Study Protocol

EXPRESS - Optimising EXome PREnatal Sequencing Services

Version	Version 1
Date	01/10/2020
Funding	NIHR HS&DR - NIHR127829
Sponsor	Great Ormond Street Hospital NHS Foundation Trust
Sponsor Number	18WB19
Study Start date	01/10/2020
Study End date	30/09/2023
Research ethics and governance approval	*In progress*

Research team

Name	Institution	Role
Prof Lyn Chitty (Co-CI)	Great Ormond Street Hospital	Overall supervision, study coordination and liaison with fetal medicine and genetics consultants and professional bodies.
Dr Melissa Hill (Co-CI)	Senior Social Scientist Great Ormond Street Hospital	Study coordination and social science research. Co-lead of determining care pathways (WS1) and lead qualitative interviews with parents (WS2).
Prof Marian Knight	University of Oxford	Expertise in maternal and child population health and epidemiology. Lead of the evaluation of service outcomes.
Prof Michael Parker	University of Oxford	Expertise in ethical analysis and ethical issues in genomics. Lead of the ethics evaluation.
Dr Mark Kroese	Director, PHG Foundation	Expertise in Public Health Medicine. Lead engagement and dissemination for policy makers and commissioners.
Ms Jane Fisher	Director, Antenatal Results and Choices (ARC)	Lead the PPIAG, provide parent perspectives and direct the dissemination of findings to parents and other stakeholders.
Dr Jean Ledger	UCL	Expertise in health policy, implementation and the evaluation of innovations in healthcare. Co-lead in defining care pathways and in-depth case studies and integrating all WS findings
Prof Naomi Fulop	UCL	Expertise in implementation science and evaluation of innovations in healthcare. Co-lead in defining care pathways and in-depth case studies and integrating all WS findings
Prof Stephen Morris	University of Cambridge	Expertise in health economics and quantitative methods. Lead of the health economics research.
Prof Sian Ellard OBE	University of Exeter	Expertise in laboratory genetics and genomics. Provide clinical and laboratory input and lead engagement with Genomic Laboratory Hubs.
Dr Alec McEwan	Nottingham University Hospitals NHS Trust	Expertise in fetal medicine. Current Honorary Secretary for BMFMS. Will provide clinical input and lead engagement with fetal medicine specialists.
Dr Dagmar Tapon	Queen Charlotte and Chelsea Hospital	Expertise in prenatal genetic counselling. Will provide clinical input and lead engagement with genetic counsellors, fetal medicine midwives and screening midwives.
Mr Dominic McMullan	West Midlands Regional Genetics Service	Expertise in laboratory genetics and genomics. Will provide laboratory input and lead engagement with laboratory scientists.
Ms Kerry Leeson-Beevers	Breaking Down Barriers Alstrom Society	PPI expertise. PPIAG Member. Will provide advice on reaching out to a diverse range of community groups.

Scientific Abstract

BACKGROUND: From October 2020 the new NHS Genomic Medicine Service will offer fetal exome sequencing (ES) for pregnancies where fetal anomalies identified by ultrasound are likely to have a genetic aetiology, as judged by a clinical geneticist. Fetal ES will be delivered through seven new genomic laboratory hubs (GLHs) across England. Fetal ES is an innovative new test with the potential to significantly improve NHS prenatal diagnostic services by increasing genetic diagnoses in a timeframe that informs prenatal decision-making. Fetal ES has not, however, previously been offered routinely in a national healthcare system and there are only minimal guidelines for its use. Research is urgently needed to guide implementation to maximise benefits for parents while optimising NHS resources

AIM: To conduct a formative and summative mixed-methods evaluation of the new fetal ES service that will provide feedback to ensure national delivery of an equitable, acceptable, ethical, robust and cost-effective care pathway that improves the quality of care for parents undergoing prenatal diagnosis in fetuses with anomalies likely to have a genetic aetiology

