childhood-onset condition but consent/assent is not given to participate, further testing will be conducted to confirm the suspicion, and the results will be returned to the individuals without further data collection for the study.[232]
- The 100,000 Genome project used broad, informed consent. Participants consented to taking part in the study, donating a sample, their medical records being accessed, and data to

explore the causes and risks of health conditions being analysed. They also consented to results being returned to them, and to receiving additional findings and carrier testing results.[75] Participants were able to separately consent for whether they wanted to receive, for example, additional genetic findings, but could not specify which particular condition they wanted to know about.[11]

- The Spanish Undiagnosed Rare Diseases Programme supports patients with undiagnosed rare conditions to obtain a diagnosis via genetic testing. It used an informed consent approach whereby participants had to consent to being admitted into the programme, registering in the Spanish Rare Diseases Patient Registry, for storage of their sample in the Spanish Rare Diseases Biobank, carrying out whole exome sequencing, and the sharing of de-identified data among rare disease experts.[154]
- GeneScreen, an adult genomic screening study for rare conditions, uses online methods of informed consent to recruit participants. Potential participants were sent information about the study by mail, with details on how to access further information and provide consent online.[35]
- The Korean Welfare Genome Project recruited 1,000 healthy adults and provided information on their genetics to explore perceptions around integrating genetic and healthcare data. Informed consent was sought from participants, who agreed to provide genetic samples, for data from health check-ups to be made available, to complete a lifestyle questionnaire, and for their de-identified data to be published.[113]

Presumed consent

- The Icelandic Healthcare Database (a population biobank used for research and commercial purposes) has an opt-out approach to consent. This approach was decided on after extensive consultation with the public. Citizens were able to opt-out of the biobank using a form available in all healthcare organisations. While this approach had public support, many experts argued against it on legal bases, stating that it did not meet ethical research standards. The Icelandic Supreme Court ruled that the opt-out approach was justified, and only 7% of citizens have opted out.[164]
- Vanderbilt University in the United States runs a DNA repository in which blood from all Vanderbilt patients is collected if they have not opted-out. The genetic data are then linked to electronic health records, de-identified and made available for future research. Patients can opt-out of this process via the routine hospital consent forms. Fewer than 3% of patients opted out.[164]

Tiered consent

- The BabySeq project took a two stage approach to consent. Initial consent was sought from parents for providing the results of childhood-onset conditions only. However, as the sequencing methods also identified a mutation related to breast cancer, parents were re-contacted to confirm whether they wanted to receive information about adult-onset conditions. Based on this, the researchers revised the protocol so that participants could not opt-out of finding results about certain conditions, but instead either consented to receiving results about all 59 genes that the American College of Medical Genetics recommends disclosing, or none. The authors note that this approach does not align with guidelines in most countries.[225]
- For current newborn bloodspot screening in the England, information about screening is provided to parents at or before antenatal appointments. Verbal consent is sought postnatally, when parents are also asked if they would like to be contacted about research linked to the screening programme in the future. Parents have some choice in which conditions are screened for, and can decline screening for sickle cell disease, cystic fibrosis and congenital

hypothyroidism individually. However, the six inherited metabolic diseases that are screened for have to be screened together due to the nature of the test, which means that parents can agree or decline screening for all six, but not individually.[217]

- The All of Us research programme is a longitudinal programme of work that aims to recruit over one million US participants from traditionally underrepresented groups. The study uses an electronic, modular informed consent process. The modules allow a tiered approach to be taken, whereby participants can provide consent for the "primary" module (taking part in surveys, linking data to other sources and collection of other health data). There are then two other modules of consent that participants can agree to, one related to the collection of data from electronic health records on a regular basis (including identifiable information), and one related to receiving genetic results relating to actionable conditions. Each of the three consent modules include an eConsent screen, evaluation questions to determine participant understanding of the research, and a signature form.[53]
- The Human Heredity and Health in Africa (H3Africa) Consortium is made up of research and infrastructure projects from across Africa that aim to improve structures for research into the genetic and epidemiology aspects of diseases affecting local populations. Research performed under the umbrella of this consortium uses an informed consent approach, preferring broad consent to allow for future uses of data. The use of broad consent for this consortium still includes specifying the type of research the data can be used for (e.g. research into certain conditions). The consortium also makes use of tiered consent, whereby participants can consent to the primary study and secondary use of data in future studies separately. Withdrawal is possible, although not if analysis has already occurred, or where samples have been sent to other researchers.[192]

5.4.3. Key areas for further research and consultation

The key remaining unanswered questions that require further research and consultation in relation to consent and decision making specifically for the (research aspect) NGP are:

- Whether proxy consent for genetic research, including the long-term use of data for research, is less clear cut than for clinical WGS. For example, is it acceptable for parents/carers to provide proxy consent for long-term storage and research use given this does not directly benefit the child?
- How can healthcare professionals and researchers involved in the NGP ensure that decisions made by parents/carers are truly informed (if informed consent approach is used)? What factors or approaches would "enable informed decision making in the context of the NGP"?
- As the NGP will hold and use data for a long period, how should children be involved in decisions to participate in the programme over time? For example, should children be asked to consent once they reach the age of maturity?
- While the NGP will share childhood-onset, actionable findings, there may still be some implications for family members, such as those relating to reproductive decision making. Should other family members be informed of the genetic results that may impact them?
- At which point(s) during pregnancy or after birth (depending on the type of genetic sample taken) should parents be approached about participating in the NGP?
- Which type of consent should be sought for the NGP, and for a nationally implemented screening programme if WGS were adopted for this purpose: opt-in or opt-out? If opt-in is used, should a tiered approach to consent be taken? For example, consent from parents/carers

for screening results and seeking consent from children later in life for research use. And/or should participants be allowed to consent for different uses of data differently

6. Interpreting, communicating and acting on findings

Chapter summary points:

- There are four categories of results that could be returned to participants in newborn genome screening programmes: 1) childhood-onset actionable conditions; 2) childhood-onset non-actionable conditions; 3) adult-onset actionable conditions; and 4) adult-onset non-actionable conditions. While it is straightforward to justify the return of data on clinically actionable childhood-onset conditions, the return of the other categories depends on the context. Return of adult-onset conditions is generally not recommended for newborn screening programmes.
- The obligation to return results beyond the initial screening intervention is less clear, but researchers, health professionals and the public generally support the return of clinically actionable findings arising from the reanalysis of genetic data.
- The return of "raw" data (e.g. full genome sequences) to children or their parents presents ethical challenges. It may create an obligation for researchers to provide interpretation support for recipients or to develop policies to mitigate against unintended consequences of third-party reinterpretation of genomic data. It is also unclear if parents have a legal right to their child's genomic data.
- There is a degree of uncertainty in WGS findings, as for many genetic variants it is not 100% certain that individuals who have them will go on to develop the associated health condition. Additionally, as the NGP is a long-term programme, the conditions on which information is provided (and what information is available for each condition) will evolve over time through ongoing research.
- There is a need to consider the balance between benefit and harm when dealing with uncertain and unsolicited findings. For uncertain findings, this means considering issues around a lack of knowledge about diagnosis or potential future treatments, and the potential impact on relatives. For unsolicited findings, there may be ethical tensions related to the programme's remit or informed consent models regarding which results should be disclosed (e.g. only childhood onset conditions).
- Ethical issues around communicating genomic findings include a risk of undermining the parents' and patients' rights not to know, despite the potential obligatory disclosure of certain uncertain or unsolicited findings and the challenges of balancing the best interests of the child with the best interests of the family.
- Care pathways are the healthcare resources and care streams available to patients seeking diagnosis and treatment after having accessed their genetic test results. Newborn genetic screening can be the beginning of potentially lengthy and costly follow-up processes, including possibly unnecessary patient care due to the risk of uncertain or false positive results, resulting in over- or misdiagnosis. This requires the creation of integrated care pathways to manage follow-up care, consideration for impacts on healthcare professionals, and consideration for workforce development and training to carry out interventions and education.

6.1 Determining which findings to return and when to share them

There are important ethical considerations in determining which results are returned to the individuals and/or their parents, both from newborn WGS screening for clinical purposes and from research activities that make use of these data in the short, medium and long term. As outlined in Section 3.3, there has been some discussion about whether there is a legal responsibility for researchers to return results to participants, but there is also an ethical dimension. Deciding which results to report, and when to do so, requires balancing benefits against risks to ensure minimal harm (particularly to the child).[66,96,97,129,145,220,268,273] This is especially important in paediatric research as children are more vulnerable than adults due to their limited autonomy and lack of understanding.[95-97,106]

However, in addition to potentially improving care,[8] returning results to participants upholds principles of respect for persons and justice and supports research engagement.[7] Those in favour of disclosing genetic results to parents or individuals argue that people have a right to know their genetic information.[7,146] Sharing results can be necessary to demonstrate benefit sharing and reciprocity.[52,71,146] If participants will not receive any direct benefit from participating, such as a diagnosis or monetary compensation, it can be argued that there should be some other reciprocal action to give something back to the participant.[52,71,146] Some argue that this reciprocity should extend to family members (for both childhood and adult onset conditions), linked to the duty to warn discussed in Section 2.1.[15,52,181] However, framing the return of genetic results as the main value received by participants may not fully address principles of equity and inclusion, and will not necessarily instil the feelings of solidarity and accountability essential for the operation of the research (see Chapter 4 for further discussion).[146] In the case of biobanks, not all participants will directly benefit from their involvement, but the biobank can benefit other people, and so the indirect reciprocity principle is applicable.[115]

If one of the main objectives of WGS for all newborns is the identification of actionable childhood-onset conditions, then some results will necessarily be returned to families as part of the programme objectives. The types of information returned at this stage requires careful consideration from an ethical perspective, but will likely also be heavily governed by public health considerations regarding screening (discussed in Section 3.1). However, families receiving clinically actionable results at the initial screening stage will be in the minority. If these data are subsequently used for biobanking and research, this raises the key questions of what information should be returned in the longer term, and when should return of this information occur. In discussing these issues, this chapter first outlines the types of information that could be returned to participants and how this could be undertaken. It also considers the implications of returning this information at different points in the life of the newborn.

6.1.1. Return of results during childhood

This chapter defines four types of conditions, each with different implications for if and when results can or should be returned: 1) childhood-onset actionable conditions; 2) childhood-onset non-actionable conditions; 3) adult-onset actionable conditions; and 4) adult-onset non-actionable conditions.[71,97,265,273] The literature discusses three main potential methods for disclosing results (6.1), which relate to the type of information that would be conveyed. Within each of these is the issue of proxy consent and that children mature over time, with the argument that children should take over decision making once they reach maturity.[129] The issue of re-consent is discussed in detail in Section 5.3.

Box 6.1. Potential approaches to reporting genetic results

1. **Not reporting results** back to participants:
    - Reporting results could lead to psychosocial impacts, even though the results might not be certain, or lead to over-/under-diagnosis.[97]
    - It may be deemed unethical to not feedback results that are actionable.[97]

2. Participants can be **given choice about whether to receive results:**
    - Parents can decide whether to receive secondary findings (but the potential variants that can be known about are restricted by researchers/clinicians).[71]
    - The reporting of results might differ depending on the conditions being screened for (e.g. child versus adult-onset, actionable versus non-actionable, see below).[97]
    - This might involve recontacting participants about new results from research to ask if they would like to receive them.[97]

3. **Results are fed back depending on their potential benefit:**
    - Results that are clinically relevant and actionable are returned.[97]
    - Determining what counts as a potential benefit is difficult, and could be broad if concepts such as personal utility are considered.[97,251]

Childhood-onset medically actionable conditions

The primary purpose of a newborn screening programme, regardless of whether WGS is used, is to identify children with childhood-onset medically actionable conditions. Returning these results is therefore ethically straightforward. Within the literature there is general agreement that it is permissible to tell parents if their child is at risk of a childhood-onset, actionable condition, with some arguing that this should also include secondary findings.[15,106,129,181,265] Recent guidance from the Global Alliance for Genomics and Health also takes this perspective.[149] This approach upholds the principles of non-maleficence, while not returning information on adult-onset conditions safeguards the child's autonomy, right to an open future and best interests.[181,265] It can be argued that parents should not be able to refuse results about childhood-onset, actionable conditions as the best interest principle should override parental autonomy;[95,97,129,265] however, this depends on the context; while it may be true for clinical tests, it may not hold for those generated as part of research.

Childhood-onset non-medically actionable conditions

Less straightforward is whether to return information about childhood-onset non-actionable conditions. Doing so can allow parents to plan and put supportive measures in place, but may also have negative psychosocial impacts for the parents and child and lead to overmedicalisation.[265] There is an argument that parents can refuse to know about these types of variants as it does not necessarily medically impact their child, and so there is little reason for the decision not to receive such results to be overridden.[265] However, there is a question of whether parents have a right to ask for this information if it is not proactively offered. Parents may appeal to the right to know, autonomy, the right to benefit from scientific research and empowerment to justify receiving this information.[7,146] However, there is no clinical utility attached to this genetic information, by definition, and thus such

information only has personal utility. If this information is being provided within an LHS with a public health objective, the use of public resources to fulfil such requests may not be considered justifiable,[105] whereas within a private user-pays system it may be more difficult not to provide this information on request.

Adult-onset conditions

Most challenging is the decision regarding whether to return results relating to adult-onset conditions to a child's parents. Knowing about the risk of adult onset conditions can lead to negative psychosocial impacts for parents and can impact the child's right not to know and right to an open future, although it is less likely to lead to overmedicalisation of the child as symptoms are unlikely to appear early.[227,265] It can be argued that parents should be able to refuse to know about adult-onset, actionable conditions as it does not cause harm to the child,[265] provided the child is still able to access this information at a later point in time, if desired. It has also been argued that if parents want to know about the risk of adult-onset, actionable conditions, then this information should not be withheld.[265] This is more contentious as it denies the child a right to an open future without conferring any immediate benefit to them, although it may provide their parents with insight into their own disease risk.[15] Information should perhaps only be shared if there is potential to prevent significant harm.[15] For adult-onset non-medically actionable conditions, as there is no medical benefit to the child or family (as no action can be taken to treat the condition), it can be argued that parents should not be informed of these risks.[106,265] Overall, the risk of adult-onset conditions may be best disclosed later in life, when the child is mature enough to consent for themselves, maintaining the right to an open future and right not to know.[97,227,265]

6.1.2. Secondary or unsolicited findings

Secondary findings are genetic variants or conditions not related to the main research or testing aims, but which are actively searched for during testing, with patient consent.[150] Incidental or unsolicited findings are not deliberately sought by researchers, clinicians or patients, but arise unexpectedly during the course of analysis and could include findings not directly related to a health condition, such as non-paternity.[106,130,213,265] There are varied positions on secondary and incidental findings, both whether they should be returned and what types of variants should be included.[15] The American College of Medical Genetics and Genomics advocates for all secondary findings to be returned, even for adult-onset conditions in children, implicitly taking the position that a child's autonomy and right to an open future may be overridden by clinicians in favour of promoting the best interest of the child (by providing them with information that will be relevant in the future) or avoiding harm to relatives.[15,181] In contrast, other organisations, including the European Society of Human Genetics and the Canadian College of Medical Geneticists, recommend minimising any search for secondary findings and only returning adult-onset findings in children where there are actionable clinical implications for family members.[15,273]

It can be morally difficult for professionals if they become aware of an incidental finding but are unable to disclose it if it is outside the programme remit.[199,250,261] There is also potential for intrapersonal conflict between a person's professional role and personal moral intuitions.[199] Some professionals may choose to skim over any controversial elements of screening results or information to focus on other issues, without talking about the more difficult aspects.[199] However, the potential risks of withholding information may be less defensible when those results provide clinical benefits to the patient.[67] However, decisions regarding secondary or unsolicited findings do not reside solely with clinical professionals: parents/guardians, and the child when old enough, should also contribute to these decisions, as research has found that participants believe disclosing results is an ethical necessity, with

comments implicitly framed in the context of "benefit-sharing" and reciprocity.[52] Disclosure of results relates to parental right to know or not know.[59,199,279] Vears (2021) puts forward a categorisation of whether parents should be able to choose to receive or refuse different types of findings (as defined above) using the Zone of Parental Discretion framework,[2] shown in Table 6.1.

Table 6.1. Summary of whether parents should be able to opt in or out of receiving different types of WGS findings.[265,§§§]

Table 6.1. Summary of whether parents should be able to opt in or out of receiving different types of WGS findings based on their child's data

Type of unsolicited findings	Benefit	Harm	Receive	Refuse
Childhood-onset actionable	Yes	No	Yes	No
Childhood-onset non-actionable	Possible	No	Yes	Yes
Adult-onset actionable	Possible	Unclear	Probably	Yes
Adult-onset non-actionable	No	More likely	Probably not	Yes

Source: Vears, D. F., et al. (2021). "Views on genomic research result delivery methods and informed consent: a review." Per Med 18: 295-310.

The categorisation in Table 6.1 assumes that no harm can arise from the disclosure of childhood-onset non-actionable conditions. However, this is within the context of a child being tested because they have clinical signs and symptoms that suggest testing is warranted. The disclosure of childhood-onset non-actionable conditions may be more problematic for both the child and parent in a population-screening context where there are no pre-existing signs or symptoms.[16,34,182,204,205,221,261] Clinically untreatable conditions can also disrupt parental expectations as there is no immediate clinical benefit for their child after they have received these unsolicited results.[52] Additionally, parents do not always view the best interests of their child in relational terms,[6] and the disclosure and management of unsolicited findings can negatively impact and burden the parent–child relationship.[54] Parents may find themselves readjusting, or restricting, the lives of their child due to anxiety and worries following unsolicited results.[31] Specific to newborns, information disclosure on unsolicited findings has the potential to cause harm through influencing parents' perception of their child, subsequently disrupting bonding, although research on children's values and preferences regarding the return of unsolicited findings is limited.[163,204]

[2] Zone of Parental Discretion is a narrowly focused ethical framework used specifically in the context of decision-making tensions between parents and clinical staff when conflicts arise that may affect the delivery of critical clinical care for a child. It was originally proposed in Gilliam. The zone of parental discretion: An ethical tool for dealing with disagreement between parents and doctors about medical treatment for a child. *Clinical Ethics* 11(1), 1-8 (2015). It emphasises parental autonomy over the best interests of the child, considering only whether parental actions will result in harm to the child. Although issues raised by returning results for non-actionable and/or adult-onset conditions will be avoided at the screening stage of the NGP as the decision has already been made to focus screening on currently actionable or clinically treatable childhood-onset conditions, this report elaborates on this as it may still be relevant for decisions regarding the long-term return of results from the biobank aspect of the NGP.

Overall, whether secondary findings should be returned, at what point, and including which variants is still an area of debate. However, the approach to informing parents of results, including whether to disclose unsolicited findings, should be reflected in the model of informed consent adopted by a programme (see also Chapter 5 and Section 3.3.3).[261]

6.1.3. Long-term return of results and data

Return of results beyond the initial screening intervention

What is not discussed to a great extent in the literature in the context of return of results is the return of information obtained from the reanalysis of genetic data held long term in repositories. Whether there are legal obligations to return such findings is unclear (discussed previously in Section 3.3.2) and depends on jurisdiction, as is how such information should be returned to participants (i.e. directly to participants or via a healthcare professional), at what level of detail, at which time point, and whether disclosure should depend on further consequences (e.g. treatment options, psychological impact).[24,59,116]

A recent systematic review of stakeholder perspectives on return of results from genomic research found that all stakeholder groups (including researchers and health professionals) prioritised returning clinically actionable findings in preference to all others, although participants and the general public were also interested in receiving findings that are not clinically actionable.[266] Returning clinically actionable results to participants can be justified by the principle of beneficence, and the American Society of Human Genetics position statement on return of results defines the obligation to return results based on whether the result is or is not clinically actionable.[24,78] What constitutes a clinically actionable finding is not rigidly defined, although the statement is clear that researchers do not have an obligation to pursue the identification of new genetic variants or alterations in variant interpretation outside the scope of their original study.[24] This perspective is oriented towards research on a specific set of conditions, and it is not clear how it would apply to a biobank where participants have provided broad consent for research.

The information available to be shared and what participants wish to receive may change over time, particularly in the context of a paediatric, life-long biobank.[246] Providing participants with ongoing information about what might be available to them, and allowing them to change their position on what they wish to know, would maximise their autonomy, as argued by Gold and Green (2022).[78] When this type of approach has been implemented in practice, over a third of participants contacted regarding clinically actionable secondary findings elected not to receive them, despite extensive research indicating that most people would *theoretically* want to receive such information.[21] However, it could be argued that there is more obligation to implement this type of approach for a biobank using data from newborns or children as the data subjects did not initially agree to participation themselves (see also the discussion on consent in Chapter 5).[97,246]

It has also been argued that research using a newborn screening repository does not burden children and requires no contact between researchers and children, and could therefore be exempt from returning results as it is harder to validate findings because it is much less feasible to obtain samples for follow-up testing and review medical records.[97] This is particularly true if the data on health conditions and other factors are drawn from electronic health records rather than participant surveys or interviews as there will be no direct, long-standing relationship between the researchers and research subjects (as is the case in conventional cohort studies). The nature of such research may remove the obligation to identify and return secondary findings (even if clinically relevant findings are found) if it can be justified that subjects are participating for altruistic purposes and not personal gain.[52,227] This

argument may be more difficult to sustain within an LHS that places obligations on researchers who use participants' data, although participants will theoretically receive indirect benefit from the research their data have been used in via improved diagnostics or treatment.

Return of "raw" data

Patients and participants may also wish to gain access to their "raw" (uninterpreted) data (e.g. full genome sequence, or complete medical records) in addition to the return of specific results (interpreted "raw" data).[275] It has been suggested that clinicians and researchers who generate genomic data have a responsibility to provide children (and their parents) with the opportunity to share these data.[153,220] However, while the return of data from medical records will likely be at least partially interpretable by the recipient, genomic data cannot be interrogated without specialist informatics tools. Thus returning genomic sequence data on a large scale may require some type of informatics support for recipients, or the development of policies to mitigate third party reinterpretation of genomic data, which is a poorly regulated area and could lead to an increased burden on public healthcare providers in terms of clinically unwarranted follow-up testing and diagnostics.[42,204,275] Under current UK legislation, people have a right to access their own health records, which may encompass genomic data; however, the situation regarding requests by parents or guardians to gain access to their child's genomic data is less clear.[202] Parents or those requesting proxy access to a child's genetic information should be doing so on behalf of the child and in the child's best interests; however, people report a range of reasons for accessing these data, including reanalysis (by themselves or a third party).[15,101,275] Thus the potential sharing of these data raises concerns about risks to the child's privacy, current and future health interests, autonomy, and development.[15,261] Providing parents or guardians with a child's raw data also transfers some responsibility for keeping these data confidential to the parents/guardians, as it will effectively be shared with them indefinitely and they could publish their child's genome on an open-access database or unintentionally leak it.[15,46,218] As new sequencing technologies are used in biomedical research and the number of third party organisations providing genome interpretation services increases, the number of research participants and patients asking for their genomic raw data is also likely to increase.[235,275]

When making decisions on parent/guardian access to a child's genetic data, the age of consent to clinical treatment, research and data processing should be considered, assessing the child's capacity and consulting the child on their views before any data are released.[15] Pre- and post-access information should remind parents/guardians of their ethical responsibilities for handling, using and sharing their child's genome, and the implications of raw data for the child's well-being, privacy and developing autonomy.[15] The context of the request for the data should also be considered, as sharing different levels of data are sufficient for different circumstances; for example, the interpreted results rather than raw sequence data may be sufficient for the context, despite a request for the raw data.[15]

6.2 Managing uncertainty

The previous sections of this chapter discussed the results from WGS as though the findings provide complete certainty about the risk of developing particular conditions, and the conditions for which results will be returned are known in advance of parents/guardians consenting to their child being involved. However, in most cases there is a degree of uncertainty in WGS findings, as not all genetic variants display full penetrance (i.e. not everyone who carries a variant that increases risk of a condition actually develops it). Additionally, in long-term research programmes, such as biobanks, the conditions on which information is provided (and what information is available for each condition) will evolve over

time through ongoing research. This section discusses issues related to the uncertainty inherent in WGS findings, and how this may evolve over a participant's lifetime.

6.2.1 Uncertainty of findings

Genomic results and information are complex, and as with any screening test raise the possibility of both false positive results (indicating that a given condition exists when it does not) and false negative results (wrongly indicating that a condition is not present). Genomic screening consists of two stages: 1) detection of a variant in the genome, through sequencing and automated software; and 2) interpretation of whether the detected variant can lead to a condition. Sequencing and automated detection of variants are at a relatively mature stage compared to the interpretation stage, and most uncertainty about the results stem from interpretation.[7,106,126,162,186,222,250,273] This can create challenges for how findings from genomic screening, in either a clinical or a research context, can be communicated to families, and how the results should or can influence clinical care. Screening is not a diagnostic assessment, rather a generalised investigation strategy for, in this context, newborns.[45]

Due to a certain degree of subjectivity in interpretation guidance and its mainly manual nature, interpretation will inevitably vary across health facilities, and sometimes even between healthcare professionals.[186,222,250] The cause of this variation is also attributed to the current lack of knowledge about genetic variants, many of which are unknown or have uncertain significance.[7,44,70,140,152,165,186,222] This can be accounted for or approached through the harmonisation of variant classification either for a specific programme or on a wider scale.[3] Examples of this have been seen within previous programmes, such as the All of Us Research Program, where variant classification concordance was established for particular variants discovered in secondary findings.[3]

There is also an acknowledgement that variant interpretations will change over time.[250] This is a particular limit of screening tests,[44] and may dissuade some parents from agreeing to their child's participation or programme engagement.[116,182] Parents also do not necessarily expect to receive uncertain results or findings from screening tests.[114] Research emphasises the importance of highlighting the potential limitations of screening tests during the consent process,[11] with evidence from the BabySeq project showing that a decline in research engagement is often due to concerns about uncertain results.[72] Other reasons cited for research participation include trust and its role in the decision about whether to participate, [11,18] including trust in the researchers conducting the study making individuals more likely to agree.[11] Other reasons noted for declining participation include general lack of interest, inconvenience and concerns about privacy.[72] Common motivations for agreeing to participate included altruism and the potential benefits for family members.[18] Looking more broadly at participation in screening programmes, authors have acknowledged that parents may not see any reason to participate if their child is seemingly healthy,[182] and may have concerns on the involvement of private interests (including external private companies).[173] Other research has highlighted how parents may choose not to participate in screening as the test cannot determine how serious the condition will be or give the probability the condition will present in the future.[182]

Considering the balance between benefit and harm

The literature reviewed has highlighted the need to consider the balance between benefit and harm, relevant specifically to uncertainty. Uncertain findings raise a slightly different set of problems, for example, a lack of knowledge about diagnosis, or potential future treatment, makes deciding on appropriate care and adequate counselling difficult.[261,279] Current newborn screening tests yield few false negative results, but do incur substantial numbers of false positives, which lead to increased emotional and financial costs.[16,279] For example, underestimating the consequences of uncertain

findings could lead to false reassurance,[263] and overestimating the consequences could lead to harmful unnecessary overtreatment, and adversely impact access to lifesaving treatment for others.[8,13,106,117,129,186,261,265,273] Uncertain results also give rise to further psychosocial impacts,[30,79,97,117,129,273] with both parents and clinicians reporting psychological distress.[6,205] [114]

Disclosure of uncertain findings may also carry impact for direct relatives, with the potential for family dynamics and relationships to be disrupted.[19,106,117,129,256,273] When findings do not clearly indicate which treatment is appropriate or whether further care is needed they can create additional burdens.[261] Further follow-up and testing can take a significant amount of time and cause additional stress or anxiety to both the child and their family.[65,70,117] Treating the child as sick, when they would otherwise be considered healthy, can lead to harmful overtreatment and produce adverse psychosocial effects.[70,261] Equally, treating a child with uncertain findings as healthy comes with the risk of the child developing symptoms which early treatment could have prevented.[261] In both cases this could place a substantial burden and overutilisation of the healthcare system.[70,162]

Evidence regarding potential harm is emerging and not yet systematically measured;[186] however, research findings have noted that the benefits of identifying and monitoring infants with an uncertain diagnosis may outweigh the potential harm.[47,140] It is also difficult to fully understand the potential benefits and risks as they may only accrue over time.[230] This difficulty can be mitigated in the context of a newborn screening programme by limiting the return of results to those with a high degree of certainty.[19] However, results from research programmes that do not use clinically approved laboratories or interpretation approaches may be more uncertain, raising questions regarding the threshold that research findings would need to meet for "certainty".

6.3. Communicating findings

Communicating uncertain and/or unsolicited findings to individuals raises multiple ethical issues.[59] As highlighted by Eichinger,[59] these include a risk of undermining the parents' and patients' rights not to know, despite the potential obligatory disclosure of certain uncertain or unsolicited findings, and the related challenges of balancing the best interests of the child with the best interests of the family.

6.3.1. Determining how results are communicated

The role of genetic counselling and specialists

Genetic counselling is important for supporting families through screening and possible results, which can often be unclear or difficult to interpret.[11] Research has also noted that new information cannot effectively be assimilated by parents post birth,[255] and the ability to retain this information may be momentary in nature, causing parents to feel underinformed and to have misconceptions about results.[182,255] Professional expertise and time are required to explain certain types of results to families,[250] with information regarding the risk of unsolicited findings and uncertainty best communicated by a trained professional.[19] Unsolicited findings also make adequate genetic counselling increasingly difficult to provide,[261] as they may raise more questions than answers for some families.[19] It often remains the responsibility of the genetic counsellor(s) to appropriately interpret results and give proper advice and explanations to parents.[279]

Most countries appear to have several options for who is responsible for providing information to families.[69] Individuals with key roles related to the return of screening results include specialists,[167] nurses,[69,191,259] midwives,[69,254,276] paediatricians[199] and medical advisors.[199] Medical advisors generally

can give both solicited and unsolicited advice about the delivery of newborn screening to all parties involved.[199] Paediatricians can also have a role as a screening healthcare provider, and answer questions relating to the diagnosis itself, incidental findings or how to deal with carrier status information.[199]

When returning findings to families, the information is often shared by a nurse or midwife,[191] with responsibility for providing pre-screening information and obtaining consent often lying with midwives.[191,254] Midwives represent a key group of health professionals involved throughout the screening process, and are often the source for information about screening for both patients and families.[276] The midwife, arguably, would then appear to be one of the most appropriate healthcare professionals to deliver results.[69] The individual(s) responsible for communicating information to families should be clearly defined within the programme guidelines.[69]

Providing nurses, midwives and other involved professionals with the most current evidence and training on genomic screening is essential for ensuring positive contributions to quality care for both the newborn and their family, particularly due to the wide array of conditions and variants which can be screened for.[191,259] Communication during return of findings can also help families cope in healthy ways, particularly if results are found to be uncertain.[114] Regardless of which healthcare professionals are involved in the provision of information and communicating findings from screening, adequate trained staff and appropriate materials to help parents are needed.[69]

6.3.2. Psychosocial impact of results

The literature reviewed noted that there is currently less known about the psychological impact of returning results in the context of WGS, compared to genetic results more generally, on both children and their parents.[205,221,222,265] Studies thus far indicate that the impact of results is mixed among parents and children. For some families receiving WGS, results come with great value when it presents an opportunity to intervene and find treatment, and for others it only creates fear and anxiety.[162] There are generally knowledge gaps relevant to the psychosocial impacts of WGS.[36,250] The impact beyond parents and the psychosocial effects of WGS to the rest of the family, and how this may subsequently impact on family dynamics, is also important to consider.[167,263]

Parental response and reaction

The results from screening potentially have a range of psychosocial implications for parents. Results can often cause increased worry[182,258] and stress on families, alongside overall increases in anxiety,[36,141,162,233,238] particularly where there is potential future uncertainty.[70] Results may also cause some parents to develop depression upon receiving positive results.[31,222,233] Research has found parental reports of thoughts of self-harm and suicide resulting from an overwhelming guilt that they have harmed their baby through feelings of personal responsibility for a condition,[31] and fear that they will not be able to support the child – with some parents possibly needing onward referral to appropriate adult mental health services.[31,222,233] Diagnosis is not a one-off event, but should be seen as the start of a process and lead to the development of a strong relationship between patient, family and health professional(s).[31]

Psychosocial impact may, however, vary across individuals – what is a significant impact for one person may be minimal for another.[96] Relatedly, there may be misaligned expectations from parents (and healthcare professionals and researchers) that something can be done about a clinically significant variant, even if this is not the case – particularly if the testing is offered by the NHS.[6,11,18,22,52,56,65,70,72,86,105,112,117,123,148,162,189,191,201,230,233,236,237,244,253,255,261] Parents may also not be

genuinely prepared for a positive result indicating their child is at risk of a genetic condition,[22,70,77] particularly when their child presents as symptomless or pre-symptomatic with risk of developing symptoms in the future.[61,162,261]

Studies have also shown parents to have reduced enthusiasm for screening programmes upon receiving potentially worrisome results,[258] and subsequently experience a decrease in their well-being and mental health.[31,237] For particularly vulnerable families (for example those socio-economically disadvanted[156]), without prior education on screening they may have negative interactions with the system. An example of this is poor communication around newborn screening, which can cause residual stress or worry[64] and potentially negatively influence a family's perception of the healthcare system.[64] A lack of information has been seen to magnify stressful emotions related to positive screening results.[64] In some cases, parents are left with feelings of confusion, fear or anger, and are unable to take action as they were not equipped with the knowledge or skills to understand the results.[64] Skills to build on include increasing knowledge about screening tests and self-efficacy to better enable participation in the newborn screening system.[64]

Parents have also reported feeling a sense of relief when they gain knowledge of their child not inheriting a family genetic condition,[167,182,261,263] whereas they would otherwise feel guilty if they had not taken the opportunity to partake in screening.[182] With potentially inheritable conditions, many parents often struggle with how to communicate this risk to their children due to fears of causing distress.[168] Therefore, receiving results has the potential to provide relief to parents and enable them to act accordingly when needed.[141,167] The knowledge gained through testing was preferential to some parents than the uncertainty of risk level,[156] particularly when results are empowering to both the patient and family.[156] Results can help parents support their child and increase their preparedness when there is a diagnosis/identified condition.[156] Findings can enable parents to look to the future and act/prepare accordingly[116,152,156] through making further necessary decisions, when advised and educated by the screening provider to do so.[64] Results can also lead to positive potential impacts of rapid diagnosis and pathway treatment. Diagnosis received from screening can often shorten the diagnostic journey for conditions identified that are currently clinically actionable or treatable,[237] and get children the care needed quicker. The impact of rapid diagnosis to treatment can possibly help alleviate parental anxiety and distress.[162]

Implications of false positive and false negative results

When receiving results from screening, there are risks of both false positive and false negative results – a negative effect or risk of screening. Studies have shown that current screening yields few false negative results, but does incur a higher number of false positives,[16] with varying implications for both the child and parent.

Preparedness for these events can limit psychological distress for the parents and highlight the need for specialist service use.[255] Designing programmes based on recipients' need for information across the entirety of the screening, diagnosis and treatment pathway may enhance effectiveness.[255] In such cases, infants who falsely screen positive may endure unnecessary diagnostic procedures and potentially invasive treatments, whilst their families also suffer worsened mental health with potentially increased stress and anxiety whilst coping with uncertainty.[70,79,84,276]

The prospect of false positive newborn screening results also raises concerns about overutilisation and an increased substantial burden on health services through further follow up testing and procedures.

[70,84] These issues are further amplified if available treatment is also expensive or associated with serious risks of adverse effects.[70,79]
Regarding false negative results, in some instances medical advisors may deviate from the protocol if they think it is likely that a screening result has been incorrectly interpreted.[199] Communication and the potential for this is something to be considered within the design of a programme, particularly with the risk of uncertain findings and how, or if, these are communicated. Following false negative tests, follow-up testing and clinic visits have been known to cause substantial financial strain, for example through the costs incurred with attending screening (such as travel costs and lost income for parents).[36] Further psychological strain can also put on families if additional testing is then needed,[237] for example through increased unwarranted anxiety[237] and children becoming "patients in waiting".[261,237]

Too many false positive screening results also potentially weaken parental and public confidence in screening programmes, and diminishes future opportunities for programmes.[79] The potential for negative psychosocial outcomes from false positive screening results is a risk associated with any screening programme, and at a national level this risk is amplified.[84] The literature highlights the need for accessible professional support and explanation for parents regarding screening results,[18,31,67] for example through genetic counselling. If parents are not adequately informed or communicated with, their well-being can be negatively impacted and their trust in health services reduced.[233]

6.4. Acting on findings

6.4.1. Care pathways

Care pathways are the healthcare resources and care streams available to patients seeking diagnosis and treatment after having accessed their genetic test results.[209] They are an integral part of wider healthcare systems and can be understood as being the last of three core elements in the case of genetic screening programmes:

1. Interventions before and during the genetic test.
2. System of care within which the genetic test is embedded, i.e. maternity care in the case of newborn screening programmes.
3. Care pathways available to patients, from genetic test to diagnosis and treatment.[209]

Newborn genetic screening does not end upon the return of data,[16,38,48] which is the beginning of a potentially lengthy and costly follow-up process[49,70,249,271] that is only made more challenging by the uncertainty of genomic sequencing data, their limited clinical utility and the sheer number of conditions screened for.[16,45,67,148,186,205,222,250]

Newborn genetic screening can result in the potential escalation of unnecessary patient care due to the risk of uncertain or false positive results, resulting in over- or misdiagnosis.[148] This leads to the medicalisation of healthy children who now must be monitored throughout their childhood.[16,199,237,261] The medicalisation of the healthy life of a child, or the creation of "patients in waiting",[261] creates increased anxieties and unnecessary stress for families,[70] particularly because children may never develop the disease.[140] Children who receive positive screening results, and are subsequently considered "at risk", may be treated differently by their parents and risk developing disordered illness behaviour, such as excessive worries or anxiety about their health.[261] Families may also suffer increased stress, anxiety and financial burden following results from their infant undergoing unnecessary diagnostic procedures and treatments.[70] Some studies noted that even if the diagnosis is correct, there

are limited treatment options for some of the conditions, while other available treatments have a negative impact or severe side effects in children.[162,182,237]

Complexities resulting from genetic screening programmes, such as those outlined above, require the creation of integrated healthcare pathways, including nutrition, psychology, social work and genetic counselling support, to adequately support patients throughout their genetic screening journey.[121] It has also been widely argued that the return of results journey should be facilitated by a genetic counsellor and followed by regular contact during the diagnosis and treatment process.[61,167,250]

6.4.2. Impact on healthcare professionals

The impact on healthcare professionals refers to the influence a newborn genetic screening programme can have on the healthcare workers implementing it. Given the complexity of the social, ethical and legal issues around genetic screening in newborns, healthcare professionals may experience moral distress when communicating with parents both before and after screening.[199] This is due to the inherently social nature of communication between healthcare professionals and parents,[1] and the fact that policy and practice are often incommensurable, resulting in situations where some guidelines are difficult to follow out of concern for the parents' well-being and mental health.[199] This tension can be especially stark when first informing parents about the screening programme and the possibility that their child could receive an abnormal screening result.[199] Midwives reported that this may lead to some professionals choosing to present the information in a way that they find least distressing to expectant parents, such as by excluding the more difficult or controversial aspects of the screening programme.[199]

Another source of tension for healthcare professionals was the reporting and disclosing of uncertain findings to patients.[199,250] Some concerns for healthcare professionals included the few incentives for clinicians to return results, fear of legal action, and lack of resources, time or expertise.[7] Not being authorised to report incidental findings, for example when a pilot programme required them to only provide information about diseases specified at the time of taking parental informed consent, was also a source of moral distress for many professionals.[199] This was especially the case when the disclosure of such results could lead to clinical benefits and improved health outcomes.[67,199] Research showed that clinicians believed providing results to patients was an ethical necessity, and these comments were implicitly framed in the context of "benefit-sharing" and reciprocity.[52] At the same time, healthcare professionals were aware that disclosing additional information to parents or acting on it by referring a child for further tests was at odds with values such as reliability and uniformity of the programme.[199] All these complexities lead to potential intrapersonal conflicts when a person's professional responsibilities and personal moral intuitions do not align.[199]

Even once the decision to disclose information has been made, it remains unclear with whom the professional should share the results of screening, at what depth, at which time point, and whether it should depend on the potential medical and psychosocial consequences.[117] Further disclosure to relatives is another challenge for health professionals, who have mixed views about their responsibility and if they, rather than families, should be the ones to inform relatives.[167] Traditionally, professionals rely on patients and family to share screening results and information to other family members, and often reinforce the importance of this during the disclosure of results.[167] Repository research means that data are used for longer periods of time (including after the child reaches maturity), which can create additional risks not found in one-time clinical trials.[96]

6.4.3. Workforce skills and training

Workforce skills and training relate to the knowledge and competencies that need to be developed by relevant professionals to carry out high-quality healthcare interventions. The professional groups involved in the planning and delivery of a newborn genetic screening programme are IT specialists,[222] clinical and laboratory geneticists,[222] medical doctors[162,222] (especially paediatricians[263]), nurses,[162] midwives,[191,255,276] health visitors, genetic counsellors,[61,167,250] psychologists,[121] and quality assurance experts.[209]

Given that newborn screening programmes are embedded in wider healthcare systems, those systems, as well as the existing workforce, need to be prepared to accommodate the accompanying changes.[16] Healthcare systems such as the NHS are already overburdened and struggle with capacity to meet existing patient needs.[222] The success of every genetic screening programme is highly dependent on being delivered by committed and reflective healthcare professionals.[199] To introduce a new screening programme, consideration should be given to the level of staff training needed to ensure that it is done well at all stages of the process: before, during and after.[209]

Before newborn genetic screening occurs

This stage of the process requires the preparation of suitable infrastructure to support the rolling out of the programme, such as laboratories capable of handling genomic sequencing for the entire population,[186] educational approaches and informational materials for patients,[6,49,167] and staff trained in biochemical genetics.[121] It also requires training doctors, nurses and midwives in educating patients and guardians, and in ethics and appropriate informed consent practices and standards.[16,59,136,191,199,213,249,255,265,276]

Genetic counselling would also need to be offered to all parents or guardians, requiring much larger numbers of counsellors routinely available to undertake this role both before and after newborn genetic screening.[222,279] Genetic counsellors are equipped with the necessary understanding of the social, ethical and legal issues around newborn genetic screening, and can adequately prepare families for the potential benefits and challenges.[43] They can also help parents make as informed a decision as possible about participation in the programme.[59] The literature outlined that when involving professionals other than genetic counsellors it is important to remember that non-genetics healthcare professionals reported low confidence in their genetics knowledge,[250,256] as well as concerns about the impact of results on patients and them not being able to access a genetic counsellor if needed.[250] Other professionals, such as genetics professionals, reported fewer concerns in relation to communicating about genetic screening programmes than their non-genetics colleagues.[250]

If the newborn genetic screening programme were rolled out without genetic counsellors, the literature suggests it would be necessary to provide ethical training for relevant healthcare professionals to enable them to deal with the moral problems they are likely to encounter, some of which are described in Section 6.4.2.[59,199] Such training would require the presence of an ethicist and would ideally be a regular occurrence given that moral problems happen regularly in newborn genetic screening due to the impossibility of preparing for every moral dilemma when protocols are developed.[199] This is especially vital given the variation in how closely healthcare practitioners adhere to protocols and guidelines, especially when there are differing levels of support for the programme in the clinical setting.[59,199]

During newborn genetic screening

Appropriate staff, whether clinical and laboratory geneticists or medical doctors, would require training in the IT skills necessary to integrate obtained data into existing systems, interpret it, store it securely and share it with authorised stakeholders.[16,162,186,222] This requires preparing the workforce for cooperation between and within different organisations to facilitate genomic sequencing, data interpretation and release of results.[70,209,256,258] This cooperation is important to avoid putting any of the healthcare professionals involved in the newborn screening programme under too much pressure.[59] It is also important because of the interdisciplinary nature of the workforce required to implement the genetic screening programme, which requires a good understanding of the technical information on sequencing and the more normative, ethical and legal aspects of the intervention.[256] It is hence necessary to ensure that the diverse professionals involved in the newborn genetic screening programme share the same understanding of the issues at stake, use common vocabulary to solve arising problems, operate within the same theoretical framework about the goals and limits of the programme, and know how to translate screening results to practical clinical settings. [256]

After newborn genetic screening

The return of results needs a dedicated and well-trained multi-disciplinary team of genetic counsellors and healthcare practitioners who can communicate meaningfully with patients and are knowledgeable about how to integrate these results into existing care pathways to ensure access to the best treatment.[31,127,258,261,263] How this is done matters to parents as they can be left feeling like they have to deal with an "information overload" following screening results disclosure.[43] Genetic counsellors should be in regular contact with patients during diagnosis and treatment to ensure adequate support and clarity around available care options.[61,167,250] A recent systematic review found that the period just prior to diagnosis is often when most support is needed, and that counselling and psychosocial support at this point, and at diagnosis, can help avoid long-term negative impacts on the family members of an affected child.[127] Minimising diagnostic delay, providing accurate information and access to specialist knowledge appear to be key to minimising parent and carer distress.[127]

After the results have been returned, patients need to access diagnosis and treatment, including the workforce capacity required to accommodate more follow-up needs.[31,148,159,222] This last stage also requires staff responsible for quality control, monitoring and cost-utility assessments.[209] More staff will also be needed as custodians of collected data, capable of making sense of the evolving science influencing the interpretation of screening results.[16,186] Decisions will also have to be made about data ownership, who will be authorised to access data and when, as well as the appropriate models of accountability for data.[219] One way to achieve this is for both data sharers and users to operate within a system of mutual accountability and data interoperability.[219]

Overall, the rolling out of a new newborn genetic screening programme requires more workforce to address healthcare needs at all stages.[222] Importantly, given the number of diverse people and processes involved in newborn genetic screening, it is uniquely vulnerable to professional mistakes and best practice lapses.[54] This is because all the people involved, from parents to professionals, make decisions on behalf of the child in question, often without adequate consideration for their future autonomy.[54] As the literature suggests, there also tends to be an underestimation of the risks associated with genetic screening for untreatable diseases and subsequent disclosure of results, especially for the child, who may integrate such information into their developing sense of identity.[54]

6.5. Implications for the Newborn Genomes Programme

6.5.1. Summary

There is a range ethical issues to be considered at the stage of interpreting, communicating and acting on findings. These issues include uncertainty of findings, management of unsolicited findings, consideration for the balance between benefit and harm, constraints of the programme, unactionable conditions, determining who communicates findings, and the psychosocial impacts of the findings.

Selecting which findings to share with participants is a key initial step for any screening or research programme. There are **four broad categories of results** that could be returned to participants in newborn genome screening programmes: 1) childhood-onset actionable conditions; 2) childhood-onset non-actionable conditions; 3) adult-onset actionable conditions; and 4) adult-onset non-actionable conditions. While it is straightforward to justify the return of data on clinically actionable childhood-onset conditions, the return of the other categories depends on the context. Return of adult-onset conditions is generally not recommended for newborn screening programmes.

Unsolicited findings pose a further ethical issue for screening programmes. The design of the programme, and its varying constraints, impact whether a condition can be disclosed to the family. It can be morally difficult for professionals if they become aware of an unsolicited finding but cannot disclose to the family if it falls outside the programme remit. There are **potential risks of withholding information**, especially when results provide clinical benefits to the patient. How potential unsolicited findings will be managed is an area to be considered within the NGP, for both the patient and professional.

The **obligation to return results** beyond the initial screening intervention is subject to debate, but researchers, health professionals and the public generally support the return of clinically actionable findings arising from the reanalysis of genetic data. However, there is less consensus regarding the return of "raw" data (e.g. full genome sequences) to children or their parents, and how this should be managed, particularly when parents seek access to these data before children are able to provide consent. For the NGP, this requires further investigation from ethical, legal and social acceptability perspectives to determine the best course of action.

Due to the complexity of genomic results and information, there are **risks of uncertainty and variation in interpretation**. In this context, screening is not a diagnostic assessment, but an investigative strategy for newborns. There is a certain degree of subjectivity in variant interpretation, therefore there will inevitably be some differences across health facilities and between some health professionals. For the NGP, these risks of uncertainty should be communicated to the family early in the screening process. As noted in the discussed literature, this could be detailed and discussed with families at the stage of programme engagement or during the process of consent.

There are various options for **who delivers results and provides information to families** regarding screening, such as genetic counsellors, midwives and nurses. Screening results can often be unclear and difficult to interpret, therefore having the provision of staff or information is key for helping families understand the results and how, when appropriate, they can act on them.

Following the return and communication of results there is the potential for **psychosocial impacts**. Results from screening can lead to a range of psychosocial implications for parents, including increased worry and stress, alongside overall increases in anxiety. This is further exacerbated when

results are uncertain. **Diagnosis should not be viewed as a one-off event, but rather the start of a process**, and encourage the development of a strong relationship between patient, family and health professional(s). Poor communication during this process can increase negative psychosocial impacts of screening results. In the case of the NGP, providing families with the necessary information and guidance for an identified variant would potentially alleviate any psychosocial impacts, including anxiety, and enable them to prepare/act accordingly. However, there is less known within the literature on the psychosocial impact of returning results in the context of WGS for children and their parents, with research thus far showing mixed impacts.

6.5.2. Examples from other projects

Communicating findings, including uncertain and/or unsolicited findings

- The SEQUAPRE study analysed the preferences of parents with undiagnosed developmental disorders for receiving hypothetical exome sequencing results.[37] The findings highlighted that parents preferred to be informed about possible variants of unknown or uncertain significance, especially those most common or likely. Parents also wished to be accompanied by a geneticist, and valued receiving extensive genetic information, in some cases beyond what was initially prescribed.[37] Importantly, research concluded that the diagnostic process should take into account the meaning and potential further implications of diagnosis for patients.[37] This should also be communicated to parents.

- The BabySeq Project is a randomised trial exploring the medical, behavioural and economic impacts of integrating genomic sequencing into the care of both healthy and sick newborns.[100,225] Following this project, research has recommended that studies are designed to minimise the risk of identifying variants linked to adult-onset conditions and those not immediately actionable to support the child's future autonomy.[100,225] This communication of uncertain or unsolicited findings needs to be addressed upfront through the consent process. However, whether to disclose or not is disputed across research.[225]

- A protocol for the Geisinger MyCode® Community Health Initiative project, or the PROGRESS study, outlines how this study will disclose adult-onset results to minors and their parents.[232] This project is still ongoing and therefore the outcomes of this disclosure are yet to be known.

- The MedSeq project explored the use of whole genome sequencing in both a healthy population and a population with suspected genetic cardiac disease.[223] Findings uncovered that patients showed good comprehension levels about the study, including the purpose, risks and policies regarding the return of results. Notably it employed a detailed consent procedure including written forms and highly trained staff, and provided patients with the opportunity to ask questions to study personnel. Patients from this study also believed that physicians communicated their results clearly and effectively, which was a reflection of the key training and genomic education that the involved physicians underwent for the project.[223] Whilst the Genomics England NGP has a different population to the MedSeq project, the exemplar of training relevant staff in how to communicate findings may be something to consider.