METHODS: A Steering Committee with academic, professional and patient members will provide oversight and a Patient and Public Involvement Advisory Group will input into all activities. Study design draws on a framework developed in previous studies of major system innovation as well as Normalisation Process Theory. There are six interrelated workstreams (WSs). WS1 will use staff interviews, surveys, non-participant observations and documentary analysis to determine clinical care pathways and produce in-depth case studies at each GLH. Data collection at multiple time points will allow tracking of service changes over time. In WS2 qualitative interviews with parents offered fetal ES or with previous experience of fetal anomalies will explore views and establish information and support needs. WS3 will analyse testing data over a 12-month period to establish service outcomes (diagnostic yield, referral rates, referral sources, final diagnoses). Data sources include; the new National Genomic Information System (NGIS) and GLH and fetal medicine databases. Statistical comparisons will identify factors (individual or service-related) associated with variation in outcomes. WS4 will analyse ethical issues associated with introducing fetal ES and develop an ethical framework for an optimal and equitable service. WS5 will determine costs and cost-effectiveness of fetal ES versus standard tests and evaluate costs of implementing an optimal fetal ES pathway. WS6 will integrate all findings and conduct workshops to determine the key features of an optimal care pathway from a service delivery, patient and professional perspective. Wide dissemination will include peer reviewed publications, reports, policy statements and lay summaries

MAIN BENEFITS: The proposed formative and summative research will inform the development of a fetal ES service that delivers equity of access and high standards of care across England with an associated improvement in prenatal diagnostic services and benefits for patients. Findings will be shared on a regular basis to facilitate improvements in service delivery. This work will also be an exemplar for evaluating other aspects of the Genomic Medicine Service and, as the NHS is an early adopter, our findings may be useful to others internationally as they implement similar services

Background

In October 2018 genetic services across England were reconfigured to establish a national Genomic Medicine Service based around seven GLHs that aim to deliver consolidated, state of the art, high throughput and high-quality genomic testing with equity of access for patients across the NHS. The Genomic Medicine Service is a world leading initiative building on work done in the 100,000 Genomes Project to embed genomic testing in clinical care for improved diagnosis and management of patients with rare and inherited disease and cancer. As part of this service rapid fetal ES will be offered for pregnancies where anomalies identified on fetal ultrasound are considered likely to have a monogenic aetiology. Fetal ES is an innovation in diagnostics, with the potential to significantly improve diagnosis and thus impact on pregnancy management. To date in England, fetal ES has only been used in a research setting.[1, 2] Offering fetal ES as a national service requires independent evaluation to develop evidence-informed best practice guidance to maximise benefits, minimise harms and ensure patient and professional views are considered. We will conduct a prospective evaluation to identify challenges (laboratory, clinical, service delivery and ethical), assess patient and health professional views and their educational needs, and determine overall costs and benefits. We will bring together quantitative data on costs and patient pathways, combining these with qualitative data on stakeholder experiences and systematic analysis of ethical issues to generate clear recommendations for service delivery.

Fetal anomalies occur in ~2-5% of pregnancies and cause ~20% of perinatal deaths.[3-5] Accurate diagnosis is required to aid parental counselling and decision-making. Traditionally, prenatal genetic testing has been limited to techniques that identify whole chromosome or relatively large chromosomal changes. In combination these diagnose ~40% of fetal anomalies but cannot detect small changes that cause many genetic disorders, thus the majority of cases remain undiagnosed. Clinicians have relied on time-consuming targeted testing of single genes or small gene panels to explore a potential genetic diagnosis, which may in itself be further complicated by incomplete phenotypic information due to the gestational age or inherent limitations in fetal ultrasound. Fetal ES can improve prenatal diagnosis by increasing analysis resolution down to the level of a single base-pair, casting a wide diagnostic net across multiple genes, which is particularly valuable as the fetal phenotype based on sonographic findings is often not specific to one condition. Further, when performed with rapid analytical laboratory processes, turnaround times allow results to be made available within the current pregnancy. As a result fetal ES has the potential to significantly improve NHS prenatal diagnostic services by increasing the number of genetic diagnoses made in a timeframe that informs parental decision making and clinical management during pregnancy.[1, 6] An accurate genetic diagnosis will improve parental counselling regarding prognosis for their baby, informing

decision-making in pregnancy and plans for delivery and treatment. It also circumvents the pre- and postnatal 'diagnostic odyssey' and allows accurate counselling about recurrence risk for future pregnancies to guide reproductive choices.