- In Genomics England's 100,000 Genomes Project, research results were fed back to the participant's treating clinician for discussion with the patient, after the NHS had validated the findings.[74] Participants were also not obligated to receive secondary results, and could choose to opt-out of this aspect of the programme.[173] If the NGP were implemented on a national

scale within the NHS it would be challenging to adopt this approach to separating research and clinical findings, given that the primary purpose of participating in screening would be to identify the risk of future health conditions. However, this may be more acceptable for the outputs of the long-term research use of repository data generated by the NGP.

Psychosocial impacts, and examples of how to mitigate them

As discussed, few studies have attempted to understand the experience following the return of findings, and the psychosocial effects of such disclosures.[37] Authors have noted the need for a more complete theoretical framework to examine the potential effects of results arising from sequencing[231]:

- Looking at the SEQUAPRE study, the findings showed that while waiting for the results, respondents preferred to be accompanied by a geneticist or a psychologist, rather than being accompanied by a nurse or by other families.[37]

- The Geisinger MyCode® Community Health Initiative protocol outlines how the project will employ genetic counsellors to disclose results, and will conduct a psychosocial assessment during the disclosure visit to monitor the psychosocial impacts.[232] Separate therapeutic sessions with participants who exhibit clinically significant distress, or other psychological outcomes, will also be scheduled.[232]

- Counselling sessions, for example, can be used to help patients understand and adapt to the various implications of their screening results.[277] Sessions can also help patients and families understand and interpret results correctly, further enabling them to use the results to their benefit.[277]

6.5.3. Key areas for further research and consultation

The key outstanding unanswered questions/topics requiring further research and consultation regarding the management of uncertain and/or unsolicited findings, and communicating findings specifically for the NGP, are as follows:

- Genomics England has returned "raw" data to participants under previous programmes; however, UK law is unclear about parental rights to their children's data. Further consultation on the legal and ethical issues surrounding this could be useful.
- The literature highlights potential tensions that arise with healthcare professionals around disclosing unsolicited findings when their professional role and moral intuition may be in conflict. Engagement with the professionals who will be involved in the NGP about this issue could mitigate potential tensions.
- Further research and consultation into how the risks of result uncertainty can be communicated appropriately and meaningfully to parents is needed.
- Evidence regarding the potential harm (particularly in the context of psychosocial impacts) of screening remains emerging within research, and consequently is not yet systematically measured. Therefore, further exploration may be needed for the psychosocial impacts and potential harm of screening results, and how to mitigate them.
- Consultation and further consideration on how to effectively prepare professionals delivering the screening results appropriately to patients and families is needed.

- If results are uncertain, this raises a question regarding the threshold that would need to be met for "certainty" within variant interpretation.
- Understanding what health system resources need to be in place to support parents and health system staff with the NGP as a research study, versus the full, national roll-out of newborn WGS, will be an important task for Genomics England. The professional groups involved in the planning and delivery of a newborn genetic screening programme are extensive, and thus broad training will be required. Further research and consultation on these matters will be critical for successful programme implementation.

7. Governance and the involvement of commercial organisations

Chapter summary points:

- There is **no universally agreed approach to governance** in health research, but consensus on broad principles is emerging.
- There is a move towards the **explicit consideration of promoting equity and stakeholder involvement** in the design and implementation of governance systems and processes, but there is no uniformly accepted and consistently effective approach:
    - Participatory governance and the AFFIRM framework, which incorporates adaptive governance and principles-based regulation approaches, provide two potential strategies for addressing this.
- **How participant or patient data will be used in research, and who will have access**, require explicit consideration and transparency as they are frequently identified as areas of concern for data subjects:
    - The Global Alliance for Genomics and Health has set out the Key Implications for Data Sharing (KIDS) framework to better support paediatric data sharing in genomic research.

Involvement of industry partners in publicly funded research initiatives is a key area of concern for participants. Providing access to commercial organisations and researchers may be challenging to reconcile with the public good rationale for an LHS, unless their involvement is circumscribed in a transparent and legally enforceable way.

7.1 Governance and data use

Governance in health research is perceived in multiple ways, but generally refers to processes and structures implemented by actors such as researchers or funding bodies, rather than the state. These rely on principles rather than law for authority to inform decisions, and encompass a broad range of actors.[143] Governance frameworks for biomedical research and biobanks should facilitate data access, while also protecting participants against potential risks; however, currently there is no consensus on best practice for the governance of genomic databases.[196] O'Doherty et al. (2021) describe the key functions of good governance of a genomic data resource as: 1) enabling data access; 2) compliance with national laws and international agreements; 3) supporting appropriate data use and mitigating potential harms; 4) promoting equity in access to and use of data; and 5) ensuring the use of genomic data for public benefit.[196] In line with this, Gille et al. (2020) emphasise the importance of the transparency and accountability of biobanks, and thus the mechanisms for oversight of how the biobank operates.[76]

Their recent review of international biobanks identified six types of governance mechanisms that address the areas outlined above[76] :

1. **Communication,** including physical and online communication points, clear mechanisms for explaining biobank processes, plain English information for participants, and a scientific protocol.
2. **Compliance** with international and national laws and codes (with documentary proof of this).

3. **Expert advice** from advisory committees, ethics committees and management committees.
4. **External review** of quality management processes and approval from a national ethics committee.
5. **Internal procedures,** including how the consent process is managed, documented policies for key aspects such as data sharing, standard operating procedures for routine activities, and a quality monitoring system to ensure the biobank meets all relevant standards.
6. **Partnerships** such as affiliation to a professional association or network, co-operation with other biobanks to facilitate the harmonisation of procedures, and membership of an umbrella organisation that supports biobank governance.

Many of the mechanisms described above, particularly expert advice, compliance, external review and partnership, help to foster the legitimacy of a biobank and thus gain social licence for its operation.[76,239] Obtaining social licence requires the development of trust, which in relation to governance can support the use of shared or reflexive governance approaches.[184] However, research has highlighted the relative absence of patients and participants in the development of data governance policies. Although much attention has been given to theoretical and practical issues relating to consent, this does not always encompass exactly how data are used and how the outcomes will be shared.[240] This may be particularly relevant when a screening research programme has a clinical component and feeds into a biobank. Outlined below are some approaches to developing governance that address this issue, and that have been suggested for biobanks and other biomedical research using large data sets.

Participatory governance is one approach that has been advocated for providing a role for patients, participants and the general public in the governance of health research.[40] This approach has been used in many contexts outside healthcare and is underpinned by: 1) problem solving that supports relationship building; 2) "bottom-up" participation through which non-experts are supported in decision making; and 3) a deliberative approach that considers all perspectives.[40] This approach is intended to support the empowerment of patients and the public, redress power imbalances, and improve public services; however, its impact in practice has been variable.[40]

Vayena and Blasimme (2021) propose the AFFIRM framework to support the development of governance for health research using large-scale data sets.[264] This framework combines an adaptive governance approach with principles-based regulation, which enables it to be flexible enough to address future research developments, while recognising the range of actors involved in governance and facilitating their involvement in the development and implementation of governance structures and processes. The authors put forward six principles to support the development of governance frameworks, outlined in Box 7.1 below.

Box 7.1. Six principles of the AFFIRM framework for governance[264]

1. **Adaptivity**: The capacity of governance structures and processes to ensure proper management of new forms of data as they are incorporated into health research practices.
2. **Flexibility**: The capacity to treat different data types depending on their actual use rather than their source alone. Flexibility means recognising the impact of technical novelties and, at a minimum, giving due consideration to their potential consequences.

3. **Monitoring**: Risk minimisation is a crucial aim of research ethics. This requires on-going monitoring.
4. **Responsiveness**: Measures are put in place to at least reduce the impact of any risks (e.g. data security breaches) on the rights, interests and well-being of research participants.
5. **Reflexivity**: Assumptions that drive the use of rapidly evolving technologies are put under careful scrutiny as to their plausibility, opportunity and consequences. Public support for, as well as trust in, scientific research may be jeopardised by the reputational effects that can arise if reflexivity and scrutiny are not maintained.
6. **Inclusiveness**: This component of systemic oversight closely resonates with one of the key features of adaptive governance: the need to include all relevant parties in the governance process.

Vayena and Blasimme (2021) argue that the use of these principles ensures transparency in the development of governance structures and processes, which in turn supports public accountability and helps to identify a common ground for all stakeholders involved in a research programme.[264] Given how recently the AFFIRM framework was proposed, further research is needed to determine its utility, particularly for genomic biobanking and LHS.

7.1.1 Data use

One of the main concerns for potential research participants relating to governance is the explicit consideration of which data would be shared with whom, and under what conditions.[69,70,105,163,220,242,279] Experiences with the disclosure of research use of newborn screening dried blood spots has highlighted that people do not view all uses of data equally. In multiple countries, the research use of these residual samples caused public concern when it became widely known, even resulting in lawsuits in the United States.[69] However, parents perceived meaningful differences between research conducted to improve the clinical system under which the data were collected, which was generally acceptable, and purposes not directly related to newborn screening, such as the identification of disaster victims, forensics and research on maternal diet.[70,112,193] A broad principle for deciding on appropriate research use is that nothing should be undertaken that would undermine the trust that participants have placed in the system and its researchers, or have the potential to be misused.[63] Some authors have also suggested that research participants should be offered an element of transparent choice, particularly about which organisations can access their data and what types of research they may be used for.[52,244] However, implementing this in practice for a life-long project in which future research questions cannot all be anticipated may be difficult.

To better support paediatric data sharing in genomic research, the Global Alliance for Genomics and Health set out the Key Implications for Data Sharing (KIDS) framework, which focuses on children's involvement in decision making, parental consent, balancing benefits and risks to the child, and data protection and release.[220]

Box 7.2. Key Implications for Data Sharing (KIDS) framework[220]

Children's involvement

- The best interests of children are primary.
- Children should be listened to and involved in decision-making processes related to genomic and associated clinical data sharing in developmentally appropriate ways.

Parental consent

- Parents should be informed in a transparent manner how information regarding their child will be securely managed and used. In a research context, data sharing infrastructures should enable children to withdraw consent, when possible, on reaching the age of majority.
- Parental authorisation for ongoing or future unspecified research should include the provision of information related to existing data governance.
- Values conveyed by family, legal guardians or primary caregivers should be respected when possible.

Balancing benefits and risks

- All healthcare professionals involved in processes of data sharing and data-intensive research have the responsibility to balance potential benefits and risks, and discuss these with parents at the time of consent.
- The decision to share paediatric genomic and associated clinical data should be supported by an evaluation of realistic risks and benefits.

Data protection and release

- Duplicative collection of research data involving paediatric patients should be avoided.
- Anonymised paediatric data[***]should be made available via publicly accessible databases. Identifiable paediatric genomic and associated clinical data should be coded[+++] and made available through a controlled or registered access process.
- Providing children and their parents the opportunity to share genomic and associated clinical data is an obligation of those who generate such data.

[***]Here the authors are referring primarily to genomic and clinical data.

[+++]The authors suggest four different approaches to remove identifying information: 1) anonymisation; 2) de-identification; 3) encryption; and 4) pseudonymisation or "coding". The method chosen will depend on characteristics of the data in question.

While useful, this framework is predicated on the idea that sharing a child's data will have benefits for the child, and therefore be in the child's best interests.[220] Although this may be a plausible assumption for research focused on a particular medical condition that aims to recruit affected children, it is unclear whether this is equally true for participants in a public health screening programme, the majority of whom are healthy.

For screening programmes and subsequent genomic research involving newborns, results from analyses of a child's genetic information will necessarily be shared with their parents or guardians (see Chapter 6 for further discussion).[156] However, there may also be grounds for sharing genomic screening results beyond the child–parent relationship. The nature of genetic information means that some conceptualise it as "belonging" to all genetic relatives, whereas clinical information remains personal, therefore the disclosure of genetic information to pertinent relatives may not be considered a breach of privacy (see also Section 2.1.1).[50,230]

The possibility of sharing information that results in broader genetic data misuse, violations of information governance and discrimination (e.g. impact on medical and life insurance, mortgages, employment) that could impact the child's future in the long term is a frequently cited concern.[6,13,15,19,72,112,119,148,160,163,219,235,236,256,261] For example, in the BabySeq programme some parents were reticent to consent to their child undergoing newborn genomic screening if the results were integrated into infants' medical records, citing concerns about potential genetic discrimination and safe data storage.[72] In contrast, another study found that parents wanted genomic test results to appear in their child's medical record, regardless of the condition, so that all healthcare professionals could access the information to guide the child's care.[221] However, these studies were both conducted in the United States and thus may not mirror the perspectives and concerns of UK parents.

Concerns regarding the potential of de-identified data to be linked back to the original donor, and subsequent discrimination, are magnified in the context of depositing a child's data in a repository for research and linking it to other data sources (e.g. genomic data and medical records).[17,141] While necessary for research purposes, linking multiple data sets increases the risk of participants potentially being identified from the linked anonymous data.[274] It has been possible to link anonymous biobank data to individuals by comparing data across multiple databases, therefore the anonymisation of data is potentially insufficient for the protection of privacy or confidentiality.[123,244]

Some people, particularly ethnic minority populations in the United States, are also concerned about inadequate privacy protections that could lead to the forensic use of genomic data for law enforcement in detrimental ways.[112,160] The potential misuse of genomic data by commercial companies is also an issue; [118,201] if commercial companies are involved in data sharing in a way that undermines public trust, this may affect participation in the screening programme and willingness to share data (see Section 8.2.5 for further discussion of commercial involvement).[173]

7.2 Public–private partnerships and the public good

The LHS approach provides a helpful practical and ethical framework for negotiating the ethical, legal and social issues raised by programmes with both clinical and research elements. However, involving private industry in a system based on a societal perspective and that emphasises solidarity, public good and reciprocity can create considerable tensions that could undermine public trust in and acceptability of the system.[71,131,155,173,208] This section discusses the potential benefits and challenges of private sector involvement, and the possible approaches to balancing these offered to date.

7.2.1. Potential benefits and challenges of public–private partnerships

The involvement of the private sector in research relating to WGS newborn screening has the potential to bring benefits to society. National WGS screening and/or research programmes are expensive both to implement and maintain, especially if lifetime biobanking is involved, and public–private partnerships may help facilitate a sustainable funding model.[173] The involvement of private industry

can also help to support one of the key objectives of an LHS approach: improving clinical care.[71,155] This may be achieved through access to better diagnostics, the development of new therapeutics or providing healthcare systems with financial advantages.[49,71,155]

However, if LHS-type initiatives that originate in the public sector and intended to provide benefit to the population engage in partnerships with industry, this will inevitably raise questions regarding commercialisation, profit, intellectual property and ownership that will challenge the relationship between the initiative and its participants.[270] Piasecki et al. (2019) suggest that participation in research can only be considered a moral duty when it takes place within a public LHS that can be assumed to contribute to the public good; this cannot be assumed in a private system and requires further justification.[208] Where a public–private partnership sits within this space is unclear, and is likely to be perceived differently by different people and in different contexts. The public in most countries, including the United Kingdom, distinguish between sharing their genomic data and medical records with for-profit versus not-for-profit researchers, generally being more positive about sharing with the latter, although governments appear to be trusted less than non-profit researchers.[169,172] Knowledge of who will use their data, for what purpose, and how the user will benefit are identified by the public as key factors that inform their trust in those who access their data.[171]

Private sector partnerships will therefore give rise to privacy and confidentiality related concerns about who participant data are shared with and for what purposes.[71,173] Failure to address these concerns adequately will likely lead to a loss of public trust and the consequent disintegration of the initiative.[71,131,155,173,208] This would be particularly problematic in the case of a newborn screening programme as it would cause substantial detriment at the population level if private involvement led to disengagement with an intervention that currently (based on newborn blood spot testing) has extremely high uptake.[173]

7.2.2. Approaches to balancing the benefits and challenges of public–private partnerships

Public–private partnerships require prospective contractual arrangements that enable the provision of access to samples and data on a non-exclusive basis for private sector organisations.[173] This enables research to take place, but circumvents potential problems relating to ownership or intellectual property claims. Such arrangements would also need to ensure that benefits are shared amongst stakeholders.[173] A solidarity-informed model for partnership could be used to ensure common interests are respected in terms of both providing health benefits and providing oversight of how data are used.[71] This could entail a fee-for-access model by which the money private organisations pay to access data is shared with the healthcare system that collected the data, or the healthcare system receives a percentage of profits in products developed using the data, or the healthcare system has shares in the private organisation.[115] These models benefit the population rather than the individual, and is in keeping with the ethos of an LHS approach.

However, more than legal assurances will be needed to ensure that the solidaristic nature of the LHS system is retained in public–private partnerships. Retaining public trust in a hybrid-clinical research system will require transparency about how patient data are used, including by private sector organisations, and what the system received in return for data access.[124] Research suggests that public perspectives on private sector involvement are nuanced and dependent on the type of private organisation and the proposed uses of shared data.[173] This suggests that a degree of participant control and choice over the use of their data, such as that implemented by some citizen science genomics resources, could go some way to mitigating concerns about public–private partnerships.[180]

The increasing complexity of data-driven research, the desire of some participants to be more engaged with how their data are used, and the power imbalance between a single participant and a research team has stimulated the emergence of data intermediaries, some of which facilitate commercial research.[239] Some of these intermediaries are non-profit co-operatives, such as MIDATA (www.midata.coop/en/home/) and SALUS COOP (www.saluscoop.org).[239] These organisations support participants to engage in research, effectively facilitating a type of unofficial collective bargaining on behalf of research participants to ensure that they can share their data while retaining a degree of control over its use. However, more commercially-oriented intermediaries have also developed, such as the Data Dividend project (www.datadividendproject.com), which focuses on financial incentives and may support data sharing for commercial research.[239] While the role of data intermediaries is recognised in the EU's proposed Data Governance Act, payment for sharing data for industry research is not addressed.[239]

7.3. Implications for the Newborn Genomes Programme

7.3.1. Summary

There is no universally agreed approach to governance in health research, but **consensus on broad principles and functions** is emerging and entails:

1. Enabling data access
2. Compliance with national laws and international agreements
3. Supporting appropriate data use and mitigating potential harms
4. Promoting equity in access to and use of data
5. Ensuring use of genomic data for public benefit
6. Ensuring transparency and accountability of biobanks.

Governance mechanisms may include communication with stakeholders, legal compliance, access to expert advice, external review, standard internal operating procedures and partnerships with associations of networks. Many of these mechanisms serve to support research initiatives to gain social licence. Recognition of the importance of social licence has led to a focus on how to support the better engagement of stakeholders in governance systems and processes. Participatory governance and the AFFIRM framework, which incorporates adaptive governance and principles-based regulation approaches, provide two potential strategies that may be useful for the NGP.

How participant or patient data will be used in research, and who will have access, require explicit consideration and transparency as they are frequently identified as areas of concern for data subjects. Participants are often particularly concerned about the possibility of being identified, or their children being identified, in data sets, and the consequences this may have if their data are accessed outside the healthcare sector (e.g. by commercial insurance companies, employers, or law enforcement). The Global Alliance for Genomics and Health set out the Key Implications for Data Sharing (KIDS) framework to better support paediatric data sharing in genomic research, which could assist in the development of the NGP.

The involvement of industry partners in publicly funded research initiatives is also a key area of concern for participants. Providing access to commercial organisations and researchers may be challenging to reconcile with the public good rationale for an LHS unless their involvement is circumscribed in a transparent and legally enforceable way. Different approaches for managing public–

private partnerships have been trialled in some studies (see below), but there is currently no established best practice. It is also unclear how healthy participants, such as most individuals in the NGP, with nothing to gain from research participation (e.g. potential for new treatments) may view public–private partnerships in practice.

7.3.2 Examples from other projects

As discussed above, there is no uniformly accepted, best practice approach to the governance of genomic research initiatives. However, O'Doherty et al. (2021) provide an in-depth assessment of the governance frameworks of six contemporary genomic research projects that provides insights into the strengths and weaknesses of different approaches.[196] The authors assert that there is no single best approach to governance as the project approach must be tailored to its context, which will vary due to many of the factors discussed in Chapters 3 and 4. However, they argue that all governance systems should be transparent in terms of how they are developed and operated, and the requirement and extent of this transparency should not vary by initiative or context.

Similarly, there is no established best practice for how to manage the involvement of commercial organisations and researchers in publicly funded research. One approach is provided by ClinicalStudyDataRequest.com, a portal that provides access to patient-level data from both industry and academic research projects. It incorporates privacy and confidentiality protections for participants, and all proposals for data use are subject to independent review. Confidentiality protections are also extended to researchers and organisations, and data must be kept confidential if the original from commercial research and the original study sponsor has an exclusive licence to any intellectual property created using its data. However, while the data are confidential, there is a requirement to make all results publicly accessible.[242]

Genomics England has already implemented an approach to public–private partnerships in the context of the 100,000 Genomes Project.[71] In addition to partnerships with public sector researchers, Genomics England set up partnerships with private companies to develop sequencing and informatics technologies, and developed a public–private consortium to ensure the outputs of the project were suitable for industry use.[173] However, a key difference between this project and the NGP is that the NGP will not be recruiting participants on the basis of having a particular condition, whereas participants in the 100,000 Genomes Project were affected by a rare health condition or cancer. These participants became involved in the 100,000 Genomes Project with the knowledge that their involvement may lead to the development of diagnostics or therapeutics for their condition, and even these individuals expressed concern regarding commercial involvement in the project.[51] The potential benefits from involvement in the NGP may seem even less tangible to parents of apparently healthy children, most of whom are unlikely to benefit from involvement beyond receiving a clean bill of health from the NGP. Whether the obligations of solidarity and reciprocity will be strong enough to override any concerns about private sector involvement and induce people to participate will depend on the other elements of the programme, particularly those discussed above, and overarching transparency and trust in the NGP.

7.3.3. Key areas for further research and consultation

The lack of consensus regarding governance approaches and the management of public–private partnerships raises a number of considerations from the NGP that would benefit from further consideration and public consultation. The key areas include:

- How stakeholders should be involved in the governance of the NGP from the design stage. The AFFIRM and KIDS principles provide a useful framework, but these are only intended to provide guidance in developing a governance framework tailored to the needs of a specific initiative.
- Information or other resources that would support potential participants to feel confident that NGP data governance will ensure their data remain confidential and are only used for purposes within the remit of the programme.
- How best to manage the involvement of the private sector in NGP research. Research has shown that participants take a more nuanced perspective on data use than simply discounting all industry involvement, and may want to determine data use based on purpose and the specific organisations involved. How this can be operationalised within the context of the NGP, given the life-long use of participant data, requires further research and public consultation.

8. Summary and areas for further investigation and consultation

The purpose of the research described in this report is to explore and summarise the literature regarding the ethical, legal and social issues raised by collecting whole genome sequencing (WGS) data from newborns for use in a research programme. This research also addresses considerations for newborn WGS if in the future it were to be added as a screening test to the national newborn screening programme. This research was commissioned early in the development of the NGP (January 2022). Therefore, it is not intended to provide a critique of the NGP specifically, as at the time of writing many aspects of the programme are still under development. We have drawn out areas that may be particularly relevant to the NGP based on the current, early design of the project. This is to help support the work of Genomics England and is not intended to dictate their areas of focus; as the NGP progresses, some of these areas may become less relevant.

This chapter restates the key findings and suggested areas for further research/consultation set out previously in Chapters 3 to 7 so that they are all collated in a single chapter for ease of use. It first redescribes the conceptual framework (outlined in Chapter 1) used to guide this research in order to orient the reader to the sections that follow, which map back to this framework. The collated summary sections then follow, and finally the collated areas for further research and consultation are presented.

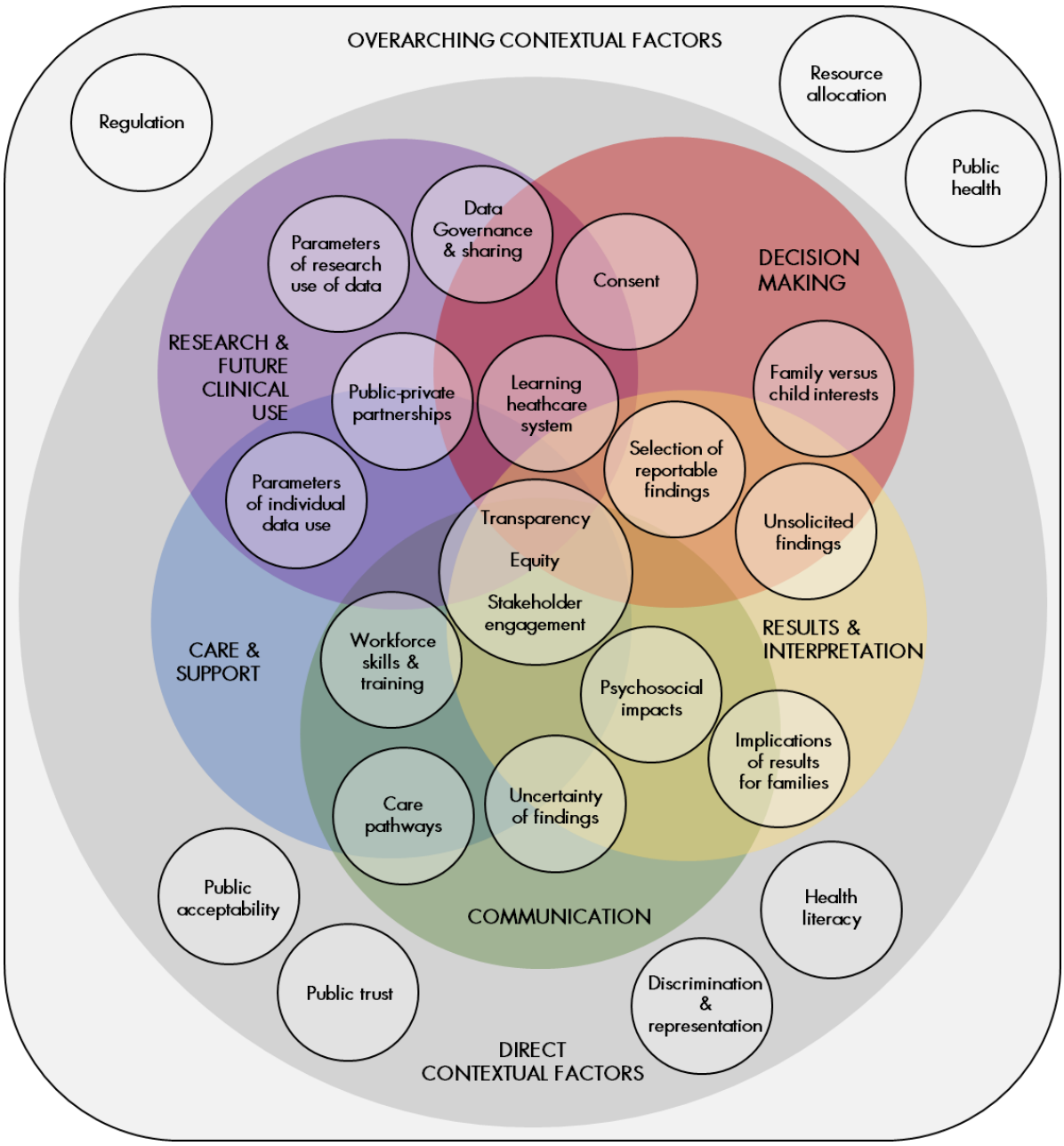
8.1.1. Conceptual framework used for this research

We developed a conceptual framework that maps and describes key ethical, legal and social dimensions/themes that need to be considered for the design and implementation of a programme involving WGS of newborns for research and/or clinical practice. These were grouped into seven broad but interrelated aspects, starting from the decision-making processes of potential participants (or their parents/guardians), through to the future use of the data such a programme would generate, and the broader societal context in which a programme would operate.

Our conceptual mapping of the issues onto these areas was revisited and refined throughout the project, with the final version shown in Figure 8.1. The five coloured circles in the diagram relate to how a newborn WGS clinical and/or research programme is developed, implemented and managed. Transparency, equity and stakeholder engagement are encompassed by all five circles as these are cross-cutting issues that need to be considered in all aspects of such a programme.

The five coloured circles in the diagram represent different groups of issues that relate to decision making by parents or guardians, interpreting WGS data, communicating findings, provision of support and care, and future use of WGS data. The five overlapping aspects of a newborn WGS screening programme sit within a broader societal context that encompasses two sets of factors that will affect the implementation of a newborn WGS clinical and/or research programme. We aggregate these into overarching and direct factors based on the degree to which the design and implementation of a programme might interact with, influence, or be influenced by them. Overarching factors include public health and economic considerations, and regulations and policies that impact different aspects of the programme. Direct factors include health (and genomic) literacy, trust in researchers and clinical services regarding use of personal data, public acceptability of using genomic data for newborn screening, the potential for discrimination, and the lack of representation of minority ethnic groups in genomic research.

Figure 8.1. Mapping ethical, legal and social issues onto the seven key aspects of newborn WGS screening/research programmes



8.2 Summary of key issues for the Newborn Genomes Programme to consider

8.2.1. Public health objectives, resource allocation and regulation

The overarching contextual factors considered relate to the expectations against which the NGP would be evaluated, and the potential constraints placed on the design and implementation of the NGP due to regulations and policies (or where the most appropriate approach is unclear due to a lack of clarity). As one of the NGP's objectives is to determine whether implementation of newborn screening using WGS is feasible, the research undertaken will need to consider the **public health requirements** of such

a screening programme, as well as whether it provides value as a research resource. The original guidance for potential screening tests devised by Wilson and Jungner has been updated to reflect current genomic screening practices, and can provide a structure for ensuring public health objectives are met.

In addition to whether WGS screening will serve the interests of the population as a whole, its **cost-effectiveness** must also be considered as it entails the use of public funds. The WGS must be at least as cost-effective as the current newborn bloodspot screening programme used in the United Kingdom. While initial modelling estimates suggest that this will be the case, and a WGS approach may in fact prove more cost-effective, substantial uncertainties remain, and pilot projects are strongly advocated for in the literature. The NGP will therefore be well positioned to make a valuable contribution to knowledge in this regard.

While there is **limited research on the regulation of genomic medicine** compared to the body of research on ethical issues, several areas have been highlighted that are important for newborn WGS screening research and clinical practice:

- **Duty of care**: The degree to which all those involved in a newborn WGS screening programme, both clinicians and researchers, have a duty of care to participants/patients is currently an area of discussion. A duty of care could theoretically extend beyond those who may directly interact with a participant to include individuals or organisations who provide services or infrastructure (e.g. testing laboratories, bioinformaticians).
- **Return of secondary or incidental results**: The principle of returning results to participants from WGS studies, whether focused on clinical practice or research, is generally agreed upon. However, what information should be returned, what constitutes best practice, and the obligations this places upon researchers to search for and share findings is still a subject of debate.
- **Consent:** There is ongoing discussion in the United Kingdom regarding the need for consent when processing data for health and social care research versus using public interest or legitimate interest as the legal basis. The basis on which data will be used must be determined for any WGS screening programme. However, even if consent is not required for the use of a participant's data, this does not necessarily remove the need to seek ethical approval.
- **Privacy and data sharing**: Privacy and data sharing in the United Kingdom is currently very closely aligned with the European General Data Protection Regulation. This means that participants in a WGS screening programme have the right to request access to their data. The NHS Constitution for England also specifies that individuals have a right to be informed about how their data will be used, and decide whether it is shared for research purposes. What this means in the context of a long-term research programme is open to discussion.

There is currently no definitive guidance on how to manage these issues in the UK, and in some areas the NGP may set a precedent for England. Development of programme-specific policies that set out how these elements will be managed has been recommended as an interim solution. The recently proposed Learning Health Research Regulation System, which emphasises a value-driven, transparent and inclusive approach, may provide a useful framework (see Section 8.3 below).

8.2.2. Public acceptability, trust and equity

The direct factors considered relate to the concepts of public acceptability, trust and trustworthiness, as well as the concepts of discrimination, participation, equity of access and use of genomic medicine.

Acceptability, trust and trustworthiness

The public acceptability of genomic research and screening is influenced by an endeavour's **trustworthiness**, or its honesty, competence and reliability; however, trustworthiness alone is insufficient to generate public trust. To engender public trust, genomic research endeavours need to engage in practices that clearly communicate their trustworthiness. These practices can include transparency, communication supported by genomic health education, and community and stakeholder involvement.

Transparency through information sharing is frequently highlighted as a key method for facilitating trust. This approach often relies on informed consent processes to convey information. However, it has been critiqued for not distinguishing between making information available and actual communication. For the latter, information must be accessible and understandable to those who need it. For actual communication to occur, approaches such as genomic health education of the public, patients and healthcare professionals may be needed. This education can happen through a variety of avenues, such as formal educational programmes, workshops, clinical interactions or the informed consent process.

Community and stakeholder involvement can help to build trust and public acceptability, assist with understanding public perspectives on ethical questions such as what information should be returned to parents, and contribute to genomic health education efforts. Community involvement can take various forms, although examples in the literature often involve the creation of a board or panel comprising members of the public. Regardless, the engagement should strive to be meaningful and bidirectional, and to empower the community to contribute to decision making in the research or screening programme.

Equity in representation, access and use

Equity concerns in genomic screening and research relate to **the potential for discrimination, and inequities in representation, access and use**. Discrimination within genomic screening and research programmes relates to the possibility that biases in the research and healthcare settings of the intervention will exacerbate existing health disparities, or lead to participants facing direct discrimination stemming from future re-analysis of data and disclosure (e.g. restricted access to education or employment). The unequal representation of population groups within genomic datasets, including ethnic minority groups, creates inequalities in the utility of genomic medicine for these groups as it results in treatments and knowledge that are unrepresentative and limited. There is also evidence of inequitable access to and use of genomic research, with potential inequities arising from unequal resources to manage follow-up care and decision making associated with genomic screening outcomes.

The lack of representation of ethnic minority groups in genomic research to date raises issues related to people's trust in healthcare systems and their prior experiences of care. Evidence suggests that persistent racial and ethnic inequalities and past experiences of racism contribute to lower levels of participation by some ethnic minority communities in genomic research. **Ethical frameworks are divided about whether ethnic minority communities have a duty to participate in genomic research,** based on the idea that everyone should contribute to the collective good, or whether given the unequal distribution of benefits in society and persistent ethnic inequalities there is instead an obligation for genomic medicine to address inequities first. This debate is further complicated by the ethical imperative to make datasets representative to avoid the exacerbation of existing inequities and potential further disincentive to participate.

While noting that some health inequities will be outside the control of a single genomic screening or research programme to address, the literature offers **potential ways to reduce inequities** in representation, access and use. Most frequently, and to address all of these issues, authors suggest engaging with communities to understand and find ways to meet their needs. Genomic education or other capacity building efforts might also encourage participation and equitable access and use, as could providing sufficient workforce to support participants with decision making and follow-up care. Tools such as dynamic consent processes may also help overcome barriers to participation by allowing for the incorporation of accessibility support (e.g. translations, health literacy education).

8.2.3. Consent and decision making

There is a range of ethical issues in relation to seeking consent for a newborn genome screening and research programme: reliance on proxy consent from parents/carers, genetic data relating to other family members, deciding if/how children should be involved in decision making, and determining which type of consent to use (and ensuring decisions are truly informed).

Reliance on proxy consent

There must be a reliance on parents/carers to provide **proxy consent** on behalf of their child to take part in the NGP. This creates a need to **balance the autonomy of the child with that of the parents/carers**. At the heart of any action taken regarding the health of the child should be respect for the child and support for their best interests, while also upholding their rights to an open future and their right not to know. However, parents/carers also have autonomy over their child, and there is a need to respect the decisions that parents/carers make for their child.

Some argue that parents'/carers' wishes for their child should only be overridden when they are likely to place the child in significant harm. Others argue that proxy consent from parents/carers on behalf of children should not happen in any circumstances (although this is not feasible in practice and would lead to a lack of research conducted on newborns and create subsequent health inequalities). Others take a more pragmatic approach, recognising that parental autonomy should not be given undue importance in relation to individual child autonomy, while acknowledging that children have a right to appropriate guidance from their parents/carers, as long as it is in their best interests.

The balance between parental and child autonomy varies depending on the type of activity being conducted (clinical or research, and the type of research). As the NGP is a research study, parents/carers should be able to decline participating. However, this becomes more complex when considering the national (clinical and research) screening programme the NGP could lead onto. Here, the pragmatic approach could be taken in that information on childhood-onset, actionable conditions is shared, which is in the best interests of the child's health, and it could be argued that parents/carers should not be able to decline as this could cause harm. However, this is more challenging when considering whether proxy consent is appropriate for the long-term storage and use of screening data for research (as would possibly be the case for the potential future screening programme). This may not have a clear, direct benefit to the child, and leads to the necessary consideration of children developing the ability to consent over time. Further issues would arise should the newborn screening include adult-onset and/or non-actionable conditions.

Navigating these issues requires striking a balance between individual autonomy and wider public health interest. While taking an individual autonomy approach can uphold choice and liberty, it can be argued that children have a duty to contribute to the social good. For the NGP, this would be the contribution genetic data could make to research and ultimately improving health outcomes. Others argue that children do not have social obligations and should not be exposed to research risks for the

benefit of others. Taking an individual approach to autonomy does not allow recognition of relational autonomy (see below), and how this influences autonomy.

Genetic data are familial in nature

Genetic information has a **relational component**, which means that while it is unique to one individual, any information about health risks is also relevant for family members. This creates the question of **whether there is a duty to warn family members** about a higher risk of a condition and leads to an exploration of the notion of relational autonomy. In the case of the NGP, this would involve conversations with healthcare professionals and wider family members to discuss the preferences and potential implications of consenting to newborn WGS screening. Throughout this process, it would be vital to place the newborn at the centre of decision making, and any preferences and opinions of others should guide decisions, but not be a key decision-making factor. Instead of taking an individual autonomy approach to consent for the NGP, a relational approach could be taken, which would mean the genetic results belong to the newborn and family (although there are concerns about maintaining confidentiality).

Children gain the ability to be involved in decision making over time

While newborns are unable to consent to participate in the NGP, they gain the ability to be involved in decision making over time, reducing the importance of parental autonomy. Because of the long-term research aspect of the NGP, this creates questions about **when children should be brought into the decision-making process,** and if consent should be sought for the NGP later in life.

Some argue that children should be offered full autonomy once they reach the age of maturity, and consent should be sought for the future use of data for research (or to withdraw from the study). Some argue that consent is not needed as long as re-contact is attempted if a significant finding is uncovered, because there is minimal risk for the child and/or there is not a significant divergence in the research from what was originally consented to. Seeking consent has implications for increasing burden (on both researchers and the child), and there are challenges with keeping contact details up to date. However, if the NGP has ongoing access to participant medical records then this burden would be lessened and the justification for not seeking consent would be harder to support.

There are different approaches to seeking consent, and challenges in ensuring parents/carers can make truly informed decisions

There are three different approaches to seeking consent: informed consent (opt-in), presumed consent (opt-out) and tiered consent (consenting to separate aspects of data usage differently, which can consist of both opt-in and opt-out aspects). The choice of which to use depends on what the data are being used for; each approach has advantages and disadvantages. Informed consent is often the gold standard approach in research as it upholds autonomy and supports trust. However, providing enough information that is understandable to participants is a challenge, especially in the case of complex genetic topics. It is also resource intensive. Presumed consent approaches may be easier and acceptable for parents/carers, and may be the preferred approach if a public health perspective is taken and newborn WGS is implemented as part of a national screening programme. However, presumed consent reduces individual autonomy and is not usually compatible with research programmes. With a tiered approach, participants can manage their own preferences (supporting autonomy) and children can consent or withdraw when they get older. In the case of the NGP, tiered consent could take the form of, for example, consent for the health screening on behalf of their child, and postponing consent to participate in research until the child is old enough to do so themselves. However, it may not always be simple to distinguish the different activities being consented to.

There is concern that **parents/carers are not able to make truly informed decision about the use of their child's data**. There are questions around whether more or less information, and how complex this information is, supports or hinders the ability to provide a truly informed decision. This is particularly important to address if consent is being sought for long-term access to and use of genomic or medical record data. Simplifying risk can support participant understanding, and there are arguments on both sides for whether this supports or undermines autonomy. These issues may mean that there is no one-size-fits all approach to seeking consent, as it is a subjective notion for each parent/carer. While the consent process can be tailored to individual participants, this may be challenging to implement for a large-scale research programme such as the NGP, or newborn screening on a national scale, due to the resources required.

The **timing of consent and what to do about parental disagreement** are also important, but not discussed in detail in the literature. Seeking consent soon after birth is unlikely to be the optimal approach as parents/carers may be stressed and will have other higher priorities. This may mean any consent provided may not be truly informed or consent may not be given at all. Taking a tiered approach to consent can mitigate this issue. It may be preferable to provide information during pregnancy, followed by brief reminders of the information soon after birth. The timing of consent is also influenced by the type of DNA sample being taken (e.g. cord, heel prick blood). Ideally, consent will come from both parents (or carers if applicable), although it is acknowledged that this is not possible in all situations. If there is disagreement between parents/carers, a consensus should be reached, but if this is not possible it may be detrimental to override one parent's/carer's strong views.

8.2.4. Interpreting, communicating and acting on findings

There is a range ethical issues to be considered at the stage of interpreting, communicating and acting on findings, including uncertainty of findings, management of unsolicited findings, consideration for the balance between benefit and harm, constraints of the programme, unactionable conditions, determining who communicates findings, and the psychosocial impacts of findings.

Selecting which findings to share with participants is a key initial step for any screening or research programme. There are **four broad categories of results** that could be returned to participants in newborn genome screening programmes: 1) childhood-onset actionable conditions; 2) childhood-onset non-actionable conditions; 3) adult-onset actionable conditions; and 4) adult-onset non-actionable conditions. While it is straightforward to justify the return of data on clinically actionable childhood-onset conditions, the return of the other categories depends on the context. The return of adult-onset conditions is generally not recommended for newborn screening programmes. **Unsolicited findings** pose a further ethical issue for screening programmes. The design of the programme, and its varying constraints, impact whether a condition can be disclosed to the family. It can be morally difficult for professionals if they become aware of an unsolicited finding but cannot disclose to the family if it falls outside the programme remit. There are **potential risks of withholding information**, especially where those results provide clinical benefits to the patient. How potential unsolicited findings will be managed is an area to be considered within the NGP, for both the patient and professional.

The **obligation to return results** beyond the initial screening intervention is subject to debate, but researchers, health professionals and the public generally support the return of clinically actionable findings arising from the reanalysis of genetic data. However, there is less consensus regarding the return of "raw" data (e.g. full genome sequences) to children or their parents, and how this should be managed, particularly when parents seek access to these data before children are able to provide

consent. For the NGP, this requires further investigation from ethical, legal and social acceptability perspectives to determine the best course of action.

Due to the complexity of genomic results and information, there are **risks of uncertainty and variation in interpretation**. In this context, screening is not a diagnostic assessment, but an investigative strategy for newborns. There is a certain degree of subjectivity in variant interpretation, and there will inevitably be some differences across health facilities and between some health professionals. For the NGP, these risks of uncertainty should be communicated to the family early in the screening process. As noted in the discussed literature, this could be detailed and discussed with families at the stage of programme engagement or during the process of consent.

There are various options for **who delivers results and provides information to families** regarding screening. This includes genetic counsellors, midwives and nurses. Screening results can often be unclear and difficult to interpret, therefore having the provision of staff or information is key for helping families understand the results and how, when appropriate, they can act on them.

Following the return and communication of results there is potential for **psychosocial impacts**. The results from screening can lead to a range of psychosocial implications for parents, including increased worry and stress, alongside overall increases in anxiety. This is further exacerbated when results are uncertain. **Diagnosis should not be viewed as a one-off event, but rather the start of the process** to encourage the development of a strong relationship between patient, family and health professional(s). Poor communication during this process can increase negative psychosocial impacts of screening results. In the case of the NGP, **providing families with the necessary information and guidance for an identified variant would potentially alleviate any psychosocial impacts, including anxiety, and enable them to prepare/act accordingly**. The literature suggests that less is known about the psychosocial impact of returning results in the context of WGS for children and their parents, with research thus far showing mixed impacts.

8.2.5. Governance and the involvement of commercial organisations

There is no universally agreed approach to governance in health research, but consensus on broad principles and functions is emerging and includes:

1. Enabling data access
2. Compliance with national laws and international agreements
3. Supporting appropriate data use and mitigating potential harm
4. Promoting equity in access to and use of data
5. Ensuring use of genomic data for public benefit
6. Ensuring transparency and accountability of biobanks.

Governance mechanisms may include communication with stakeholders, legal compliance, access to expert advice, external review, standard internal operating procedures and partnerships with associations of networks. Many of these mechanisms serve to support research initiatives to gain a social licence. Recognition of the importance of a social licence has led to a focus on how to support the better engagement of stakeholders in governance systems and processes. Participatory governance and the AFFIRM framework, which incorporates adaptive governance and principles-

based regulation approaches, provide two potential strategies for addressing this that may be useful for the NGP.

How participant or patient data will be used in research, and who will have access, require explicit consideration and transparency as they are frequently identified as areas of concern for data subjects. Participants are often particularly concerned about the possibility of being identified, or their children being identified, in datasets, and the consequences this may have if their data are accessed outside the healthcare sector (e.g. by commercial insurance companies, employers or law enforcement). The Global Alliance for Genomics and Health has set out the Key Implications for Data Sharing (KIDS) framework to better support paediatric data sharing in genomic research, which could assist in the development of the NGP.

The involvement of industry partners in publicly funded research initiatives is also a key area of concern for participants. Providing access to commercial organisations and researchers may be challenging to reconcile with the public good rationale for an LHS, unless their involvement is circumscribed in a transparent and legally enforceable way. Different approaches for managing public–private partnerships have been trialled in some studies, but there is currently no established best practice. It is also unclear how healthy participants, such as most individuals in the NGP, with nothing to gain from research participation (e.g. potential for new treatments) may view public–private partnerships in practice.

8.3 Areas for further research and public consultation

8.3.1. Public health objectives, resource allocation and regulation

The nature of overarching factors means that there are few direct actions that can be taken to resolve issues in this area. However, many researchers suggest that uncertainty around the interpretation of regulation can be managed through the establishment of clear guidance, frameworks or decision-making tools that set out how issues have been addressed within a specific programme. In particular, it is suggested to develop such tools in relation to:

- Navigating situations in which both clinical and research regulations apply, particularly to specify which should take precedence.
- Management of incidental or secondary findings, including what information will be offered (and whether it will be verified in a clinically certified laboratory), who will receive it and how it will be provided. If only findings of a certain type will be returned (e.g. clinically actionable), specify the process by which this will be determined.
- How consent and return of results will be handled for minors.
- How requests from participants for access to their "raw" genomic data, or their medical records, will be managed.

The recently proposed Learning Health Research Regulation System, which emphasises a value-driven, transparent and inclusive approach, may provide a useful a framework for developing the necessary tools and guidance. Even if a completely integrated learning health system is not implemented it has been suggested that this approach can be useful in terms of research regulation. Key elements of this approach include:

- Taking a multi-disciplinary approach to systems design that incorporates bioethics, social sciences and humanities, as well as meaningful participation from patients and the public.

- Investigating how congruent the central values of health care and health research are, and how they can be used to improve regulation.
- The use of self-reflection and feedback loops in system design and delivery to learn from failures early on and avoid them later, potentially supported by additional expertise via regulatory stewardship.

8.3.2. Public acceptability, trust and equity

In contrast to the factors discussed in Chapter 7, direct contextual factors can potentially be influenced by how a programme is designed and implemented. Based on the literature, there are several areas important to consider as part of the NGP, but which may require further research and/or consultation:

- Community engagement is frequently suggested as a key method of engendering trust with the public in general, and with marginalised and underrepresented communities specifically; however, there are few examples in the literature of what this looks like in practice for genomic research. Furthermore, the persistent underrepresentation of ethnic minority groups in biorepositories suggests that issues of trust and access have yet to be overcome. Further research or consultation is needed on how to meaningfully engage with communities and on what "successful" community engagement in a genomic research context looks like will strengthen NGP design and implementation.
- Relatedly, the literature reviewed did not address how to balance different and potentially competing views from different stakeholder groups. If a broad range of stakeholders is consulted, as much of the literature suggests, it is possible that tensions will arise over suggested courses of action. Further research into how best to manage these tensions could facilitate more effective stakeholder engagement.
- Further research could also explore public perceptions of public- and government-backed genomic research endeavours, and how these impact perceptions of trustworthiness. Large-scale public–private partnerships during the response to the Covid-19 pandemic, and the various messaging around and coverage of these efforts, may have shifted public attitudes towards government, or commercial, involvement in research.
- Transparency is seen as a key method of demonstrating trustworthiness; however, when research is uncertain, people may perceive it as less trustworthy.[58] This presents challenges for researchers working in areas of rapid change or uncertainty regarding how to achieve transparency in a manner that demonstrates trustworthiness, rather than undermining it by contributing to confusion and uncertainty. Further research or consultation is needed on this topic.
- The relationship between genomic health literacy and decision making, and the potential for education to increase the participation of ethnic minority groups, could be usefully explored further. Although current research suggests a relationship between genomic health literacy and decisions to participate in research, it is not clear how this intersects with social and relational factors such as community preferences, or cultural or political beliefs. For example, people may choose to prioritise community concerns or cultural or political beliefs over clinical decision-making strategies. As the programme explores the role of individual autonomy in decision making, it could also investigate both the value and limits of genomics education in supporting this.

8.3.3. Consent and decision making

The key remaining unanswered questions that require further research and consultation in relation to consent and decision making specifically for the NGP are as follows:

- While there seems to be an accepted argument supporting the use of proxy consent for screening newborns for clinical purposes (i.e. to identify the risk of childhood-onset, actionable health conditions), the issue around obtaining proxy consent for the long-term use of data for research is less clear cut. For example, is it acceptable for parents to provide proxy consent for long-term storage and research use given that this does not directly benefit the child?
- How can healthcare professionals and researchers involved in the NGP ensure that "genuine" informed consent is sought (if this approach to consent is used)? What would "genuine" consent mean in the context of the NGP?
- As the NGP will hold and use data for a long period, how should children be involved in decisions to participate in the programme over time. For example, should children be asked to give their consent once they reach the age of maturity?
- While the NGP will share childhood-onset, actionable findings, there may still be some implications for family members, such as those relating to reproductive decision making. Should other family members be informed of the genetic results that may impact them?
- At which point(s) during pregnancy or after birth (depending on the type of genetic sample taken) should parents be approached about participating in the NGP?
- Which type of consent should be sought for the NGP, and for a nationally implemented screening programme if WGS were adopted for this purpose: opt-in or opt-out? If opt-in is used, should a tiered approach to consent be taken, for example, seeking consent from parents/carers for screening results and seeking consent from children later in life for research use, and/or allow participants to consent for different uses of data differently?