There are, however, practical, organisational and ethical challenges requiring consideration when implementing fetal ES as a national service.[7] For example, how can equity of access across the country be achieved? What information and support do patients need? How can we maintain informed choice when offering complicated testing that may additionally identify genetic diseases or predisposition to cancer in a parent or future child? What health professional training is needed? How can communication across specialties (genetics / fetal medicine / laboratory) be supported? What are the costs of fetal ES and how do these compare with standard tests? What are the limitations in prenatal ultrasound-based phenotyping? Will there be unintended consequences and how can we minimise potential harms? These challenges require careful evaluation and raise questions about service delivery, information provision and consent processes for families.

On October 2020 fetal ES will become part of the new national NHS Genomic Medicine Service test directory, available in all pregnancies complicated by fetal anomalies with a likely monogenic aetiology. To date, there is no published research on public sector implementation of fetal ES for prenatal diagnosis, indeed professional guidance emphasises the need for data on the implementation of fetal ES.[8] This research is necessary to identify challenges arising and ensure fetal ES is implemented in a manner that is efficient to the NHS, acceptable to parents and professionals, whilst maximising patient benefit.

A systematic literature review of prenatal genomic sequencing studies that included published studies and conference abstracts,[1] found diagnostic rates varied between 6% and 80%, with more recent studies showing yields between 20% and 32%.[6, 9-11] Differences in inclusion criteria and trio (parents and fetus) versus fetus only sequencing largely account for the range of diagnostic rates. Reports suggest diagnostic yields will be greater in fetuses with multiple anomalies[12] or in cases preselected following genetic review[7]. With fetal ES delivered from seven GLHs there is the potential for wide variation in referrals, uptake and diagnostic rates. It is crucial that we evaluate this service to determine how best to triage cases and provide guidelines to support an equitable and efficient national service. Moreover, as it is highly likely that differences will arise in how GLHs and clinicians include ES in clinical practice, with further variation reflecting the size of the regions served and socio-economic factors, a key component of our work will be a comparison between GLHs with an emphasis

on capturing changes, contextual moderators and learning over time, to identify optimal processes in delivering this innovative service.

As well as establishing rates of referral and diagnosis across England, we will also consider practical, ethical, social and economic issues. Practical issues such as turnaround times are critical in the prenatal setting as parents will use test results for decision making, including termination, pregnancy management and delivery planning. A recent review of ethical issues[7] showed that integrating fetal ES into clinical care will involve multiple considerations around how the tests are offered, what results are reported, identification of secondary findings and variants of uncertain significance (VUS), implications for other family members, management of genetic privacy and data protection, and the importance of ensuring informed consent.[7] Evaluation of these issues following clinical implementation is key to equitable and efficient service delivery.

The cost effectiveness of fetal ES has not been formally evaluated. In addition, very few empirical research studies have looked at the views and preferences of parents[13-15] or health professionals.[16, 17] These studies, mainly based around hypothetical scenarios, largely support offering prenatal sequencing but raised concerns over the potential for increased parental anxiety, management of parent expectations, cost, which results to report and when to reinterpret results, and highlighted the need for health professional education and new approaches to genetic counselling that avoid information overload and yet support informed choice during a distressing and time-pressured period.[15, 16] It will be important to consider how to counsel parents around the range of findings and possible uncertainty. Recent research with parents given uncertain findings on prenatal microarray revealed minimal impact on wellbeing, but dissatisfaction with genomic testing and a need for additional support.[18]

Another important focus for our research will be to look closely at the potential impact of implementing fetal ES on various community groups, including communities where interfamilial marriages are common. Recent research in the UK gathering the views of professionals and lay stakeholders has highlighted the need for consistent national policy relating to the increased genetic risk associated with customary consanguineous marriages and the need for further research in this area was noted.[19]

In the new Genomic Medicine Service, fetal ES will be offered across England through all seven GLHs - the first national public sector service to be offered worldwide. Current guidance on how fetal ES

should be delivered is minimal and this study is an opportunity to evaluate the fetal ES service at its inception and produce national guidance on implementation and care pathways that will influence how the service is delivered as it moves forward. In this study we will learn what practices work well (and why) to inform development of national guidance for an equitable, ethical and robust service that is acceptable to all stakeholders. We will also be well positioned to identify, early on within the process of implementation, any unintended consequences or potential harms/risks for parents, staff or organisations delivering fetal ES.