8.3.4. Interpreting, communicating and acting on findings

The key outstanding unanswered questions/topics requiring further research and consultation regarding the management of uncertain and/or unsolicited findings and communicating findings specifically for the NGP are as follows:

- Genomics England has returned "raw" data to participants under previous programmes; however, UK law is unclear about parental rights to their children's data. Further consultation on the legal and ethical issues surrounding this could be useful.
- The literature highlights potential tensions that arise with healthcare professionals around disclosing unsolicited findings when their professional role and moral intuition may be in conflict. Engagement with the professionals who will be involved in the NGP about this issue could mitigate potential tensions.
- Further research and consultation on how the risks of uncertainty within results can be communicated appropriately and meaningfully to parents is needed.
- Evidence regarding the potential harm (particularly in the context of psychosocial impacts) of screening is emerging within research, and consequently not yet systematically measured. Therefore, further exploration may be needed to understand the psychosocial impacts and potential harm of screening results, and how to mitigate these issues.
- Consultation and further consideration on how to effectively prepare the professionals delivering the screening results appropriately to patients and families is needed.

- If results are uncertain, this raises a question regarding the threshold that would need to be met for "certainty" within variant interpretation.
- Understanding what health system resources need to be in place to support parents and health system staff with the NGP as a research study versus the full, national roll-out of newborn WGS will be an important task for Genomics England. The professional groups involved in the planning and delivery of a newborn genetic screening programme are extensive, and thus broad training will be required. Further research and consultation on these matters will be critical for successful programme implementation.

8.3.4. Governance and the involvement of commercial organisations

The lack of consensus regarding governance approaches and the management of public–private partnerships raises a number of considerations from the NGP that would benefit from further consideration and public consultation. The key areas include:

- How stakeholders should be involved in the governance of the NGP from the design stage. The AFFIRM and KIDS principles provide a useful framework, but these are only intended to provide guidance in developing a governance framework tailored to the needs of a specific initiative.
- Information or other resources are needed that would support potential participants to feel confident that NGP data governance will ensure their data remain confidential and are only used for purposes within the remit of the programme.
- How best to manage the involvement of the private sector in NGP research. Research has shown that participants take a more nuanced perspective to data use than simply discounting all industry involvement, and may want to determine the use of the data based on the purpose and the specific organisations involved. How this can be operationalised within the context of the NGP, given the life-long use of participant data, requires both further research and public consultation.

9. References

1 Addison, C. An ethics of enchantment: Forming affect and information in experimental paediatric medicine. Journal of the Royal Anthropological Institute (2022).

2 Adjekum, A., Ienca, M. & Vayena, E. What Is Trust? Ethics and Risk Governance in Precision Medicine and Predictive Analytics. OMICS 21, 704-710, doi:10.1089/omi.2017.0156 (2017).

3 Amendola, L.M., Muenzen, K., Biesecker, L.G., et al. Variant Classification Concordance using the ACMG-AMP Variant Interpretation Guidelines across Nine Genomic Implementation Research Studies. The American Journal of Human Genetics 107, 10, doi: 10.1016/j.ajhg.2020.09.011 (2020).

4 Anderlik, M.R. & Rothstein, M.A. Privacy and confidentiality of genetic information: What Rules for the New Science? Annual Review of Genomics and Human Genetics 2, 401-433 (2001).

5 Andermann, A., Blancquaert, I., Beauchamp, S. & Dery, V. Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years. Bulletin of the World Health Organization 86, 317-319, doi:10.2471/blt.07.050112 (2008).

6 Anderson, J. et al. Parents perspectives on whole genome sequencing for their children: qualified enthusiasm? Journal of Medical Ethics 43, 535-539 (2017).

7 Angrist, M. & Jamal, L. Living laboratory: Whole-genome sequencing as a learning healthcare enterprise. Clinical Genetics 87, 311-318, doi:10.1111/cge.12461 (2015).

8 Ascencio-Carbajal, T., Saruwatari-Zavala, G., Navarro-Garcia, F. & Frixione, E. Genetic/genomic testing: Defining the parameters for ethical, legal and social implications (ELSI). BMC Medical Ethics 22, 156, doi:10.1186/s12910-021-00720-5 (2021).

9 Ashcroft, R.E. Human rights and ethics in genomic research: Rethinking the model. Pharmacogenomics 8, 391-395 (2007).

10 Ballantyne, A. Adjusting the focus: A public health ethics approach to data research. Bioethics 33, 357-366, doi:10.1111/bioe.12551 (2019).

11 Ballard, L.M., Horton, R.H., Dheensa, S., Fenwick, A. & Lucassen, A.M. Exploring broad consent in the context of the 100,000 Genomes Project: A mixed methods study. European Journal of Human Genetics 28, 732-741, doi:10.1038/s41431-019-0570-7 (2020).

12 Barton, A., Cumyn, A., Dault, R. & Ethier, J.F. Gift, Reciprocity and Learning Health Systems. American Journal of Bioethics 21, 91-93, doi:10.1080/15265161.2021.1891341 (2021).

13 Bayefsky, M.J. The human genome as public: Justifications and implications. Bioethics 31, 209-219, doi:10.1111/bioe.12329 (2017).

14 Beauchamp, T. in The Stanford Encyclopedia of Philosphy (ed E.N. Zalta) (Stanford University, 2019).

15 Beauvais, M.J.S. et al. Parental Access to Children's Raw Genomic Data in Canada: Legal Rights and Professional Responsibility. Frontiers in Genetics 12, 535340, doi:10.3389/fgene.2021.535340 (2021).

16 Berg, J.S. et al. Newborn Sequencing in Genomic Medicine and Public Health. Pediatrics 139, doi:10.1542/peds.2016-2252 (2017).

17 Berkman, B.E., Howard, D. & Wendler, D. Reconsidering the Need for Reconsent at 18. Pediatrics 142, e20171202 (2018).

18 Berrios, C. et al. Enrolling Genomics Research Participants through a Clinical Setting: The Impact of Existing Clinical Relationships on Informed Consent and Expectations for Return of Research Results. Journal of Genetic Counseling 27, 263-273, doi:10.1007/s10897-017-0143-2 (2018).

19 Bertier, G., Sénécal, K., Borry, P. & Vears, D.F. Unsolved challenges in pediatric whole-exome sequencing: A literature analysis. Critical Reviews in Clinical Laboratory Sciences 54, 134-142, doi:10.1080/10408363.2016.1275516 (2017).
20 Blizinsky, K.D. & Bonham, V.L. Leveraging the learning health care model to improve equity in the age of genomic medicine. Learning Health Systems 2, e10046 (2018).
21 Blout Zawatsky, C.L. et al. Returning actionable genomic results in a research biobank: Analytic validity, clinical implementation, and resource utilization. American Journal of Human Genetics 108, 2224-2237, doi:10.1016/j.ajhg.2021.10.005 (2021).
22 Boardman, F.K., Sadler, C. & Young, P.J. Newborn genetic screening for spinal muscular atrophy in the UK: The views of the general population. Molecular Genetics and Genomic Medicine 6, 99-108, doi:10.1002/mgg3.353 (2018).
23 Boell, S. K. & Cecez-Kecmanovic, D. A hermeneutic approach for conducting literature reviews and literature searches. *Communications of the Association for information Systems* **34**, 12 (2014).
24 Bombard, Y. et al. The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results. American Journal of Human Genetics 104, 578-595, doi:10.1016/j.ajhg.2019.02.025 (2019).
25 Botham, J., Shilling, V. & Jones, J. Patient and public understanding of the concept of 'personalised medicine' in relation to cancer treatment: A systematic review. Future Healthcare Journal 8, e703 (2021).
26 Botkin, J.R. Transparency and choice in learning healthcare systems. Learning Health Systems 2, e10049, doi:10.1002/lrh2.10049 (2018).
27 British Medical Association. Parental responsibility: Guidance from the British Medical Association (2008).
28 Brooks, D. et al. Developing a framework for integrating health equity into the learning health system. Learning Health Systems 1, e10029 (2017).
29 Brothers, K. B. Biobanking in pediatrics: the human nonsubjects approach. *Per Med* **8**, 79, doi:10.2217/pme.10.70 (2011).
30 Brothers, K.B. et al. When Participants in Genomic Research Grow Up: Contact and Consent at the Age of Majority. Journal of Pediatrics 168, 226-231 e221, doi:10.1016/j.jpeds.2015.09.020 (2016).
31 Bryon, M. Breaking the diagnosis of cystic fibrosis to parents: A process not a one-off event. Paediatric Respiratory Reviews 35, 103-105, doi:10.1016/j.prrv.2020.04.006 (2020).
32 Buckeridge, D.L. Precision, Equity, and Public Health and Epidemiology Informatics: A Scoping Review. Yearbook of Medical Informatics 29, 226-230, doi:10.1055/s-0040-1701989 (2020).
33 Bunnik, E.M., de Jong, A., Nijsingh, N. and de Wert, G.M. The New Genetics and Informed Consent: Differentiating Choice to Preserve Autonomy. Bioethics 27, 348-355 (2013).
34 Cacciatore, P., Visser, L.A., Buyukkaramikli, N., Ploeg, C.P.B. v.d. & Marle, M.E. v.d. A.-v. The Methodological Quality and Challenges in Conducting Economic Evaluations of Newborn Screening: A Scoping Review. International Journal of Neonatal Screening 6, doi:10.3390/ijns6040094 (2020).
35 Cadigan R.J, B.R., Rini C, Waltz M, Kuczynski K.J, Muessig K, Goddard K.A.B, Henderson Online Education and e-Consent for GeneScreen: A Preventive Genomic Screening Study. Public Health Genomics 20, 235-246 (2017).
36 Carlton, J. et al. Acceptability of childhood screening: A systematic narrative review. Public Health 193, 126-138, doi:10.1016/j.puhe.2021.02.005 (2021).

37 Chassagne, A. et al. Exome sequencing in clinical settings: preferences and experiences of parents of children with rare diseases (SEQUAPRE study). European Journal of Human Genetics 27, 701-710, doi:10.1038/s41431-018-0332-y (2019).

38 Chaudhari, B.P., Manickam, K. & McBride, K.L. A pediatric perspective on genomics and prevention in the twenty-first century. Pediatric Research 87, 338-344, doi:10.1038/s41390-019-0597-z (2020).

39 Childerhose, J.E. et al. Participant Engagement in Translational Genomics Research: Respect for Persons-and Then Some. Ethics and Human Research 41, 2-15, doi:10.1002/eahr.500029 (2019).

40 Chuong, K.H. & O'Doherty, K.C. in The Cambridge Handbook of Health Research Regulation, Ch. 12, 121-129 (2021).

41 Clayton, E.W. Can I Be Sued for that? Liability risk and the Disclosure of Clinically Significant Genetic Research Findings. Genome Research 24, 719 (2014).

42 C Clayton, E.W. et al. Does the law require reinterpretation and return of revised genomic results? Genetic Medicine 23, 833-836, doi:10.1038/s41436-020-01065-x (2021).

43 Collins, V., Halliday, J., Kahler, S. & Williamson, R. Parents' experiences with genetic counseling after the birth of a baby with a genetic disorder: An exploratory study. Journal of Genetic Counseling 10, 53-72 (2001).

44 Cornel, M.C., Rigter, T., Jansen, M.E. & Henneman, L. Neonatal and carrier screening for rare diseases: How innovation challenges screening criteria worldwide. Journal of Community Genetics 12, 257-265, doi:10.1007/s12687-020-00488-y (2021).

45 Costanzo, C.D. Newborn screening and informed consent in a constitutional perspective. The Italian "model" and some knots still to be untied. BioLaw Journal 2021, 111-127, doi:10.15168/2284-4503-777 (2021).

46 Crawford, D.C., Cooke Bailey, J.N. & Briggs, F. Mind the gap: Resources required to receive, process and interpret research-returned whole genome data. Human Genetics 138, 691-701 (2019).

47 Currier, R.J. Single-Gene Sequencing in Newborn Screening: Success, Challenge, Hope. Hastings Center Report 48, S37-S38, doi:10.1002/hast.883 (2018).

48 Daniels, H., Jones, K.H., Heys, S. & Ford, D.V. Exploring the Use of Genomic and Routinely Collected Data: Narrative Literature Review and Interview Study. *Journal of Medical Internet Research* **23**, e15739, doi:10.2196/15739 (2021).

49 DeCristo, D.M. et al. Actionability of commercial laboratory sequencing panels for newborn screening and the importance of transparency for parental decision-making. *Genome Medicine* **13**, 50, doi:10.1186/s13073-021-00867-1 (2021).

50 Dheensa, S., Fenwick, A. & Lucassen, A. 'Is this knowledge mine and nobody else's? I don't feel that.' Patient views about consent, confidentiality and information-sharing in genetic medicine. *Journal of Medical Ethics* **42**, 174-179, doi:10.1136/medethics-2015-102781 (2016).

51 Dheensa, S., Lucassen, A. & Fenwick, A. Fostering trust in healthcare: Participants' experiences, views, and concerns about the 100,000 genomes project. *European Journal of Medical Genetics* **62**, 335-341, doi:10.1016/j.ejmg.2018.11.024 (2019).

52 Dheensa, S., Samuel, G., Lucassen, A.M. & Farsides, B. Towards a national genomics medicine service: The challenges facing clinical-research hybrid practices and the case of the 100 000 genomes project. *Journal of Medical Ethics* **44**, 397-403, doi:10.1136/medethics-2017-104588 (2018).

53 Doerr, M,G.S., Moore, S, Suver, C, Wilbanks, J & Wagner, J. Implementing a universal informed consent process for the All of Us Research Program. *Pacific Symposium on Biocomputing* **24**, 427-438 (2019).

54 Dondorp, W., Bolt, I., Tibben, A., Wert, G.D. & Summeren, M.V. 'We Should View Him as an Individual': The Role of the Child's Future Autonomy in Shared Decision-Making About Unsolicited Findings in Pediatric Exome Sequencing. *Health Care Analysis* **29**, 249-261, doi:10.1007/s10728-020-00425-7 (2021).

55 Dove, E.S. et al. Beyond individualism: Is there a place for relational autonomy in clinical practice and research? *Clinical Ethics* **12**, 150-165, doi:10.1177/1477750917704156 (2017).

56 Downie, L., Halliday, J., Lewis, S. & Amor, D.J. Principles of Genomic Newborn Screening Programs: A Systematic Review. *JAMA Network Open* **4**, e2114336, doi:10.1001/jamanetworkopen.2021.14336 (2021).

57 Dupras, C. et al. Governing the futures of non-invasive prenatal testing: An exploration of social acceptability using the Delphi method. *Social Science and Medicine* **304**, 112930, doi:10.1016/j.socscimed.2020.112930 (2022).

58 Edinburgh Law School. *How can health research regulatory systems strengthen their trustworthiness?* University of Edinburh (2021).

59 Eichinger, J. et al. The full spectrum of ethical issues in pediatric genome-wide sequencing: A systematic qualitative review. *BMC Pediatrics* **21**, 387, doi:10.1186/s12887-021-02830-w (2021).

60 Eisenhauer E.R., Tait, A.R., Rieh, S.Y. & Arslanian-Engoren, C.M. Participants' Understanding of Informed Consent for Biobanking: A Systematic Review. *Clinical Nursing Research* **28**, 30-51 (2019).

61 Esquerda, M. et al. Ethical questions concerning newborn genetic screening. *Clinical Genetics* **99**, 93-98, doi:10.1111/cge.13828 (2021).

62 Etchegary, H., Nicholls, S., Tessier, L. et al. Consent for newborn screening: Parents' and health-care professionals' experiences of consent in practice. *European Journal of Human Genetics* **24**, 1530-1534 (2016).

63 Evans-Jordan, S.B. & Skolbekken, J.A. Scientific Citizenship's Youngest Domain: Function Creep in Norway's Newborn Screening Programme. *Science, Technology and Society* **26**, 98-115, doi:10.1177/0971721820964891 (2021).

64 Evans, A., Lynch, M., Johnson, M. & Bonhomme, N. Assessing the newborn screening education needs of families living in medically underserved areas. *Journal of Genetic Counseling* **29**, 658-667, doi:10.1002/jgc4.1252 (2020).

65 Fabie, N.A.V., Pappas, K.. & Feldman, G.L. The Current State of Newborn Screening in the United States. *Pediatric Clinics of North America* **66**, 369-386, doi:10.1016/j.pcl.2018.12.007 (2019).

66 Faden, R.R. et al. An ethics framework for a learning health care system: A departure from traditional research ethics and clinical ethics. *Hastings Center Report* S16-27, doi:10.1002/hast.134 (2013).

67 Farrell, P.M., Langfelder-Schwind, E. & Farrell, M.H. Challenging the dogma of the healthy heterozygote: Implications for newborn screening policies and practices. *Molecular Genetics and Metabolism* **134**, Aug-19, doi:10.1016/j.ymgme.2021.08.008 (2021).

68 Favaretto, M., De Clercq, E., Gaab, J. & Elger, B.S. First do no harm: An exploration of researchers' ethics of conduct in Big Data behavioral studies. *PLoS One* **15**, e0241865, doi:10.1371/journal.pone.0241865 (2020).

69 Franková, V. et al. Regulatory landscape of providing information on newborn screening to parents across Europe. *European Journal of Human Genetics* **29**, 67-78, doi:10.1038/s41431-020-00716-6 (2021).

70 Friedman, J.M. et al. Genomic newborn screening: Public health policy considerations and recommendations. *BMC Medical Genomics* **10**, 9, doi:10.1186/s12920-017-0247-4 (2017).

71 Gaille, M., Horn, R. & Consortia, U.-F.G. The ethics of genomic medicine: Redefining values and norms in the UK and France. *European Journal of Human Genetics* **29**, 780-788, doi:10.1038/s41431-020-00798-2 (2021).

72 Genetti, C.A. et al. Parental interest in genomic sequencing of newborns: Enrollment experience from the BabySeq Project. *Genetics in Medicine* **21**, 622-630, doi:10.1038/s41436-018-0105-6 (2019).

73 Genomic Analysis in Children Task and Finish Group. *Summary of recommendations*, Genomics England (2019).

74 Genomics England. The 100 000 Genomes Project protocol. (2015).

75 Genomics England. *Getting Your Results*, Genomics England, https://www.genomicsengland.co.uk/initiatives/100000-genomes-project/participant-resources (n.d.)

76 Gille, F., Vayena, E. & Blasimme, A. Future-proofing biobanks' governance. *European Journal of Human Genetics* **28**, 989-996, doi:10.1038/s41431-020-0646-4 (2020).

77 Girdler, S.J., Girdler, J.E., Tarpada, S.P. & Morris, T.M. Nonmaleficence in medical training: Balancing patient care and efficient education. *Indian Journal of Medical Ethics* **4**, 129-133 (2018).

78 Gold, N.B. & Green, R.C. Reevaluating the "right not to know" in genomics research. *Genetic Medicine* **24**, 289-292, doi:10.1016/j.gim.2021.10.003 (2022).

79 Goldenberg, A.J. et al. Including ELSI research questions in newborn screening pilot studies. *Genetic Medicine* **21**, 525-533, doi:10.1038/s41436-018-0101-x (2019).

80 Gooding, P. Supported decision-making: a rights-based disability concept and its implications for mental health law. *Psychiatry, Psychology and Law* **20**, 431-451 (2013).

81 Government of the United Kingdom. *Child adoption*, https://www.gov.uk/child-adoption/birth-parents-your-rights (n.d.)

82 Government of the United Kingdom. *Parental rights and responsibilities*, https://www.gov.uk/parental-rights-responsibilities (n.d.)

83 Greenhalgh, T., Thorne, S. & Malterud, K. Time to challenge the spurious hierarchy of systematic over narrative reviews? *European journal of clinical investigation* **48** (2018).

84 Grob, R., Roberts, S. & Timmermans, S. Families' Experiences with Newborn Screening: A Critical Source of Evidence. *Hastings Center Report* **48**, S29-S31, doi:10.1002/hast.881 (2018).

85 Grosse, S.D. & Van Vliet, G. Challenges in Assessing the Cost-Effectiveness of Newborn Screening: The Example of Congenital Adrenal Hyperplasia. *International Journal of Neonatal Screening* **6**, doi:10.3390/ijns6040082 (2020).

86 Gyngell, C., Newson, A.J., Wilkinson, D., Stark, Z. & Savulescu, J. Rapid Challenges: Ethics and Genomic Neonatal Intensive Care. *Pediatrics* **143**, S14-s21, doi:10.1542/peds.2018-1099D (2019).

87 Hajj, H.E., Bish, D.R. & Bish, E.K. Equity in genetic newborn screening. *Naval Research Logistics* **68**, 44-64, doi:10.1002/nav.21882 (2021).

88 Halbert, C.H. Equity in Genomic Medicine. *Annual Review of Genomics and Human Genetics* **23** (2022).

89 Haldane, V. et al. Community participation in health services development, implementation, and evaluation: A systematic review of empowerment, health, community, and process outcomes. *PLoS One* **14**, e0216112, doi:10.1371/journal.pone.0216112 (2019).

90 Hall, D.E., Prochazka, A.V. & Fink, A.S. Informed consent for clinical treatment. *Canadian Medical Association Journal* **184**, 533-540, doi:10.1503/cmaj.112120 (2012).

91 Hallinan, D. Broad consent under the GDPR: an optimistic perspective on a bright future. *Life Sciences, Society and Policy* **16**, 1, doi:10.1186/s40504-019-0096-3 (2020).

92 Hansson, M.G. in *GDPR and Biobanking: Individual Rights, Public Interest and Research Regulation across Europe* (eds S. Slokenberga, O. Tzortzatou, & J. Reichel) 31-42, Springer (2021).
93 Hartsock, J.A., Schwartz, P.H., Waltz, A.C. & Ott, M.A. Anticipatory Waivers of Consent for Pediatric Biobanking. *Ethics & Human Research* **41**, 14-21, doi:10.1002/eahr.500008 (2019).
94 Hassan, L., Dalton, A., Hammond, C. & Tully, M.P. A deliberative study of public attitudes towards sharing genomic data within NHS genomic medicine services in England. *Public Understanding of Science* **29**, 702-717, doi:10.1177/0963662520942132 (2020).
95 Hens, K., Levesque, E. & Dierickx, K. Children and biobanks: A review of the ethical and legal discussion. *Human Genetics* **130**, 403-413, doi:10.1007/s00439-011-1031-8 (2011).
96 Hens, K., Nys, H., Cassiman, J.J. & Dierickx, K. Risks, benefits, solidarity: A framework for the participation of children in genetic biobank research. *Journal of Pediatrics* **158**, 842-848, doi:10.1016/j.jpeds.2010.12.036 (2011).
97 Hens, K. et al. Developing a policy for paediatric biobanks: principles for good practice. *European Journal of Human Genetics* **21**, 2-7, doi:10.1038/ejhg.2012.99 (2013).
98 Hilgartner, S., Prainsack, B. & Hurlbut, J.B. in *Handbook of Science and Technology Studies* (eds U. Felt, R. Fouche, C.A. Miller, & L. Smith-Doerr), MIT Press (2016).
99 Hindorff, L.A., Bonham, V.L. & Ohno-Machado, L. Enhancing diversity to reduce health information disparities and build an evidence base for genomic medicine. *Personalized Medicine* **15**, 403-412, doi:10.2217/pme-2018-0037 (2018).vvvvvvvvvvvvvvv
100 Holm, I. A. et al. Returning a Genomic Result for an Adult-Onset Condition to the Parents of a Newborn: Insights From the BabySeq Project. *Pediatrics* **143**, e20181099H (2019).
101 Holm, S. Informed consent and the bio-banking of material from children. *Genomics, Society and Policy* **1**, 16-26 (2005).
102 Hopkins, H., Kinsella, S. & Evans, G. Implications of whole genome sequencing for newborn screening: A public dialogue. 1-104, Genomics England (2021).
103 Hopkins, H., Kinsella, S., Evans, G. & Reid, S. Putting Good Into Practice: A public dialogue on making public benefit assessments when using health and care data, Hopkins Van Mil, (2021).
104 Horowitz, C.R. et al. The Genomic Medicine Integrative Research Framework: A Conceptual Framework for Conducting Genomic Medicine Research. *American Journal of Human Genetics* **104**, 1088-1096, doi:10.1016/j.ajhg.2019.04.006 (2019).
105 Horton, R. & Lucassen, A. Ethical Considerations in Research with Genomic Data. *The New Bioethics*, 1-15, doi:10.1080/20502877.2022.2060590 (2022).
106 Howard, H.C. et al. Whole-genome sequencing in newborn screening? A statement on the continued importance of targeted approaches in newborn screening programmes. *European Journal of Human Genetics* **23**, 1593-1600, doi:10.1038/ejhg.2014.289 (2015).
107 Howard Sharp, K.M., J.N., Ouma, A., Harrison, L., Gerhardt, E., Taylor, L., Hamilton, K., McGee, R.B., Nuccio, R., Quinn, E., Hines-Dowell, S., Kesserwan, C., Sunkara, A., Gattuso, J.S., Pritchard, M., Mandrell, B., Relling, M.V., Haidar, C.E., Kang, G., Johnson, L.M. & Nichols, K. Factors Associated with Declining to Participate in a Pediatric Oncology Next Generation Sequencing Study. *JCO Precision Oncology* **4**, 202-211 (2020).
108 Human Fertilisation & Embryology Authority. *Donating your eggs*, https://www.hfea.gov.uk/donation/donors/donating-your-eggs/ (n.d.)
109 Hurle, B. et al. What does it mean to be genomically literate?: National Human Genome Research Institute Meeting Report. *Genetic Medicine* **15**, 658-663, doi:10.1038/gim.2013.14 (2013).
110 Ipsos MORI, Genomics England, Sciencewise & UK Research and Innovation. *A public dialogue on genomic medicine: time for a new social contract?*, Ipsos MORI (2019).