Aims and Objectives

Aim

To conduct a formative and summative mixed-methods evaluation of the new fetal ES service to deliver feedback that will ensure national delivery of an equitable, acceptable, ethical, robust and cost-effective care pathway that improves the quality of care for parents undergoing prenatal diagnosis in fetuses with anomalies likely to have a genetic aetiology.

Objectives

1. Determine the clinical care pathways for fetal ES in each of the 7 Genomic Laboratory Hubs
2. Establish whether fetal ES is understandable and acceptable to key stakeholders
3. Identify the education and information needs of parents and health professionals, and how they are best addressed
4. Establish the outcomes (diagnostic yield, referral rates, sources of referral, final diagnoses) of the fetal ES service, compare these between regions and identify any factors (individual or service-related) associated with variation in outcomes
5. Identify any new ethical issues arising from offering the fetal ES programme in the NHS and how health professionals can best be supported in addressing them
6. Determine the key features that constitute the optimal fetal ES pathway from a service delivery, patient and professional perspective
7. Generate new evidence of the cost of fetal ES versus standard tests for diagnosing fetal anomalies
8. Establish the cost and cost-effectiveness of implementing the optimal fetal ES pathway
9. Provide formative feedback to stakeholders for the developing fetal ES service

Methods

Study Design and Conceptual Framework

In this study we will evaluate a research innovation (fetal ES) as it shifts to clinical practice nationwide within a wider and newly configured service (the NHS Genomic Medicine Service). We will draw on a framework developed in two other studies of major system innovation which highlighted the key processes: the decision to change; developing and agreeing new service models; how changes are implemented; and implementation outcomes (Fig 1).[20, 21] In this study the evaluation of the outcomes of the fetal ES service (what works and at what cost) will be grounded in our understanding of the planning and implementation of the service (how and why). In addition, as this is the first time fetal ES will be implemented across a public health setting – and on a large scale - we will draw on Normalisation Process Theory (NPT)[22-24] which emphasises agency, cooperation and coordination in a social system as key elements in the successful embedding of a complex intervention (Fig 1).

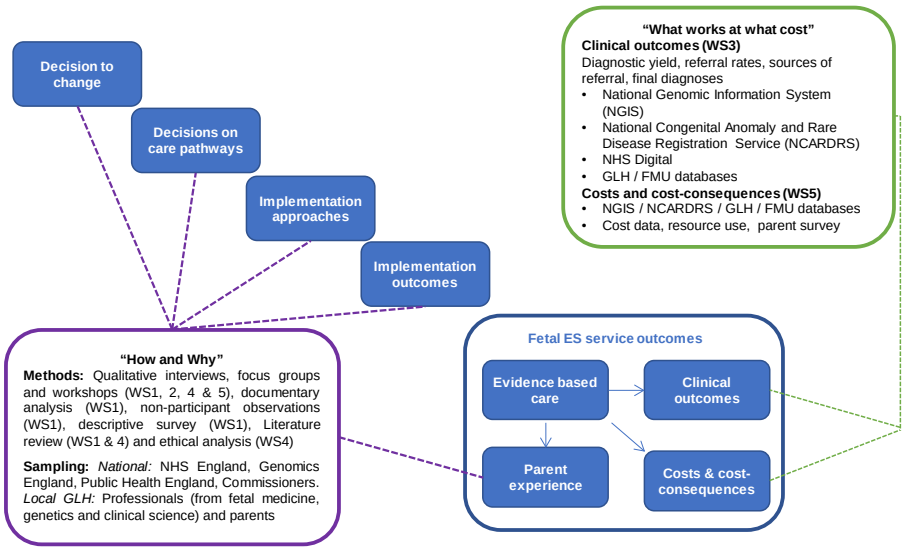

Fig 1: Conceptual framework underpinning our evaluation of the ES service. Adapted from Fulop et al[3,4]