111 Iskrov, G., Ivanov, S., Wrenn, S. & Stefanov, R. Whole-Genome Sequencing in Newborn Screening-Attitudes and Opinions of Bulgarian Pediatricians and Geneticists. *Frontiers in Public Health* **5**, 308, doi:10.3389/fpubh.2017.00308 (2017).

112 Jansen, M.E. et al. Parental perspectives on retention and secondary use of neonatal dried bloodspots: A Dutch mixed methods study. *BMC Pediatrics* **19**, doi:10.1186/s12887-019-1590-8 (2019).

113 Jeon, Y., Jeon, S., Blazyte, A., Kim, Y.J., Lee, J.J., Bhak, Y., Cho, Y.S., Park, Y., Noh, E.K., Manica, A., Edwards, J.S., Bolser, D., Kim, S., Lee, Y., Yoon, C., Lee, S., Kim, B.C., Park, N.H. & Bhak, J. Welfare Genome Project: A Participatory Korean Personal Genome Project With Free Health Check-Up and Genetic Report Followed by Counseling. *Frontiers in Genetics* **12**, 633731 (2021).

114 Johnson, F., Ulph, F., Macleod, R. & Southern, K. Receiving results of uncertain clinical relevance from population genetic screening: Systematic review & meta-synthesis of qualitative research. *Nature* **30**, 520-531 (2022).

115 Johnson, S.B., Slade, I., Giubilini, A. & Graham, M. Rethinking the ethical principles of genomic medicine services. *European Journal of Human Genetics* **28**, 147-154, doi:10.1038/s41431-019-0507-1 (2020).

116 Johnston, J. & Juengst, E. Are Parents Really Obligated to Learn as Much as Possible about Their Children's Genomes? *Hastings Center Report* **48**, S14-S15, doi:10.1002/hast.877 (2018).

117 Johnston, J. et al. Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies. *Hastings Center Report* **48 Suppl 2**, S2-S6, doi:10.1002/hast.874 (2018).

118 Jones, K., Daniels, H., Heys, S., Lacey, A. & Ford, D.V. Toward a Risk-Utility Data Governance Framework for Research Using Genomic and Phenotypic Data in Safe Havens: Multifaceted Review. *Journal of Medical Internet Research* **22**, e16346, doi:10.2196/16346 (2020).

119 Jones, K.H., Daniels, H., Squires, E. & Ford, D.V. Public Views on Models for Accessing Genomic and Health Data for Research: Mixed Methods Study. *Journal of Medical Internet Research* **21**, e14384, doi:10.2196/14384 (2019).

120 Juengst, E.T. & Rie, A.V. Transparency, trust, and community welfare: Towards a precision public health ethics framework for the genomics era. *Genome Medicine* **12**, 98, doi:10.1186/s13073-020-00800-y (2020).

121 Kanungo, S., Patel, D.R., Neelakantan, M. & Ryali, B. Newborn screening and changing face of inborn errors of metabolism in the United States. *Annals of Translational Medicine* **6**, 468, doi:10.21037/atm.2018.11.68 (2018).

122 Kapadia, D. et al. *Ethnic Inequalities in Healthcare: A Rapid Evidence Review* (2022).

123 Kasperbauer, T.J., Gjerris, M., Waldemar, G. & Sandøe, P. Communicating Identifiability Risks to Biobank Donors. *Cambridge Quarterly of Healthcare Ethics* **27**, 123-136, doi:10.1017/s0963180117000457 (2018).

124 Kass, N.E. & Faden, R.R. Ethics and Learning Health Care: The Essential roles of engagement, transparency, and accountability. *Learn Healthare System* **2**, e10066, doi:10.1002/lrh2.10066 (2018).

125 Kass, N.E. et al. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. *Hastings Center Report*, S4-S15, doi:10.1002/hast.133 (2013).

126 Kemper, A.R., Boyle, C.A., Brosco, J.P. & Grosse, S.D. Ensuring the Life-Span Benefits of Newborn Screening. *Pediatrics* **144**, doi:10.1542/peds.2019-0904 (2019).

127 Kenny, T. et al. The importance of psychological support for parents and caregivers of children with a rare disease at diagnosis. *Rare Disease and Orphan Drugs Journal* **1**, doi:10.20517/rdodj.2022.04 (2022).

128 Kilbride, M.K. Genetic Privacy, Disease Prevention, and the Principle of Rescue. *Hastings Center Report* **48**, 10-17, doi:10.1002/hast.849 (2018).

129 Knoppers, B.M., Avard, D., Senecal, K., Zawati, M.H. & Members, P.G.I.P.P. Return of whole-genome sequencing results in paediatric research: A statement of the P3G international paediatrics platform. *European Journal of Human Genetics* **22**, 3-5, doi:10.1038/ejhg.2013.176 (2014).

130 Knoppers, B.M. & Chadwick, R. The ethics weathervane. *BMC Medical Ethics* **16**, 58, doi:10.1186/s12910-015-0054-4 (2015).

131 Knoppers, B.M. & Chadwick, R. Human Genetic Research: Emerging Trends in Ethics. *Nature Reviews: Genetics* **6**, 75-79 (2005).

132 Knoppers, B.M. & Chadwick, R. The Human Genome Project: Under an International Ethical Microscope. *Science* **265**, 2035-2036 (1994).

133 Knoppers, B.M., Harris, J.R., Budin-Ljosne, I. & Dove, E.S. A human rights approach to an international code of conduct for genomic and clinical data sharing. *Human Genetics* **133**, 895-903, doi:10.1007/s00439-014-1432-6 (2014).

134 Knoppers, B.M., Thorogood, A. & Chadwick, R. The Human Genome Organisation: Towards next-generation ethics. *Genome Medicine* **5**, 38 (2013).

135 Kohler, J.N., Turbitt, E. & Biesecker, B.B. Personal utility in genomic testing: A systematic literature review. *European Journal of Human Genetics* **25**, 662-668, doi:10.1038/ejhg.2017.10 (2017).

136 Kong, C., Efrem, M. & Campbell, M. Education versus screening: the use of capacity to consent tools in psychiatric genomics. *Journal of Medical Ethics* **46**, 137-143, doi:10.1136/medethics-2019-105396 (2020).

137 Kraft, S.A. et al. Beyond consent: building trusting relationships with diverse populations in precision medicine research. *The American Journal of Bioethics* **18**, 3-20 (2018).

138 Kraft, S.A. et al. Demonstrating "respect for persons" in clinical research: Findings from qualitative interviews with diverse genomics research participants. *Journal of Medical Ethics* **47**, e8 (2021).

139 Kunst, N. et al. Population-Based Newborn Screening for Germline TP53 Variants: Clinical Benefits, Cost-Effectiveness, and Value of Further Research. *Journal of the National Cancer Institute*, doi:10.1093/jnci/djac013 (2022).

140 Labonte, M.L. Addressing uncertainty: The emergence of the crms/cfspid diagnostic category following newborn screening for cystic fibrosis. *OBM Genetics* **5**, doi:10.21926/obm.genet.2103139 (2021).

141 Lantos, J.D. Ethical and Psychosocial Issues in Whole Genome Sequencing (WGS) for Newborns. *Pediatrics* **143**, S1-s5, doi:10.1542/peds.2018-1099B (2019).

142 Laurie, G. in *The Cambridge Handbook of Health Research Regulation*, 391-400 (2021).

143 Laurie, G. in *The Cambridge Handbook of Health Research Regulation*, 1-10 (2021).

144 Lee, L.M. Public health ethics theory: Review and path to convergence. *Journal of Law, Medicine & Ethics* **40**, 85-98, doi:10.1111/j.1748-720X.2012.00648.x (2012).

145 Lee, S. S. The Ethics of Consent in a Shifting Genomic Ecosystem. *Annu Rev Biomed Data Sci* **4**, 145-164, doi:10.1146/annurev-biodatasci-030221-125715 (2021).

146 Lee, S.S. The Ethics of Consent in a Shifting Genomic Ecosystem. *Annual Review of Biomedical Data Science* **4**, 145-164, doi:10.1146/annurev-biodatasci-030221-125715 (2021).

147 Leibson, T. & Koren, G. Informed consent in pediatric research. *Paediatric Drugs* **17**, 5-11, doi:10.1007/s40272-014-0108-y (2015).

148 Levy, H.L. Ethical and Psychosocial Implications of Genomic Newborn Screening. *International Journal of Neonatal Screening* **7**, doi:10.3390/ijns7010002 (2021).

149 Lewis, A.C.F., Knoppers, B.M. & Green, R.C. An international policy on returning genomic research results. *Genome Medicine* **13**, 115, doi:10.1186/s13073-021-00928-5 (2021).
150 Lewis, C. *et al.* Parents' motivations, concerns and understanding of genome sequencing: a qualitative interview study. *Eur J Hum Genet* **28**, 874-884, doi:10.1038/s41431-020-0575-2 (2020).
151 Liberati, A. *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology* **62**, e1-e34 (2009).
152 Lindor, N.M., Thibodeau, S.N. & Burke, W. Whole-Genome Sequencing in Healthy People. *Mayo Clinic Proceedings* **92**, 159-172, doi:10.1016/j.mayocp.2016.10.019 (2017).
153 Long, J.C. et al. A dynamic systems view of clinical genomics: A rich picture of the landscape in Australia using a complexity science lens. *BMC Medical Genomics* **14**, doi:10.1186/s12920-021-00910-5 (2021).
154 López-Martín, E., Martinez-Delgado, B., Bermejo-Sánchez, E., Alonso, J., SpainUDP Network, Posada, M. SpainUDP: The Spanish Undiagnosed Rare Diseases Program. *International Journal of Environental Research and Public Health* **15**, 1746 (2018).
155 Lucassen, A., Montgomery, J. & Parker, M. in *Annual Report of the Chief Medical Officer 2016: Generation Genome* (ed C. Langenberg), Department of Health and Social Care (2016).
156 Manzini, A. & Vears, D.F. Predictive Psychiatric Genetic Testing in Minors: An Exploration of the Non-Medical Benefits. *Journal of Bioethical Inquiry* **15**, 111-120, doi:10.1007/s11673-017-9828-3 (2018).
157 Marchant, G. et al. From Genetics to Genomics: Facing the Liability Implications in Clinical Care. *Journal of Law, Medicine & Ethics* **48**, 11-43, doi:10.1177/1073110520916994 (2020).
158 Mathews, D.J. & Jamal, L. Revisiting respect for persons in genomic research. *Genes (Basel)* **5**, 1-12, doi:10.3390/genes5010001 (2014).
159 Matulat, P. & Parfitt, R. The Newborn Hearing Screening Programme in Germany. *International Journal of Neonatal Screening* **4**, 29, doi:10.3390/ijns4030029 (2018).
160 May, T. Are Public Repository Requirements Exacerbating Lack of Diversity? *Trends in Genetics* **36**, 390-394, doi:10.1016/j.tig.2020.03.004 (2020).
161 May, T. et al. Community-Based Participatory Research and its Potential Role in Supporting Diversity in Genomic Science. *Journal of Health Care for the Poor and Underserved* **32**, 1208-1224 (2021).
162 McCandless, S.E. & Wright, E.J. Mandatory newborn screening in the United States: History, current status, and existential challenges. *Birth Defects Research* **112**, 350-366, doi:10.1002/bdr2.1653 (2020).
163 McGowan, M.L. et al. Adolescent and Parental Attitudes About Return of Genomic Research Results: Focus Group Findings Regarding Decisional Preferences. *Journal of Empirical Research on Human Research Ethics* **13**, 371-382, doi:10.1177/1556264618776613 (2018).
164 McGuire, A.L., Beskow, L.M. Informed consent in genomics and genetic research. *Annual Review of Genomics and Human Genetics* **11**, 361-381 (2010).
165 McInnes, G. et al. Opportunities and challenges for the computational interpretation of rare variation in clinically important genes. *American Journal of Human Genetics* **108**, 535-548, doi:10.1016/j.ajhg.2021.03.003 (2021).
166 Meagher, K.M., Juengst, E.T. & Henderson, G.E. Grudging trust and the limits of trustworthy biorepository curation. *The American Journal of Bioethics* **18**, 23-25 (2018).
167 Mendes, Á. et al. Communication of Information about Genetic Risks: Putting Families at the Center. *Family Process* **57**, 836-846, doi:10.1111/famp.12306 (2018).

168 Metcalfe, A., Plumridge, G., Coad, J., Shanks, A., and Gill, P. Parents' and children's communication about genetic risk: A qualitative study, learning from families' experiences. *European Journal of Human Genetics* **19**, 640-646 (2011).
169 Middleton, A. et al. Global public perceptions of genomic data sharing: What shapes the willingness to donate DNA and health data? *The American Journal of Human Genetics* **107**, 743-752 (2020).
170 Mighton, C. et al. Patient and public preferences for being recontacted with updated genomic results: A mixed methods study. *Human Genetics* **140**, 1695-1708 (2021).
171 Milne, R. et al. Demonstrating trustworthiness when collecting and sharing genomic data: public views across 22 countries. *Genome Medicine* **13**, 1-12 (2021).
172 Milne, R. et al. Trust in genomic data sharing among members of the general public in the UK, USA, Canada and Australia. *Human Genetics* **138**, 1237-1246, doi:10.1007/s00439-019-02062-0 (2019).
173 Minari, J., Brothers, K.B. & Morrison, M. Tensions in ethics and policy created by National Precision Medicine Programs. *Human Genomics* **12**, 22, doi:10.1186/s40246-018-0151-9 (2018).
174 Minssen, T., Rajam, N. & Bogers, M. Clinical trial data transparency and GDPR compliance: Implications for data sharing and open innovation. *Science and Public Policy* **47**, 616-626, doi:10.1093/scipol/scaa014 (2020).
175 Mitchell, C. et al. Exploring the potential duty of care in clinical genomics under UK law. *Medical Law International* **17**, 158-182, doi:10.1177/0968533217721966 (2017).
176 Mitchell, E., Oddie, S., Dorling, J., Gale, C., Johnson, M.J. & McGuire, W. Implementing two-stage consent pathway in neonatal trials. *Archives of Disease in Childhood – Fetal and Neonatal Edition*, doi:10.1136/archdischild-2021-322960 (2021).
177 Molster, C.M. et al. The Evolution of Public Health Genomics: Exploring Its Past, Present, and Future. *Frontiers in Public Health* **6**, 247, doi:10.3389/fpubh.2018.00247 (2018).
178 Moody, L., Choudhry, K. Parental views on informed consent for expanded newborn screening. *Health Expectations* **16**, 239-250 (2013).
179 Morain, S., Kass, N.E. & Faden, R.R. in *The Oxford Handbook of Public Health Ethics* (eds Anna C. Mastroianni, Jeffrey P. Kahn, & Nancy E. Kass) Ch. 14, 158-172, Oxford University Press (2019).
180 Morain, S.R., Majumder, M.A. & McGuire, A.L. Learning Health System – Moving from Ethical Frameworks to Practical Implementation. *Journal of Law, Medicine & Ethics* **47**, 454-458, doi:10.1177/1073110519876180 (2019).
181 Morrissey, C. & Walker, R.L. The Ethics of General Population Preventive Genomic Sequencing: Rights and Social Justice. *Journal of Medicine and Philosophy* **43**, 22-43, doi:10.1093/jmp/jhx034 (2018).
182 Moultrie, R.R. et al. Parental Views on Newborn Next Generation Sequencing: Implications for Decision Support. *Maternal and Child Health Journal* **24**, 856-864, doi:10.1007/s10995-020-02953-z (2020).
183 Mourby, M., Gowans, H., Aidinlis, S., Smith, H. & Kaye, J. Governance of academic research data under the GDPR – Lessons from the UK. *International Data Privacy Law* **9** (2019).
184 Muller, S.H.A., Kalkman, S., van Thiel, G., Mostert, M. & van Delden, J.J.M. The social licence for data-intensive health research: Towards co-creation, public value and trust. *BMC Medical Ethics* **22**, 110, doi:10.1186/s12910-021-00677-5 (2021).
185 Neuhaus, C.P. Does Solidarity Require "All of Us" to Participate in Genomics Research? *Hastings Center Report* **50 Suppl 1**, S62-S69, doi:10.1002/hast.1157 (2020).
186 Newson, A.J. The promise of public health ethics for precision medicine: the case of newborn preventive genomic sequencing. *Human Genetics*, doi:10.1007/s00439-021-02269-0 (2021).

187 NGA Law. *Parenthood after donor conception: sperm donors and co-parent fathers*, https://www.ngalaw.co.uk/knowledge-centre/parenthood-after-donor-conception-sperm-donors-and-co-parent-fathers#:~:text=Donation%20through%20a%20licensed%20clinic,legal%2C%20financial%20and%20inheritance%20claims (n.d.)

188 NHS Digital. *Understanding the national data opt-out*, https://digital.nhs.uk/services/national-data-opt-out/understanding-the-national-data-opt-out (2019).

189 Nicholls, S.G. et al. What is in a Name? Parent, Professional and Policy-Maker Conceptions of Consent-Related Language in the Context of Newborn Screening. *Public Health Ethics* **12**, 158-175, doi:10.1093/phe/phz003 (2019).

190 Nicholls, S.G. & Southern, K. Parental decision-making and acceptance of newborn bloodspot screening: An exploratory study. *PLoS One* **8**, e79441 (2013).

191 Nisselle, A. et al. Lessons learnt from implementing change in newborn bloodspot screening processes over more than a decade: Midwives, genetics and education. *Midwifery* **79**, doi:10.1016/j.midw.2019.102542 (2019).

192 Nnamuchi, O. H3Africa: An Africa exemplar? Exploring its framework on protecting human research participants. *Developing World Bioethics* **18**, 156-164 (2018).

193 Nordfalk, F. & Ekstrøm, C.T. Newborn dried blood spot samples in Denmark: The hidden figures of secondary use and research participation. *European Journal of Human Genetics* **27**, 203-210, doi:10.1038/s41431-018-0276-2 (2019).

194 Nuffield Council on Bioethics. Children and clinical research: Ethical issues, Nuffield Council on Bioethics (2015).

195 Nurchis, M.C. et al. Incremental net benefit of whole genome sequencing for newborns and children with suspected genetic disorders: Systematic review and meta-analysis of cost-effectiveness evidence. *Health Policy* **126**, 337-345, doi:10.1016/j.healthpol.2022.03.001 (2022).

196 O'Doherty, K.C. et al. Toward better governance of human genomic data. *Nature Genetics* **53**, 2-8, doi:10.1038/s41588-020-00742-6 (2021).

197 O'Neill, O. Linking trust to trustworthiness. *International Journal of Philosophical Studies* **26**, 293-300 (2018).

198 O'Neill, O. & Bardrick, J. Trust, trustworthiness and transparency. European Foundation Centre (2015).

199 Oerlemans, A.J.M., Kluijtmans, L.A.J. & Burg, S.V.D. The moral life of professionals in newborn screening in the Netherlands: A qualitative study. *Public Health Ethics* **10**, 19-34, doi:10.1093/phe/phw011 (2017).

200 Offringa, M. & Klassen, T.P. Deferred Consent in Pediatric Drug Trials: Moving from Why to How. *Pediatric Drugs* **23**, 533-535, doi:10.1007/s40272-021-00480-0 (2021).

201 Ormondroyd, E., Border, P., Hayward, J. & Papanikitas, A. Genomic health data generation in the UK: a 360 view. *European Journal of Human Genetics*, 1-Aug, doi:10.1038/s41431-021-00976-w (2021).

202 Parkin, E. & Loft, P. Patient health records: access, sharing and confidentiality, House of Commons Library (2020).

203 Passmore, S.R. et al. "I'm a Little More Trusting": Components of trustworthiness in the decision to participate in genomics research for African Americans. *Public Health Genomics* **22**, 215-226 (2019).

204 Pereira, S. & Clayton, E. W. Commercial Interests, the Technological Imperative, and Advocates: Three Forces Driving Genomic Sequencing in Newborns. *Hastings Cent Rep* **48 Suppl 2**, S43-s44, doi:10.1002/hast.885 (2018).

205 Pereira, S. & Clayton, E.W. Commercial Interests, the Technological Imperative, and Advocates: Three Forces Driving Genomic Sequencing in Newborns. *Hastings Center Report* **48 Suppl 2**, S43-s44, doi:10.1002/hast.885 (2018).
206 Persaud, A. & Bonham, V.L. The role of the health care provider in building trust between patients and precision medicine research programs. *The American Journal of Bioethics* **18**, 26-28 (2018).
207 Phillips, A.M. & Hervey, T.K. in *GDPR and Biobanking: Individual Rights, Public Interest and Research Regulation across Europe* (eds S. Slokenberga, O. Tzortzatou, & J. Reichel), 145-183, Springer (2021).
208 Piasecki, J. & Dranseika, V. Research versus practice: The dilemmas of research ethics in the era of learning health-care systems. *Bioethics* **33**, 617-624, doi:10.1111/bioe.12571 (2019).
209 Pitini, E. et al. A proposal of a new evaluation framework towards implementation of genetic tests. *PLoS One* **14**, e0219755, doi:10.1371/journal.pone.0219755 (2019).
210 Platt, T., Platt, J., Thiel, D. & Kardia, S.L.R. Engaging a state: Facebook comments on a large population biobank. *Journal of Community Genetics* **8**, 183-197, doi:10.1007/s12687-017-0302-z (2017).
211 Powell, C.M. What Genomic Sequencing Can Offer Universal Newborn Screening Programs. *Hastings Center Report* **48**, S18-S19, doi:10.1002/hast.878 (2018).
212 Powell, S.N. et al. Parental Guidance Suggested: Engaging parents as partners in research studies of genomic screening for a pediatric population. *Frontiers in Genetics* **13** (2022).
213 Prero, M.Y. et al. Disclosure of Misattributed Paternity. *Pediatrics* **143**, doi:10.1542/peds.2018-3899 (2019).
214 Prictor, M., Huebner, S., Teare, H.J.A., Burchill, L. & Kaye, J. Australian Aboriginal and Torres Strait Islander Collections of Genetic Heritage: The Legal, Ethical and Practical Considerations of a Dynamic Consent Approach to Decision Making. *Journal of Law, Medicine and Ethics* **48**, 205-217, doi:10.1177/1073110520917012 (2020).
215 Prictor, M., Teare, H.J. & Kaye, J. Equitable participation in biobanks: The risks and benefits of a "dynamic consent" approach. *Frontiers in Public Health*, 253 (2018).
216 Prictor M, T. H., Kaye J. Equitable Participation in Biobanks: The Risks and Benefits of a "Dynamic Consent" Approach. *Front Public Health* **6** (2018).
217 Public Health England. Guidelines for newborn blood spot sampling. (London, 2016).
218 Rahimzadeh, V., Bartlett, G. & Knoppers, B.M. A policy Delphi study to validate the key implications of data sharing (KIDS) framework for pediatric genomics in Canada. *BMC Medical Ethics* **22**, 71, doi:10.1186/s12910-021-00635-1 (2021).
219 Rahimzadeh, V., Knoppers, B.M. & Bartlett, G. Ethical, Legal, and Social Issues (ELSI) of Responsible Data Sharing Involving Children in Genomics: A Systematic Literature Review of Reasons. *AJOB Empirical Bioethics* **11**, 233-245, doi:10.1080/23294515.2020.1818875 (2020).
220 Rahimzadeh, V. et al. Key Implications of Data Sharing in Pediatric Genomics. *JAMA Pediatrics* **172**, 476-481, doi:10.1001/jamapediatrics.2017.5500 (2018).
221 Rahm, A.K. et al. Parental attitudes and expectations towards receiving genomic test results in healthy children. *Translational Behavioral Medicine* **8**, 44-53, doi:10.1093/tbm/ibx044 (2018).
222 Remec, Z. I. et al. Next-Generation Sequencing in Newborn Screening: A Review of Current State. *Frontiers in Genetics* **12**, 662254, doi:10.3389/fgene.2021.662254 (2021).
223 Roberts, J.S. et al. Patient understanding of, satisfaction with, and perceived utility of whole-genome sequencing: Findings from the MedSeq Project. *Genetics in Medicine* **20**, 1069-1076, doi:10.1038/gim.2017.223 (2018).
224 Rodriguez-Rincon, D. et al. Exploring the Societal Burden of Multiple Sclerosis: A Study into the Non-Clinical Impact of the Disease. *Including Changes with Progression*.