Understanding how fetal ES fits within existing NHS care pathways, screening protocols and local health networks will be critical since we anticipate staff will have to coordinate new diagnostic activities around existing services and processes. We will therefore need to understand how adaptation and coordination are evolving in practice. For example, cooperation between the seven GLHs nationally and between staff and existing maternity services within regional health systems may be critical to the timely delivery of useful diagnostic information to parents to inform decision making. This requires consideration of the wider implementation context (local, organisational and health system) and the complex and dynamic nature of implementation.[25] The core construct of "innovation

features" encourages us to consider the evidence for the innovation and the potential for unintended consequences or harms which are critical in an evaluation of implementing this very new test.

Our mixed-methods programme of research will combine qualitative analyses of the service (WS1), stakeholder perspectives (WS1 and WS2) and analysis of ethical considerations (WS4) with quantitative analyses of clinical outcomes (WS3) and cost effectiveness (WS5). A nationwide evaluation that includes all seven GLHs will allow us to look at different organisational contexts and make comparisons of the service delivery and attitudes across GLHs. As our research will commence in the first year of the fetal ES service we have proposed a formative evaluation that will deliver lessons for the developing service within the timeframe of the study.

Study oversight

The study will have oversight from a Steering Committee and a PPI Advisory Group (PPIAG). The PPIAG will input into all aspects of the project, bringing the perspective of parents to our study to ensure that patient and public priorities and needs are central to the research.

Setting

The focus of our study is the national implementation of fetal ES, within the newly reconfigured NHS Genomic Medicine Service in England. Fetal ES will initially be performed through two of the seven GLHs (London North GLH and Wessex & West Midlands GLH) who will be referred parents from throughout the UK. Fetal ES will ultimately be delivered through all seven GLHs who will be referred parents from fetal medicine units (FMUs) and clinical geneticists in their defined geographical areas. As such, the setting for all WSs will be the seven GLHs and their linked clinical genetic services and FMUs. To compare service organisation, delivery and attitudes across the GLHs, case studies will be conducted in each GLH. Recruitment of health professionals and parents will be from each GLH thereby including multiple fetal medicine and maternity units across England to ensure representation of each GLH and maximal variation in the ethnic and social diversity seen in the populations attending the units in each GLH's geography.

The seven GLHs are;

- Wessex & West Midlands GLH led by Birmingham Women's & Children's NHS Foundation Trust
- East Midlands & East of England GLH led by Cambridge University Hospitals NHS Foundation Trust
- North West GLH led by Manchester University NHS Foundation Trust
- North Thames GLH led by Great Ormond Street Hospital for Children NHS Foundation Trust

- London South GLH led by Guy's and St Thomas' NHS Foundation Trust
- South West GLH led by North Bristol NHS Trust
- Yorkshire and North East GLH led by The Newcastle upon Tyne Hospitals NHS Foundation Trust

The key stakeholder groups involved in the study are;

- Parents who will be offered fetal ES in the new service.
- Parents with previous experiences of fetal anomalies
- Lay groups that support parents undergoing prenatal testing
- Health professionals offering, coordinating and delivering fetal ES
- NHS Commissioners

Throughout the study outputs will be fed back to the fetal ES service through quarterly reports both to the NHS Genomics Laboratory Hub Partnership Board, and other relevant bodies.

Workstream 1. Define the clinical care pathways across the GLHs and identify facilitators, barriers and unintended consequences of service delivery

The objective of this WS is to gain a detailed understanding of the fetal ES care pathways in the seven GLHs, examine the implementation processes that emerge in practice, and gather professional perspectives of any implementation issues. This will lead to the development of a model of the optimal care pathway.

WS1 will run for the duration of the study in order to capture any changes in process over time and allow assessments at different stages of implementation. Qualitative data about the service will be collected at multiple points; e.g. surveys with health professionals in Months 6-12 (Phase 2), qualitative interviews with health professionals in Months 24-33 (Phase 3) and 6 monthly phone calls to a key contact at each GLH to monitor change with a standardised question list. Crucial points when offering fetal ES that will require particular attention are: case selection (a key determinant of diagnostic yield), links between fetal medicine, clinical genetics and laboratories, laboratory pipelines, the interpretation and reporting of results and turn-around times for results.