225 Ross, L.F. & Clayon, E. Ethical Issues in Newborn Sequencing Research: The Case Study of BabySeq. *Pediatrics* **144**, e20191031 (2019).
226 Rothwell, E., Wong, B., Johnson, E. & Botkin, J.R. Education for fathers about newborn screening and leftover dried blood spots. *Journal of Community Genetics* **8**, 239-241, doi:10.1007/s12687-017-0305-9 (2017).
227 Rotz, S.J. & Kodish, E. Ethical conundrums in pediatric genomics. *Hematology: the American Society of Hematology Education Program* **2018**, 301-306, doi:10.1182/asheducation-2018.1.301 (2018).
228 Rulli, T. & Millum, J. Rescuing the duty to rescue. *Journal of Medical Ethics* **42**, 260-264, doi:10.1136/medethics-2013-101643 (2016).
229 Sabatello, M., Callier, S., Garrison, N.A. & Cohn, E.G. Trust, precision medicine research, and equitable participation of underserved populations. *The American Journal of Bioethics* **18**, 34-36 (2018).
230 Samuel, G.N., Dheensa, S., Farsides, B., Fenwick, A. & Lucassen, A. Healthcare professionals' and patients' perspectives on consent to clinical genetic testing: Moving towards a more relational approach. *BMC Medical Ethics* **18**, 47, doi:10.1186/s12910-017-0207-8 (2017).
231 Sanderson, S.C. et al. Psychological and behavioural impact of returning personal results from whole-genome sequencing: The HealthSeq project. *European Journal of Human Genetics* **25**, 280-292, doi:10.1038/ejhg.2016.178 (2017).
232 Savatt, J.M., Wagner, J.K., Joffe, S., Rahm, A.K., Williams, M.S., Bradbury, A.R., Davis, F.D., Hergenrather, J., Hu, Y., Kelly, M.A., Kirchner, H.L., Meyer, M.N., Mozersky, J., O'Dell, S.M., Pervola, J., Seeley, A., Sturm, A.C. & Buchanan, A.H. Pediatric reporting of genomic results study (PROGRESS): A mixed-methods, longitudinal, observational cohort study protocol to explore disclosure of actionable adult- and pediatric-onset genomic variants to minors and their parents. *BMC Pediatrics* **20** (2020).
233 Savich, R.D. et al. Willingness of women to participate in obstetrical and pediatric research involving biobanks. *Journal of Community Genetics* **11**, 215-223, doi:10.1007/s12687-019-00446-3 (2020).
234 Schaefer, G.O., Tai, E.S. & Sun, S.H. Navigating conflicts of justice in the use of race and ethnicity in precision medicine. *Bioethics* **34**, 849-856, doi:10.1111/bioe.12757 (2020).
235 Schickhardt, C., Fleischer, H. & Winkler, E.C. Do patients and research subjects have a right to receive their genomic raw data? An ethical and legal analysis. *BMC Medical Ethics* **21**, 7, doi:10.1186/s12910-020-0446-y (2020).
236 Seidel, M.G. Baby genome screening: Paving the way to genetic discrimination? *British Medical Journal* **358**, j3294, doi:10.1136/bmj.j3294 (2017).
237 Sen, K., Harmon, J. & Gropman, A.L. Select Ethical Aspects of Next-Generation Sequencing Tests for Newborn Screening and Diagnostic Evaluation of Critically Ill Newborns. *International Journal of Neonatal Screening* **7**, doi:10.3390/ijns7040076 (2021).
238 Seydel, C. Baby's First Genome. *Nature Biotechnology*, doi:10.1038/s41587-022-01306-1 (2022).
239 Shabani, M. The Data Governance Act and the EU's move towards facilitating data sharing. *Molecular Systems Biology* **17**, e10229, doi:10.15252/msb.202110229 (2021).
240 Shabani, M. Will the European Health Data Space change data sharing rules? *Science* **375**, 1357-1359 (2022).
241 Shabani, M., Chassang, G. & Marelli, L. in *GDPR and Biobanking: Individual Rights, Public Interest and Research Regulation across Europe* (eds S. Slokenberga, O. Tzortzatou, & J. Reichel), 45-60, Springer (2021).

242 Shabani, M., Thorogood, A. & Murtagh, M. in *The Cambridge Handbook of Health Research Regulation*, Ch. 19, 187-196 (2021).

243 Shah, S.K. et al. What does the duty to warn require? *The American Journal of Bioethics* **13**, 62-63 (2013).

244 Shi, X. & Wu, X. An overview of human genetic privacy. *Annals of the New York Academy of Sciences* **1387**, 61-72, doi:10.1111/nyas.13211 (2017).

245 Shim, J.K. Cultural health capital: A theoretical approach to understanding health care interactions and the dynamics of unequal treatment. *Journal of Health and Social Behavior* **51**, 1-15 (2010).

246 Singleton, M.K., Moon, M. & Jorgensen, E.V. Beyond Biobanking: Future Use of Specimens and Data from Pediatric Participants. *Journal of Pediatrics* **221S**, S49-S52, doi:10.1016/j.jpeds.2020.01.021 (2020).

247 Slokenberga, S. in *GDPR and Biobanking: Individual Rights, Public Interest and Research Regulation across Europe* (eds S. Slokenberga, O. Tzortzatou, & J. Reichel), 11-30, Springer (2021).

248 Staunton, C. in *GDPR and Biobanking: Individual Rights, Public Interest and Research Regulation across Europe* (eds S. Slokenberga, O. Tzortzatou, & J. Reichel), 91-104, Springer (2021).

249 Sundby, A. et al. Attitudes of stakeholders in psychiatry towards the inclusion of children in genomic research. *Human Genomics* **12**, 12, doi:10.1186/s40246-018-0144-8 (2018).

250 Szego, M.J. et al. Views from the clinic: Healthcare provider perspectives on whole genome sequencing in paediatrics. *European Journal of Medical Genetics* **62**, 350-356, doi:10.1016/j.ejmg.2018.11.029 (2019).

251 Thorogood, A., Dalpe, G. & Knoppers, B.M. Return of individual genomic research results: Are laws and policies keeping step? *European Journal of Human Genetics* **27**, 535-546, doi:10.1038/s41431-018-0311-3 (2019).

252 Turnbull, C. et al. The 100 000 Genomes Project: Bringing whole genome sequencing to the NHS. *British Medical Journal* **361**, k1687, doi:10.1136/bmj.k1687 (2018).

253 Ulph, F., Dharni, N., Bennett, R. & Lavender, T. Consent for newborn screening: Screening professionals' and parents' views. *Public Health* **178**, 151-158, doi:10.1016/j.puhe.2019.08.009 (2020).

254 Ulph, F., Lavender, D.T. & Bennett, R. Consent for newborn screening and storage of blood samples. *British Journal of Midwifery* **25**, 730-732, doi:10.12968/bjom.2017.25.11.730 (2017).

255 Ulph, F. et al. Provision of information about newborn screening antenatally: A sequential exploratory mixed-methods project. *Health Technology Assessment* **21**, 1-240, doi:10.3310/hta21550 (2017).

256 Umbach, N. et al. Clinical application of genomic high-throughput data: Infrastructural, ethical, legal and psychosocial aspects. *European Neuropsychopharmacology* **31**, 1-15, doi:10.1016/j.euroneuro.2019.09.008 (2020).

257 Understanding Patient Data. *Why an opt-out rather than an opt-in or consent?*, https://understandingpatientdata.org.uk/news/why-an-opt-out, (2018).

258 Urv, T.K. & Parisi, M.A. Newborn Screening: Beyond the Spot. *Advances in Experminental Medicine and Biology* **1031**, 323-346, doi:10.1007/978-3-319-67144-4_19 (2017).

259 Uveges, M.K. & Holm, I.A. Current Trends in Genetics and Neonatal Care. *Advanced Neonatal Care* **21**, 473-481, doi:10.1097/anc.0000000000000834 (2021).

260 van Campen, J.C. et al. Next Generation Sequencing in Newborn Screening in the United Kingdom National Health Service. *International Journal of Neonatal Screening* **5**, 40, doi:10.3390/ijns5040040 (2019).

261 van der Burg, S. & Oerlemans, A. Fostering caring relationships: Suggestions to rethink liberal perspectives on the ethics of newborn screening. *Bioethics* **32**, 171-183, doi:10.1111/bioe.12425 (2018).

262 Van der Ploeg, C.P.B. et al. Cost-effectiveness of newborn screening for severe combined immunodeficiency. *European Journal of Pediatrics* **178**, 721-729, doi:10.1007/s00431-019-03346-3 (2019).

263 VanNoy, G.E. et al. Challenging the Current Recommendations for Carrier Testing in Children. *Pediatrics* **143**, S27-s32, doi:10.1542/peds.2018-1099F (2019).

264 Vayena, E. & Blasimme, A. in *The Cambridge Handbook of Health Research Regulation*, Ch. 26, 257-265 (2021).

265 Vears, D.F. Should we respect parents' views about which results to return from genomic sequencing? *Human Genetics*, doi:10.1007/s00439-021-02293-0 (2021).

266 Vears, D. F. *et al.* Return of individual research results from genomic research: A systematic review of stakeholder perspectives. *PLoS One* **16**, e0258646, doi:10.1371/journal.pone.0258646 (2021).

267 Vickers, A.J., Vertosick, E., Carlsson, S.V., Ehdaie, B. & Kim, S.Y.H. Patient accrual and understanding of informed consent in a two-stage consent design. *Clinical Trials* **18**, 377-382, doi:10.1177/1740774520988500 (2021).

268 Wendler, D. A new justification for pediatric research without the potential for clinical benefit. *American Journal of Bioethics* **12**, 23-31, doi:10.1080/15265161.2011.634482 (2012).

269 Whitley, E.A., Kanellopoulou, N. & Kaye, J. Consent and research governance in biobanks: Evidence from focus groups with medical researchers. *Public Health Genomics* **15**, 232-242, doi:10.1159/000336544 (2012).

270 Winickoff, D.E. & Neumann, L.B. Towards a Social Contract for Genomics: Property and the Public in The 'Biotrust' Model. *Genomics, Society and Policy* **1**, 8-21 (2005).

271 Woerner, A.C., Gallagher, R.C., Vockley, J. & Adhikari, A.N. The Use of Whole Genome and Exome Sequencing for Newborn Screening: Challenges and Opportunities for Population Health. *Frontiers in Pediatrics* **9**, 663752, doi:10.3389/fped.2021.663752 (2021).

272 Wolf, S.M. et al. Integrating Rules for Genomic Research, Clinical Care, Public Health Screening and DTC Testing: Creating Translational Law for Translational Genomics. *Journal of Law, Medicine & Ethics* **48**, 69-86, doi:10.1177/1073110520916996 (2020).

273 Wouters, R.H.P., Cornelis, C., Newson, A.J., Bunnik, E.M. & Bredenoord, A.L. Scanning the body, sequencing the genome: Dealing with unsolicited findings. *Bioethics* **31**, 648-656, doi:10.1111/bioe.12375 (2017).

274 Wouters, R.H.P. et al. Towards a Responsible Transition to Learning Healthcare Systems in Precision Medicine: Ethical Points to Consider. *Journal of Personalized Medicine* **11**, doi:10.3390/jpm11060539 (2021).

275 Wright, C.F. et al. Returning genome sequences to research participants: Policy and practice. *Wellcome Open Research* **2**, 15, doi:10.12688/wellcomeopenres.10942.1 (2017).

276 Wright, S.J., Ulph, F., Lavender, T., Dharni, N. & Payne, K. Understanding Midwives' Preferences for Providing Information About Newborn Bloodspot Screening. *MDM Policy & Practice* **3**, 2.38147E+38115, doi:10.1177/2381468317746170 (2018).

277 Yamamoto, K. et al. Population-based biobank participants' preferences for receiving genetic test results. *Journal of Human Genetics* **62**, 1037-1048, doi:10.1038/jhg.2017.81 (2017).

278 Yamamoto, M., Sakurai, K., Mori, C. & Hata, A. Participant mothers' attitudes toward genetic analysis in a birth cohort study. *Journal of Human Genetics* **66**, 671-679 (2021).

279 Yang, L., Chen, J. & Shen, B. Newborn Screening in the Era of Precision Medicine. *Advances in Experimental Medicine and Biology* **1005**, 47-61, doi:10.1007/978-981-10-5717-5_3 (2017).

280 Zacharias, R.L., Smith, M.E. & King, J.S. The Legal Dimensions of Genomic Sequencing in Newborn Screening. *Hastings Center Report* **48 Suppl 2**, S39-S41, doi:10.1002/hast.884 (2018).
281 Zimani, A. N., Peterlin, B. & Kovanda, A. Increasing genomic literacy through national genomic projects. *Frontiers in Genetics* **12** (2021).

10. Appendix A and methodology

For this report, we conducted a multi-stage review of the literature on ethical, legal and social issues raised by newborn WGS screening programmes, incorporating expert input at key stages. We undertook a narrative review informed by an initial rapid evidence assessment (REA) that provided an overview of the breadth and depth of the literature. This annex provides an in-depth overview of the methodological approach.

The aims of this research were to:

1. Identify values and principles relevant to genomics research and healthcare, especially in the context of newborns and newborn screening.
2. Review and discuss the role of key ethical frameworks that have been proposed or utilised in the context of newborn screening, and the possible limitations of ethical frameworks.
3. Synthesise and summarise the evidence and key arguments.

The stages of the research were as follows:

1. Initial literature search and screening
2. Expert workshop #1
3. Initial extraction and synthesis
4. Thematic analysis
5. Expert workshop #2
6. Follow-up literature searches and synthesis.

Each of these will be explored in further detail below.

10.1 Stage 1 – Initial literature search and screening

10.1.1 Task 1 – Literature searches

Databases selected for academic literature searching were PubMed and Scopus. Three types of search were conducted in each database to better target different areas of the literature: a main search, a newborn search and a search targeting clinical-research hybrid systems. This enabled literature covering specific aspects of newborn and clinical-research hybrid research to be identified without returning a large number of search hits by using a broader search. A total of 4,960 unique articles (main search = 4,600, newborn search = 275, clinical-research hybrid = 85) were returned from across the two databases. The search hits from the different databases and specific search terms and parameters are provided in Table A.A.1 below. All searches were conducted on 2 February 2022, limited to articles published since 2017 and in English. Given the breadth of the topics considered,

grey literature searchers were used to conduct targeted searches on key topics. Google was used for grey literature searching, with no limit on the number of pages of results reviewed.

Table A.A.2. Search protocol and number of search hits[3]

PubMed search		
General search	*Newborn search*	*Clinical-research hybrid systems search*
Ethics[mh] OR ethic*[tiab] OR bioethic*[tiab] OR "Personal Autonomy"[mh] OR "Informed Consent"[mh] OR Confidentiality[mh] OR Privacy[mh] OR autonomy[tiab] OR consent[tiab] OR confidentiality[tiab] OR privacy[tiab] OR "incidental finding*"[tiab] OR "unsolicited finding*"[tiab] OR "variant of unknown significance"[tiab] OR "variants of unknown significance"[tiab] OR "secondary finding*"[tiab] OR "patient choice*"[tiab] OR "parental choice*"[tiab] OR "parent choice*"[tiab] OR "resource allocation*"[tiab] OR "future use*"[tiab] OR "unintended consequence*"[tiab] OR commercial[tiab] OR equit*[tiab] OR "data governance"[tiab] OR "data	"newborn screening"[tiab] OR "neonatal screening"[tiab] OR "neo natal screening"[tiab] OR "pediatric screening"[tiab] OR "paediatric screening"[tiab] OR "infant screening"[tiab] OR "screening of infant*"[tiab] OR (screen*[ti] AND (newborn[ti] OR neonatal[ti] OR "neo natal"[ti] OR pediatric*[ti] OR paediatric*[ti] OR infant*[ti])) AND Ethics[mh] OR ethic*[tiab] OR bioethic*[tiab] OR "Personal Autonomy"[mh] OR "Informed Consent"[mh] OR Confidentiality[mh] OR Privacy[mh] OR autonomy[tiab] OR consent[tiab] OR confidentiality[tiab] OR privacy[tiab] OR "incidental finding*"[tiab] OR "unsolicited finding*"[tiab] OR "variant of unknown significance"[tiab] OR	Clinical[tiab] AND research[tiab] AND hybrid[tiab] AND Ethics[mh] OR ethic*[tiab] OR bioethic*[tiab] OR "Personal Autonomy"[mh] OR "Informed Consent"[mh] OR Confidentiality[mh] OR Privacy[mh] OR autonomy[tiab] OR consent[tiab] OR confidentiality[tiab] OR privacy[tiab] OR "incidental finding*"[tiab] OR "unsolicited finding*"[tiab] OR "variant of unknown significance"[tiab] OR

[3] Removed in Endnote title/abstract searching terms: mouse, zebrafish, mice, rats, dog, pigs, macaques, cattle, sheep, salmonella, chicken, fish, bovine, plants, marine, fowl, farm, poultry. Reviewed and removed some articles with adult in title, food in journal/title, outbreak.

storage"[tiab] OR justice[tiab] OR legal[tiab] OR "data sharing"[tiab] OR inequalit*[tiab] OR trust[tiab] OR biobank*[tiab] OR biorepositor*[tiab] OR "predictive testing"[tiab] OR "data use"[tiab] OR (research[tiab] AND on[tiab] AND data[tiab]) AND "whole genome sequencing"[mh] OR genomics[mh] OR "Sequence Analysis, DNA"[mh] OR "Genetic Testing"[Majr] OR "genome sequencing"[tiab] OR "exome sequencing"[tiab] OR "genomic sequencing"[tiab] OR "genomic test*"[tiab] OR "genomic stud*"[tiab] OR (genomescale[tiab] AND sequencing[tiab]) OR "genetic screening"[tiab] AND ("2017/01/01"[Date - Entry] : "3000"[Date - Entry]) AND (humans[mh] OR inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT prenatal[tiab] OR "pre natal"[tiab] OR embryo[tiab] OR foetus[tiab] OR fetus[tiab] OR sperm[tiab] OR egg[tiab] OR "in vitro fertilization"[tiab] OR "in vitro fertilisation"[tiab] OR preimplantation[tiab] OR "pre implantation"[tiab] OR "genome editing"[tiab] OR germline[tiab] OR "case report"[tiab] OR "direct to consumer"[tiab]	"variants of unknown significance"[tiab] OR "secondary finding*"[tiab] OR "patient choice*"[tiab] OR "parental choice*"[tiab] OR "parent choice*"[tiab] OR "resource allocation*"[tiab] OR "future use*"[tiab] OR "unintended consequence*"[tiab] OR commercial[tiab] OR equit*[tiab] OR "data governance"[tiab] OR "data storage"[tiab] OR justice[tiab] OR legal[tiab] OR "data sharing"[tiab] OR inequalit*[tiab] OR trust[tiab] OR biobank*[tiab] OR biorepositor*[tiab] OR "predictive testing"[tiab] OR "data use"[tiab] OR (research[tiab] AND on[tiab] AND data[tiab]) AND ("2017/01/01"[Date - Entry] : "3000"[Date - Entry]) AND (humans[mh] OR inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]) NOT prenatal[tiab] OR "pre natal"[tiab] OR embryo[tiab] OR foetus[tiab] OR fetus[tiab] OR sperm[tiab] OR egg[tiab] OR "in vitro fertilization"[tiab] OR "in vitro fertilisation"[tiab] OR preimplantation[tiab] OR "pre implantation"[tiab] OR "genome editing"[tiab] OR germline[tiab] OR "case report"[tiab] OR "direct to consumer"[tiab]	"variants of unknown significance"[tiab] OR "secondary finding*"[tiab] OR "patient choice*"[tiab] OR "parental choice*"[tiab] OR "parent choice*"[tiab] OR "resource allocation*"[tiab] OR "future use*"[tiab] OR "unintended consequence*"[tiab] OR commercial[tiab] OR equit*[tiab] OR "data governance"[tiab] OR "data storage"[tiab] OR justice[tiab] OR legal[tiab] OR "data sharing"[tiab] OR inequalit*[tiab] OR trust[tiab] OR biobank*[tiab] OR biorepositor*[tiab] OR "predictive testing"[tiab] OR "data use"[tiab] OR (research[tiab] AND on[tiab] AND data[tiab]) NOT "clinical trial"[tiab]

Scopus search		
General search	*Newborn search*	*Clinical-research hybrid systems search*
Limit to journal; article OR review; keywords: human/humans	**Limit to journal, article OR review; keywords: human/humans**	
(TITLE-ABS-KEY(ethic* OR bioethic* OR autonomy OR consent OR confidentiality OR privacy OR "incidental finding*" OR "unsolicited finding*" OR "variant of unknown significance" OR "variants of unknown significance" OR "secondary finding*" OR "patient choice*" OR "parental choice*" OR "parent choice*" OR "resource allocation*" OR "future	TITLE-ABS-KEY("newborn screening" OR "neonatal screening" OR "neo natal screening" OR "pediatric screening" OR "paediatric screening" OR "infant screening" OR "screening of infant*") OR (TITLE(screen*) AND (TITLE(newborn OR neonatal OR "neo natal" OR pediatric* OR paediatric* OR infant*))) AND TITLE-ABS-KEY(ethic* OR bioethic* OR	TITLE-ABS-KEY("clinical research hybrid") OR TITLE-ABS-KEY("hybrid clinical research") AND TITLE-ABS-KEY(ethic* OR bioethic* OR autonomy OR consent OR confidentiality OR privacy OR "incidental finding*"

use*" OR "unintended consequence*" OR commercial OR equit* OR "data governance" OR "data storage" OR justice OR legal OR "data sharing" OR inequalit* OR trust OR biobank* OR biorepositor* OR "predictive testing" OR "data use" OR "research on data") OR (TITLE-ABS-KEY (dataset*) W/2 TITLE-ABS-KEY (access OR link* OR shar*)) AND TITLE-ABS-KEY(genomics OR "DNA sequence analysis" OR "genome sequencing" OR "exome sequencing" OR "genomic sequencing" OR "genomic test*" OR "genomic stud*" OR "genomescale sequencing" OR "genetic screening" OR "genetic testing") NOT TITLE-ABS-KEY(prenatal OR "pre natal" OR embryo OR foetus OR fetus OR sperm OR egg OR "in vitro fertilization" OR "in vitro fertilisation" OR preimplantation OR "pre implantation" OR "genome editing" OR germline OR "case report" OR "direct to consumer")	autonomy OR consent OR confidentiality OR privacy OR "incidental finding*" OR "unsolicited finding*" OR "variant of unknown significance" OR "variants of unknown significance" OR "secondary finding*" OR "patient choice*" OR "parental choice*" OR "parent choice*" OR "resource allocation*" OR "future use*" OR "unintended consequence*" OR commercial OR equit* OR "data governance" OR "data storage" OR justice OR legal OR "data sharing" OR inequalit* OR trust OR biobank* OR biorepositor* OR "predictive testing" OR "data use" OR "research on data") OR (TITLE-ABS-KEY (dataset*) W/2 TITLE-ABS-KEY (access OR link* OR shar*)) NOT TITLE-ABS-KEY(prenatal OR "pre natal" OR embryo OR foetus OR fetus OR sperm OR egg OR "in vitro fertilization" OR "in vitro fertilisation" OR preimplantation OR "pre implantation" OR "genome editing" OR germline OR "case report" OR "direct to consumer")	OR "unsolicited finding*" OR "variant of unknown significance" OR "variants of unknown significance" OR "secondary finding*" OR "patient choice*" OR "parental choice*" OR "parent choice*" OR "resource allocation*" OR "future use*" OR "unintended consequence*" OR commercial OR equit* OR "data governance" OR "data storage" OR justice OR legal OR "data sharing" OR inequalit* OR trust OR biobank* OR biorepositor* OR "predictive testing" OR "data use" OR "research on data") OR (TITLE-ABS-KEY (dataset*) W/2 TITLE-ABS-KEY (access OR link* OR shar*)) NOT TITLE-ABS-KEY("clinical trial")
Total across both databases: 4,600	**Total across both databases: 275**	**Total across both databases: 85**
Overall total unique documents: 4,960		

10.1.2. Task 2 – Screening

Following the literature search, the title and abstracts of sources were screened against the inclusion/exclusion criteria using Excel. Only sources that met the inclusion criteria progressed to the next stage. To ensure reliability of the screening process across the research team, a pilot of 20 papers were screened by all team members. The screening acted as an initial sift to ensure that only relevant sources were read in full, which was particularly important for the output of the protocol-driven literature search that typically returns a high number of sources not relevant to the research question.

Table A.A.3. Inclusion/exclusion criteria for literature reviewed

	Inclusion criteria	Exclusion criteria
Location	All	None
Topic	Use of whole genome sequencing or exome sequencing for population screening.	Use of whole genome or exome sequencing at an individual level (e.g. diagnostics).

	Inclusion criteria	Exclusion criteria
	Discusses ethical considerations of using genomics or genetic testing for population screening or the development of data repositories.	Discusses aspects of WGS unrelated to ethical, legal or social considerations, or unrelated to screening or repository development. Molecular biology/basic science.
Population	All ages.	None.
	Humans.	Animals and plants.
Language	English.	Other languages.
Study type	Peer-reviewed journal publications, commentaries/opinion pieces, published reports from governments, editorials, non-governmental organisations (NGOs) or independent research organisations, PhD theses.	Documents without clear organisational authorship, letters, book reviews, sub-PhD-level theses.

10.1.3 Task 3 – Mapping and prioritisation of articles

During the screening stage, articles identified as relevant were "tagged" with key words based on the topic(s) covered in relation to the conceptual framework (see Section 1.3.2). Articles were also tagged to distinguish whether they discussed ethical, social and legal issues, ethical principles/frameworks, or both. Tagging was also used to identify whether the article focused on newborns and/or other age groups, and which countries it related to (if any). This process enabled the team to map the number of articles identified as relevant from the screening stage, and the number of articles identified covering each of the overarching topics (e.g. informed consent, care pathways).

10.2 Stage 2 – Expert workshop #1

10.2.1 Task 1 – Summary of mapping results and updating of conceptual framework

Quantitative summaries were developed regarding the depth and breadth of the available academic and grey literature relating to the areas and topics outlined in the conceptual framework (Section 1.3.2). This included consideration of how many sources were directly relevant to the UK context versus other countries, and an initial assessment of the gaps in the available data. Qualitative summaries of any new areas or issues that have emerged from the literature but were not included in the original conceptual framework were developed, and the framework was revised to accommodate these.

10.2.2. Task 2 – Expert workshop #1

To provide additional insight into the emerging findings from the literature review, a two-hour online workshop with subject-matter experts and team members from Genomics England was conducted. The objective of the workshop was to identify and prioritise any significant gaps in the review of the literature at the interim stage, and to prioritise areas for exploration in the next stage of the review. Experts in genomics and the ethical and social issues surrounding genomic sequencing and interpretation attended.

Table A.A.4. Subject matter experts for consultation

Name	Title	Affiliation

Ms Emma Hudson	Health Economist	University of Cambridge, Department of Public Health and Primary Care
Dr Richard Milne	Senior Social Scientist	Society & Ethics Research, Wellcome Connecting Science
Prof Neena Modi	Professor of Neonatal Medicine/Consultant in Neonatal Medicine	Imperial College London/Chelsea and Westminster NHS Foundation Trust
Dr Harriet Teare	Programme Director UK SPINE Knowledge	University of Oxford
Prof Caroline Wright	Chair in Genomic Medicine	University of Exeter, College of Medicine and Health
Dr Jonathan Roberts	NHS Genetic Counsellor	Addenbrooke's Hospital

During the workshop, an overview of the literature reviewed to date, based on the preliminary results from the mapping of the literature, and an overview of the conceptual framework were provided. Workshop attendees reflected on important gaps in the evidence base, and prioritised gaps for further research. Attendees reflected on the ethical questions raised by the research, and prioritised ethical issues for consideration in the narrative review component of the research.

10.3 Stage 3 – Initial extraction and synthesis

10.3.3. Task 1 – REA extraction

As the number of relevant articles was too high (425) to fully analyse and synthesise within the short timeframe of this study, papers were prioritised for full-text review. To do this, we reviewed the titles and abstracts of the relevant articles and identified those that should be prioritised for extraction, considering the following factors:

- **Population:** Prioritising articles focusing on newborn (genetic) screening over articles focusing on adult populations.
- **Reason for screening:** Excluding articles focused on screening individuals suspected of having a genetic health condition (i.e. screening for non-preventative reasons). Prioritising articles focused on screening for a broad range of conditions, rather than just one.
- **Initiative type:** Prioritising articles discussing biobank/repositories and clinical-hybrid research programmes.
- **Depth of discussion:** Prioritising articles which discussed ethical, legal and social issues in detail and as a focus of the paper, rather than considering these issues briefly/tangentially.
- **Recency of paper**: Articles published more recently were prioritised over older articles covering the same topic(s).

One reviewer independently prioritised each article as a priority (or not), and any differences in assignment were discussed and finalised within the team. From this process, 115 papers were selected for initial data extraction (but documents from the full set of 425 were revisited and incorporated once themes were developed, see below). The analysis of the included articles was carried out in a structured manner using an Excel data extraction template informed by the conceptual framework. The final data extraction tools were tested for reliability across different groups of reviewers using five sources to affirm that it exhibits the features of transparency and replicability.

Table A.A.5. Example data extraction template for collecting information from identified literature

Component	Information extracted
Reference	Study authors, title, date and journal details.
About the article	Article type, aims, type of study and brief methodology.
Geographical location	Country and region, if specified.
Population	Population, if specified.
Programme name and description (if relevant)	Name and short overview of the genetic screening programme(s) of focus, if relevant.
Concept – Autonomy	Considerations balancing the interest and choice of both the parents and child. Information relating to the personal autonomy of the newborn, including in the future.
Concept – Informed consent	Considerations in relation to (informed) consent and patient choice. This may include models of consent, particularly proxy consent by parents and how this Is managed when the child is older, and/or dynamic consent. Also, information relating to the information given to parents, and when, and other support.
Concept – Withdrawal from research	Considerations in relation to how withdrawal from research is managed in practical terms, and what the consequences might be for the individual who withdraws (clinically and research-wise).
Concept – Transparency and trust	Considerations in relation to public involvement in genomics research, and transparency and trust. This may include the transparency of organisations (including private) involved, or trust from parents/child/public in the research and clinical services.
Concept – Unsolicited findings	Considerations in relation to unsolicited/incidental/secondary findings.
Concept – Uncertain findings	Considerations in relation to uncertain findings, genetic determinism and variants of unknown significance.
Concept – Communication of results	Considerations in relation to sharing and communicating results with parents, child (later in life) and healthcare professionals.
Concept – Participant information and engagement	Considerations relating to how to provide information, consent and engage individuals in research when recruiting/seeking consent in a clinical setting.
Concept – Discrimination and representation	Considerations in relation to equity in design and implementation, potential for discrimination, inequalities, measures taken to alleviate discrimination.
Concept – Equity of access and use	Considerations in relation to whether the same service is available to everyone and how this is ensured, and whether everyone who receives information has the same ability to make use of it.
Concept – Health literacy	Considerations in relation to the extent of understanding what genetic screening is and its implications.

Among the final set of articles, full-text articles were retrieved. Data from the identified articles were extracted following the extraction template, in adherence to scientific standards of transparency and replicability.[151] Data were extracted by six members of the research team independently and then combined into one extraction template.

10.3.2 Task 2 – Narrative review analysis

A subset of articles were identified that reflected on ethical principles and frameworks, and their application to specific issues in genomic medicine and research. These were analysed as part of the first stage of the narrative review. The aim of this was to provide a summary and critique of the key ethical frameworks relevant for newborn WGS and the design of the NGP, including discussion of any examples of their application. It was informed by the workshop findings of key gaps and areas for prioritisation. A hermeneutic approach analysis was taken,[23,83] critically reflecting on the individual studies to provide insight into the role and possible limitations of ethical frameworks in the context of newborn WGS screening. Taking this approach, we moved back and forth between elements as our understanding of the body of relevant literature grew.

Data extraction involved two key elements: analytic reading, and mapping and classification of articles. Analytical reading was structured by dividing the articles into broad topic areas based on the mapping work undertaken during Stage 2. This gave researchers an overview of the topic area and helped them identify key articles, which were prioritised for more in-depth analytic reading. This entailed reading the abstract, introduction, discussion and conclusions, or the full text, while taking notes.[23]
A coding framework was set up using MAXQDA, with the codes based on the conceptual framework and the types of ethical principles and frameworks (e.g. autonomy, equality, solidarity). The mapping and classifying step involved using the coding framework in MAXQDA to extract data from all the articles, allowing for a systematic analysis of key principles and frameworks. The researchers regularly communicated with each other about any emergent concepts that needed to be included in the coding framework, maintaining consistency across the research team. We assessed the data to understand the relevant ethical principles and frameworks, and the connections and contradictions between them, as well as identify any evidence gaps.

10.4. Stage 4 – Thematic analysis

10.4.1 Task 1 – Analysis of data relating to ethical, legal and social issues

The Excel extraction table allowed researchers to scan, collate and assess the evidence available in support of each research question, which facilitated a structured and targeted write-up of the review. The information from the extraction template was analysed thematically, following the structure of the conceptual framework. Issues relevant to genomic medicine were outlined, highlighting existing and emerging ethical questions particularly relevant to the newborn screening context. Gaps in the available evidence base were also identified.

10.4.2. Task 2 – Analysis of data relating to ethical principles and frameworks

The aim of this analysis was to provide a summary and critique of the key ethical frameworks relevant for newborn WGS and the design of the NGP, including discussion of any examples of their application. It was informed by the workshop findings of key gaps and areas for prioritisation. A hermeneutic approach analysis was taken,[23,83] critically reflecting on the individual studies to provide insight into the role and possible limitations of ethical frameworks in the context of newborn WGS screening. Taking this approach, we moved back and forth between elements as our understanding of the body of relevant literature grew.

Data extraction involved two key elements: analytic reading, and mapping and classification of articles. Analytical reading was structured by dividing the articles into broad topic areas based on the mapping work done during Stage 2. This gave researchers an overview of the topic area and helped them to

identify key articles, which were prioritised for more in-depth analytic reading. This entailed reading the abstract, introduction, discussion and conclusions, or the full text, while taking notes.[23] The mapping and classifying step involved using the coding framework in MAXQDA to extract data from all the articles, allowing for a systematic analysis of key principles and frameworks. The researchers regularly communicated with each other about any emergent concepts that needed to be included in the coding framework, maintaining consistency across the research team. We assessed the data to understand the relevant ethical principles and frameworks and the connections and contradictions between them, as well as identify any evidence gaps.

10.5. Stage 5 – Expert workshop #2

A second two-hour online workshop was held, with the same experts as the first, to get expert opinions on the conclusions from the REA and narrative review regarding the availability of ethical frameworks, as well as ideas to support the design and development of the NGP. Experts shared their reflections on the strengths and weaknesses of the frameworks, including any important issues that they did not address. The workshop was also used to understand if there were any issues that may benefit from further study prior to undertaking the development of a newborn WGS programme.

10.6 Stage 6 – Follow-up literature searches and synthesis

10.6.1. Task 1 – Follow-up literature searches

Following the development of the key themes for the research, gaps identified by the research team and workshop participants were further investigated with targeted follow-up searches (using Google Scholar and PubMed, and via snowballing from extracted articles). The inclusion criteria were broader for these supplemental searches than for the original searches to help fill gaps in knowledge (e.g. no limit on publication date, and broader focus on issues identified in research in general rather than specific to screening). Additional documents were incorporated into the MAXQDA repository and used to further develop the summary of each thematic area.

10.6.2. Task 2 – Overall synthesis

In total, 572 documents were identified as being relevant to the topic (although not all of these are directly cited in this report). An internal synthesis workshop with the research team was held to develop and synthesise findings across the different stages of the project. By bringing together project team members who have worked across tasks we were able to draw on all the learning across the different stages of the project to produce a complete analysis of key ethical, legal and social issues related to newborn WGS, including relevant ethical frameworks. The outcomes of this internal workshop provided significant input to the final report and the overall conclusions of the study.

11. Appendix B – Examples of other potentially relevant initiatives

Programme name	eMERGE
Country	United States
Population	All
Programme details	eMERGE is a national network organised and funded by the National Human Genome Research Institute (NHGRI). It combines DNA biorepositories with electronic medical record

	(EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine. In its projects, eMERGE studies and pilots genomic medicine translation through discovery, implementation, tools and policy.
Relevant references: • Hoell, C.A., Aufox, S., Nashawaty, N., Myers, M.F. & Smith, M.E. Comprehension and personal value of negative non-diagnostic genetic panel testing. *Journal of Genetic Counselling* (2021).		

Programme name	BabySeq
Country	United States
Population	Newborns
Programme details	The BabySeq Project is studying families of both healthy and sick newborns via a randomised clinical trial where half have their baby's genome sequenced.
Relevant references: • Ross, L.F., & Clayton, E.W. Ethical Issues in Newborn Sequencing Research: The Case Study of BabySeq. *Pediatrics* (2019). • Holm, I.A., McGuire, A., Pereira, S., Rehm, H., Green, R.C. & Beggs, A.H. Returning a Genomic Result for an Adult-Onset Condition to the Parents of a Newborn: Insights From the BabySeq Project. *Pediatrics* (2019)	

Programme name	GeneScreen
Country	Italy
Population	Adults
Programme details	The GeneScreen Carrier Screen provides a closer look at genes to see if a couple is at risk of passing a hereditary genetic disorder to their offspring. GeneScreen Carrier Screening Test allows for comprehensive care and enables patients to make more informed reproductive decisions. Offering GeneScreen to a patient before pregnancy allows her to gain knowledge about her reproductive health early.
Relevant references: • Waltz, M., Cadigan, R.J., Prince, A.E.R., Skinner, D. & Henderson, G.E. Age and perceived risks and benefits of preventive genomic screening. *Genetics in Medicine* (2018). • Cadigan, R.J., Butterfield, R., Rini, C., Waltz, M., Kuczynski, K.J., Muessig, K., Goddard, K.A.B. & Henderson, G.E. Online Education and e-Consent for GeneScreen, a Preventive Genomic Screening Study. *Public Health Genomics* (2017).	

Programme name	MedSeq
Country	United States
Population	All

Programme details	The MedSeq Project, funded by the NIH, was the very first study exploring the use of whole genome sequencing (GS) in both a healthy population and a population with suspected genetic cardiac disease. The MedSeq Project was designed to explore the medical, behavioral and economic impacts of incorporating GS into everyday medicine.
Relevant references: • Jamal, L.J., Robinson, J.O., Christensen, K.D., Blumenthal-Barby, J., Slashinski, M.J., Perry, D.L., Vassy, J.L., Wycliff, J., Green, R.C. & McGuire, A.L. When bins blur: Patient perspectives on categories of results from clinical whole genome sequencing. *AJOB Empirical Bioethics* (2017). • Roberts, J.S., Robinson, J.O., Diamond, P.M., Bharadwaj, A., Christensen, K.D., Lee, K.B., Green, R.C. & McGuire, A.L. Patient understanding of, satisfaction with, and perceived utility of whole-genome sequencing: findings from the MedSeq Project. *Genetics in Medicine* (2018).	

Programme name	100,000 genomes
Country	United Kingdom
Population	All
Programme details	The 100,000 Genomes Project was a British initiative to sequence and study the role that genes play in health and disease. Recruitment was completed in December 2018, although research and analysis is still ongoing, with the sequencing of 100,000 genomes from around 85,000 NHS patients affected by rare disease or cancer.
Relevant references: • Dheensa, S., Lucassen, A. & Fenwick, A. Fostering trust in healthcare: Participants' experiences, views, and concerns about the 100,000 genomes project. *European Journal of Medical Genetics* (2019). • Lewis, C., Hammond, J., Hill, M., Searle, B., Hunter, A., Patch, C., Chitty, L.S. & Sanderson, S.C. Young people's understanding, attitudes and involvement in decision-making about genome sequencing for rare diseases: A qualitative study with participants in the UK 100, 000 Genomes Project. *European Journal of Medical Genetics* (2020).	

Programme name	SEQUAPRE
Country	France
Population	Adults
Programme details	The SEQUAPRE study performed a quantitative analysis of the preferences of 513 parents of children with undiagnosed developmental disorders with respect to the disclosure of hypothetical results. In-depth analysis showed that parents had ambivalent feelings about the findings whatever the results returned. The contrasting results from these studies raise questions about the value of the information provided and

	parents' high expectations regarding the results. The nature of parental expectations has emerged as an important topic in efforts to optimise accompaniment and support for families during the informed decision-making process, and after disclosure of the results in an overall context of uncertainty.
Relevant references: • Chassagne, A., Pélissier, A., Houdayer, F., Cretin, E., Gautier, E., Salvi, D., Kidri, S., Godard, A., Thauvin-Robinet, C., Masurel, A., Lehalle, D., Jean-Marçais, N., Thevenon, J., Lesca, G., Putoux, A., Cordier, M.P., Dupuis-Girod, S., Till, M., Duffourd, Y., Rivière, J.B., Joly, L., Juif, C., Putois, O., Ancet, P., Lapointe, A.S., Morin, P., Edery, P., Rossi, M., Sanlaville, D., Béjean, S., Peyron, C. & Faivre, L. Exome sequencing in clinical settings: preferences and experiences of parents of children with rare diseases (SEQUAPRE study). *European Journal of Human Genetics* (2019).	

Programme name	HealthSeq
Country	United States
Population	Adults
Programme details	HealthSeq is an exploratory longitudinal study designed to explore motivations for whole-genome sequencing, satisfaction and the impact of personal whole-genome sequencing results.
Relevant references: • Sanderson, S.C., Linderman, M.D., Suckiel, S.A., Zinberg, R., Wasserstein, M., Kasarskis, A., Diaz, G.A. & Schadt, E.E. Psychological and behavioural impact of returning personal results from whole-genome sequencing: the HealthSeq project. *European Journal of Human Genetics* (2017).	

Programme name	SpainUDP
Country	Spain
Population	Adults
Programme details	SpainUDP offers a multidisciplinary approach to patients who have long sought a diagnosis without any success. During the first phase of the protocol, undiagnosed cases are sent to SpainUDP by individual patients or families, patient organisations, or hospitals. After careful analysis of phenotype, data from sequencing experiments (WES) is processed with a standard pipeline, and detailed standardised phenotypic information (mapped to the Human Phenotype Ontology, HPO) is connected to genetic data. In addition, the participation of SpainUDP in international initiatives such as the European projects RD-Connect and Solve RD, the Undiagnosed Diseases Network International (UDNI), and the MatchMaker Exchange (MME) platform, allows the establishment of a global data sharing strategy across multiple projects submitting data to these international initiatives.

Relevant references: • López-Martín, E., Martinez-Delgado, B., Bermejo-Sánchez, E. & Alonso, J. 'SpainUDP: The Spanish undiagnosed rare diseases program. *International Journal of Environmental Research and Public Health* (2018).

Programme name	OVCARE
Country	United States
Population	Adults
Programme details	An ovarian cancer research programme consisting of a multidisciplinary team that includes researchers, pathologists, geneticists, epidemiologists and gynaecologic surgeons, spanning multiple institutions.
Relevant references: • Asiimwe, R., Lam, S., Leung, S., Wang, S., Wan, R., Tinker, A., McAlpine, J.N., Woo, M.M.M., Huntsman, D.G. & Talhouk, A. From biobank and data silos into a data commons: Convergence to support translational medicine. *Journal of Translational Medicine* (2021).	

Programme name	International Genome Sample Resource (IGSR)
Country	United Kingdom
Population	All
Programme details	IGSR was set up to ensure the future usability and accessibility of data from the 1000 Genomes Project and to extend the data set produced by the project to include new data generated and new populations, where sampling has been carried out in line with IGSR sampling principles.
Relevant references: • Fairley, S., Lowy-Gallego, E., Perry, E. & Flicek, P. The International Genome Sample Resource (IGSR) collection of open human genomic variation resources. *Nucleic Acids Research* (2020).	

Programme name	UK Cystic Fibrosis Registry
Country	United Kingdom
Population	All
Programme details	A secure centralised database that is sponsored and managed by the Cystic Fibrosis Trust. It records the health data of people with cystic fibrosis, who have given their consent for the registry.
Relevant references: • Schlüter, D.K., Southern, K.W., Dryden, C., Diggle, P. & Taylor-Robinson, D. Impact of newborn screening on outcomes and social inequalities in cystic fibrosis: a UK CF registry-based study. *Thorax* (2020).	

Programme name	GenomeAsia100K
Continent	Asia

Population	All
Programme details	A non-profit consortium collaborating to sequence and analyse 100,000 Asian individuals' genomes to help accelerate Asian population specific medical advances and precision medicine.
Relevant references: • McGonigle, I. & Schuster, S.C. Global science meets ethnic diversity: Ian McGonigle interviews GenomeAsia100K Scientific Chairman Stephan Schuster. *Genetics Research* (2019).	

Programme name	Polish Universal Neonatal Hearing Screening Program (PUNHSP)
Country	Poland
Population	Newborns
Programme details	This programme is aimed at early diagnosis and intervention in children with hearing impairments, and is an example of a well-managed programme.
Relevant references: • Greczka, G., Zych, M., Szyfter, W. & Wróbel, M. Analysis of the changes in the Polish Universal Neonatal Hearing Screening Program over 15 years of activity. *Otolaryngologia Polska* (2018).	

Programme name	All of Us
Country	United States
Population	All
Programme details	A longitudinal research initiative with ambitious national recruitment goals, including of populations traditionally underrepresented in biomedical research, many of whom have high geographic mobility. The programme has a distributed infrastructure, with key programmatic resources spread across the United States.
Relevant references: • Doerr, M., Grayson, S., Moore, S., Suver, C., Wilbanks, J. & Wagner, J. Implementing a universal informed consent process for the All of Us Research Program. *Pacific Symposium on Biocomputing* (2019).	

Programme name	H3Africa
Continent	Africa
Population	All
Programme details	A conglomeration of research and infrastructure projects spread throughout Africa that aim to apply genomic methodology to diseases affecting the people in the region. Its operation is innovative as it is doing something new: filling a hitherto void in the genomic research capability of African scientists and infusing resources and manpower to institutions and investigators across Africa. In addition to developing and sustaining capacity in

	genomic research and biorepositories, H3Africa is also invested in developing an appropriate ethical regulatory regime to govern research in these areas.
Relevant references: • Nnamuchi, A. H3Africa: An Africa exemplar? Exploring its framework on protecting human research participants. *Developing World Bioethics* (2018). • Bentley, A.R., Callier, S. & Rotimi, C. The Emergence of Genomic Research in Africa and New Frameworks for Equity in Biomedical Research. *Ethnicity & Disease* (2019).	

Programme name	National Human Genome Research Institute (NHGRI)
Country	(International)
Population	All
Programme details	NHGRI recently published a new strategic vision for the future of human genomics, the product of an extensive, multi-year engagement with numerous research, medical, educational and public communities. The theme of this 2020 vision – The Forefront of Genomics – reflects NHGRI's critical role in providing responsible stewardship of the field of human genomics, especially as genomic methods and approaches become increasingly disseminated throughout biomedicine. The new NHGRI strategic vision features a set of guiding principles and values that provide an ethical and moral framework for the field.
Relevant references: • Bonham, V.L. & Green, E.D. The genomics workforce must become more diverse: A strategic imperative. *American Journal of Human Genetics* (2021).	

Programme name	FindMyVariant study
Country	United States
Population	Adults
Programme details	The MyVariant team is a group based at the University of Washington dedicated to helping patients and families understand unique genetic variants.
Relevant references: • Tsai, G.J., Chen, A.T., Garrett, L.T., Burke, W., Bowen, D.J. & Shirts, B.H. Exploring relatives' perceptions of participation, ethics, and communication in a patient-driven study for hereditary cancer variant reclassification. *Journal of Genetic Counselling* (2020).	

Programme name	ClinSeq study
Country	United States
Population	All

Programme details	Racial minority populations are underrepresented in genomics research. This study enrolled African-descended individuals in a sequencing study and reported their characteristics. Some 467 individuals who self-identified as African, African American or Afro-Caribbean were recruited to the ClinSeq study and surveyed about knowledge, motivations, expectations and traits.
Relevant references: • Lewis, K.L., Heidlebaugh, A.R., Epps, S., Han, P.K.J., Fishler, K.P., Klein, W.M.P., Miller, I., M., Ng, D., Hepler, C., Biesecker, B.B. & Biesecker, L.G. Knowledge, motivations, expectations, and traits of an African, African-American, and Afro-Caribbean sequencing cohort and comparisons to the original ClinSeq cohort. *Genetics in Medicine* (2019).	

Programme name	Tohoku Medical Megabank Project
Country	Japan
Population	All
Programme details	This project carries out a long-term health survey focused on areas affected by the Great East Japan Earthquake. It provides research infrastructure for the development of personalised genomic medicine by building up a biobank that includes materials and information from 150,000 individuals.
Relevant references: • Yamamoto, K., Hachiya, T., Fukushima, A., Nakaya, N., Okayama, A., Tanno, K., Aizawa, F., Tokutomi, T., Hozawa, A. & Shimizu, A. Population-based biobank participants' preferences for receiving genetic test results. *Journal of Human Genetics* (2017).	

Programme name	Welfare Genome Project
Country	Korea
Population	Adults
Programme details	The Welfare Genome Project (WGP) provided 1,000 healthy Korean volunteers with detailed genetic and health reports to test the social perception of integrating personal genetic and healthcare data on a large scale.
Relevant references: • Jeon, Y., Jeon, S., Blazyte, A., Kim, Y.J., Lee, J.J., Bhak, Y., Cho, Y.S., Park, Y., Noh, E.K., Manica, A., Edwards, J.S., Bolser, D., Kim, S., Lee, Y., Yoon, C., Lee, S., Kim, B.C., Park, N.H. & Bhak, J. Welfare Genome Project: A Participatory Korean Personal Genome Project With Free Health Check-Up and Genetic Report Followed by Counselling. *Frontiers in Genetics* (2021).	

Programme name	Genomes for Kids (G4K)
Country	United States
Population	(0-21)

Programme details	A study examining the feasibility of the comprehensive clinical genomic analysis of tumors and paired normal samples.
Relevant references: • Howard Sharp, K.M., Jurbergs, N., Ouma, A., Harrison, L., Gerhardt, E., Taylor, L., Hamilton, K., McGee, R.B., Nuccio, R., Quinn, E., Hines-Dowell, S., Kesserwan, C., Sunkara, A., Gattuso, J.S., Pritchard, M., Mandrell, B., Relling, M.V., Haidar, C.E., Kang, G., Johnson, L.M. & Nichols, K.E. Factors associated with declining to participate in a pediatric oncology next-generation sequencing study. *JCO Precision Oncology* (2019).	

Programme name	Geisinger MyCode® Community Health Initiative
Country	United States
Population	Adults
Programme details	Geisinger Health System (GHS) provides a platform for precision medicine. Key elements are the integrated health system, stable patient population and electronic health record (EHR) infrastructure. In 2007, Geisinger launched MyCode, a system-wide biobanking programme to link samples and EHR data for broad research use.
Relevant references: • Savatt, J.M., Wagner, J.K., Joffe, S., Rahm, A.K., Williams, M.S., Bradbury, A.R., Davis, F.D., Hergenrather, J., Hu, Y., Kelly, M.A., Kirchner, H.L., Meyer, M.N., Mozersky, J., O'Dell, S.M., Pervola, J., Seeley, A., Sturm, A.C. & Buchanan, A.H. Pediatric reporting of genomic results study (PROGRESS): a mixed-methods, longitudinal, observational cohort study protocol to explore disclosure of actionable adult- and pediatric-onset genomic variants to minors and their parents. *BMC Pediatrics* (2020).	