Phase 1: Understanding the goals and challenges for the current service

In the first 6 months of the study we will use three approaches to gain an understanding of the anticipated goals and early challenges for offering fetal ES in the new Genomic Medicine Service.

1) To identify key challenges for service delivery we will conduct a mixed-methods systematic literature review on the use of fetal ES in both research and clinical settings worldwide. Research questions for this review will include; In what settings has fetal ES been offered? What evaluations of fetal ES services have occurred (if any)? What can we learn from other settings that is relevant to implementation in the NHS? The review will be conducted according to PRISMA-P guidelines[26] and included studies will be critically appraised using the Kmet tool.[27]

2) To explore the drivers of implementing fetal ES in England and to examine the overarching ambitions and potential challenges for the service we will conduct 8-10 interviews at a national level with key staff from NHS England, Public Health England and Genomics England. We will also undertake a documentary analysis and collect any available business case and policy documents relating to the implementation of fetal ES.

3) To gather the views of staff we will conduct two focus groups with 10-12 participants. Health professionals from fetal medicine, genetics and clinical science will be invited to participate. To identify potential regional differences, one focus group will be conducted in the North of England and one in the South of England. The focus groups will explore health professionals' ambitions for the service, current challenges in delivery and plans for changing and developing the service.

Phase 2: Establish emergent care pathways and produce an overview description of services

In months 6-18 of the study, we will use three approaches to produce a taxonomy of the different care pathways and service delivery descriptions emerging in practice for all seven GLHs. Some examples of the information we will gather include phenotypic and other criteria for referral for fetal ES, proportion of FMUs making referrals, evidence of interactions between FMU, genetics and laboratory teams, turn-around times for results and reporting criteria. This work will document early indications of consensus and variation in service delivery, organisation and design and will form the foundation for understanding why the different networks vary in service provision (if they do), and how processes then change over time.

1) Survey with professionals across the seven GLHs: We will survey clinical and laboratory staff working in the seven GLHs and the regional genetics services and fetal medicine units that refer to the GLHs across England. The development of survey content will be informed by the

data collected in Phase 1. The survey will determine how eligibility criteria are applied, consider information available to clinicians (such as high-quality ultrasound scans for phenotyping), explore training and education needs and overall views. We will also examine referral pathways and patient flow from general maternity units to fetal medicine units to genetics services. The research team will identify relevant staff through contacts in each GLH and invite them by email to take part in the survey which will be conducted in person or by phone with 15 professionals from each GLH. We will purposively sample health professionals from a range of backgrounds including clinical geneticists, genetic counsellors, fetal medicine consultants, midwives and clinical scientists. Professionals with clinical responsibilities and those undertaking laboratory work will be represented, as differences of opinion between these groups has been reported in studies of ethical issues in reproductive genetics.[28]

2) Observations of multidisciplinary team meetings (MDTs): Observation of MDTs will allow us to explore results interpretation, criteria used and reporting processes at each GLH. We will conduct 2-5 observations of the MDTs held for interpreting and reporting fetal ES sequencing results at each GLH. Observations will be standardised using an observer rating scale specifically designed for assessing MDT meetings for cancer treatment[29] that will be adapted for fetal ES. Fieldwork notes will also be kept by the researchers.

3) Monitoring of service delivery over time: Every 6 months we will speak with a key contact at each GLH to ask a standardised list of questions that will allow us to monitor service delivery and changes to care pathways.

Phase 3: In depth case studies

We will produce an in-depth case studies of fetal ES services for all seven GLHs. We will refer to MRC guidance[30] on the conduct of process evaluations for studying the implementation of complex health interventions and Normalisation Process Theory (NPT)[22, 23] to explain how the new fetal ES services have developed over time, and across different contexts. We will explore implementation processes, mechanisms of impact and local factors.[30] As the fetal ES service is entirely new to the NHS there is no baseline, so case studies will address how the service is being delivered against service objectives, aspirations and adaptations, and the plans identified by professionals in Phase 1 and 2.

We will use a case study approach[31-33] to data collection. Qualitative data will be collected from semi-structured interviews with ~35 staff from a range of backgrounds, key documents, non-participant

observations of relevant team meetings in each GLH and two focus groups with health professionals (one North, one South). To gain insights into the views of some religious and ethnic minority groups, hospital chaplains will be included in the staff interviews as faith-based authorities. Interview and focus group questions will be developed based on literature review and the findings of phase 1 and 2 to probe service delivery issues (e.g. unexpected consequences or difficulties, and how overcome), local variations and professional perceptions of running this service.

For the documentary analysis we expect to collect;

- policy documents relating to fetal ES
- patient information sheets and consent form templates
- training records / training content
- local unit meeting minutes where fetal ES is a focus
- service specifications
- standard operating procedures (SOPs)

Phase 4: Development of the optimal fetal ES care pathway

Data from all phases will be collated with available data from other study arms to develop an early model of the optimal care pathway that will be used for the economic analysis (WS5).

Recruitment of professionals

To recruit professionals to semi-structured interviews, focus groups and the survey professionals from relevant backgrounds will be identified by the research team with the help of the local PI at each GLH and will be invited to take part in the study. We will purposively sample health professionals from a range of backgrounds including clinical geneticists, counsellors, fetal medicine consultants, midwives, clinical scientists and hospital chaplains. An invitation email along with a participant information sheet describing the purpose of the study will be emailed to potential participants. For the non-participant observations we will notify the attendees in advance of the meeting of our intention to observe the meeting and obtain written consent at the time of the meeting.

Data analysis

Interviews and focus groups will be digitally recorded and professionally transcribed verbatim. All qualitative data (interviews, focus groups, observations, fieldwork notes, survey responses (open-ended questions and comments) and documents) will be anonymised and then analysed using the principles of thematic analysis.[34] Data analysis will combine inductive and deductive approaches[35] as

themes will be drawn from the literature and emerge from the empirical data. Data will be coded into meaningful units of text and then grouped into broader categories and themes that will be progressively reviewed and redefined. Qualitative data will be managed using NVivo version 12 (QSR International, Pty Ltd). To ensure the validity and rigour of the analysis two experienced qualitative researchers will conduct the analysis according to recommended protocols.[36] The MDT observations and fieldwork notes will be analysed thematically, with attention to impacts of MDTs on clinical pathways. Frequencies will be used to summarise findings from the quantitative survey data.

WS1 Formative Outputs: 1) Descriptions of care pathways for fetal ES at each GLH 2) In-depth case studies describing service provision at each GLH. 3) Evidence of any changes in the service over time and any differences between services offered in each GLH. Any significant differences that appear to impact outcomes will be fed back to the service within our quarterly progress reports in order to influence change in a timely manner. 4) An 'ideal type' or 'optimal' care pathway for the economic analysis (WS5).

WS1 Summative Output: Recommendations for service delivery and health professional education.

Workstream 2: Parental views and experiences of fetal ES

To gather parental views and experiences of fetal ES, data will be collected using qualitative interviews with at least 35 parents offered fetal ES (recruited through FMUs) and 20 parents with previous experience of fetal anomalies who have not had fetal ES (recruited through Antenatal Results and Choices (ARC)). Participants will be purposefully sampled to ensure there is maximum variation in terms of clinical experiences (e.g. type of tests undertaken; declined to have fetal ES; types of results (diagnosis, VUS, or no result); chose termination; chose to continue the pregnancy) and socio-demographic factors such as ethnicity and socio-economic background.

Interviews will be conducted with written informed consent. Using a semi-structured topic guide developed with consideration of the existing literature, the clinical expertise of our research team and PPIAG input, we will explore parents' views and consider, information and support needs, perceived risks and benefits of incorporating ES into clinical care and preferences for which results should be returned (including views on additional findings and uncertain results). For parents offered ES we will also ask about their experiences, including what genetic counselling they received, their decision making, motivations for having or declining testing and costs incurred.

Recruitment of parents offered fetal ES

Invitations to parents to take part in an interview will only be given after the parents have been offered ES and have made their decision to accept or decline testing and as such will not impact on their decision making about this test. Approaching parents who have chosen to have fetal ES for interviews will be facilitated by the patient choice model for testing within the Genomic Medicine Service, which includes, at point of testing, the choice for parents to allow their data to be used for research and to be contacted for research. The clinical team at fetal medicine units that have offered fetal WES will identify parents that accepted or declined fetal WES. A letter explaining the interview study and the Participant Information Sheet will be sent to potential participants. The letter will include an invitation to participate in an interview and they will be asked to contact the research team via telephone or email if they are interested in participating. As this will be a stressful and emotional time for parents, the researcher conducting the interviews will be guided by the clinical team as to the best time to send the letter to the parents.

Recruitment of parents with previous experience of fetal anomalies

We will recruit parent with previous experience of fetal anomalies (with and without experience of fetal ES) through Antenatal Results and Choices (ARC). We will place an advertisement for the interview study on the ARC website, Facebook page and newsletter explaining the study and asking parents to contact the research team if interested in participating in an interview. They will then be sent a participant information sheet.

Data collection and analysis

Interviews will be digitally recorded, professionally transcribed, anonymised and analysed using the principles of thematic analysis[34] as described for workstream 1. Recruitment for qualitative interviews will continue until saturation is reached, our suggestion of approximately 50 interviews is based on our previous research focused on new approaches to prenatal testing.[37, 38]

WS2 Formative Output: In-depth understanding of parental views to feed into other WSs.

WS2 Summative Output: Recommendations for parent information and counselling needs.

Workstream 3: Factors associated with variation in outcomes across the GLHs

In this research arm we will establish the outcomes (diagnostic yield, referral rates, sources of referral, final diagnoses) of the fetal ES service. These outcomes will then be compared between regions to

identify any factors (individual or service-related) associated with variation in outcomes. A new National Genetics Information System (NGIS) will record all genomic testing done in the Genomic Medicine Service and parents will be asked at the point of testing to allow their data to be used for research purposes. The NGIS will include pregnancy-level information on sociodemographics (age, socioeconomic status (Index of Multiple Deprivation, IMD) based on woman's area of residence, ethnicity), gestation at referral for testing and results of ES. Cases will be identified from GLHs and extracted for one year.

Data collection and analysis

Pregnancy outcome data will be sourced from FMUs on all women referred for fetal ES (Data collection will be done via the GLH's and is considered by the HRA to be service evaluation). Pregnancy outcomes will be validated though collaboration with the National Congenital Anomaly and Rare Disease Registration Service. Data will be obtained at the pregnancy level on all women giving birth in England over the same time-period from NHS Digital (women's age, IMD score for area of residence and ethnicity), and linked within NHS Digital on the basis of women's NHS number to the NGIS/FMU data before analysis of an anonymised dataset. Multi-level models will then be built examining the influence on outcomes of individual and GLH level factors (based on network pathways identified in WS1).

Descriptive analyses: The following information will be described for each GLH:

- Number of women giving birth in the GLH area annually (mapped on the basis of births in referring units and their associated home births)
- Characteristics of women giving birth in each GLH area: Age (mean, SD), IMD score (% in each quintile), ethnicity (grouped according to UK census classification)
- Number of women referred for fetal ES annually
- Characteristics of women referred for fetal ES in each GLH area: Age (mean, SD), IMD score (% in each quintile), ethnicity (grouped according to UK census classification), source of referral, final diagnosis made, gestation at diagnosis (median, IQR) and pregnancy outcome (termination, pregnancy loss, live birth, stillbirth).

Other characteristics of each GLH will have been described as part of WS1 (the characteristics to be included will be defined in WS1 but are likely to include categorical factors such as case selection, links between fetal medicine, clinical genetics and laboratories, laboratory pipelines, turn-around times and the interpretation and reporting of results)

Overall referral rates with 95% confidence intervals in each GLH will be calculated, and referral rates within population subgroups (IMD quintiles, ethnic groups) calculated to assess equity across the system and ensure the needs of ethnic minority and hard to reach populations are being appropriately considered. Factors associated with variation in referral rates (population characteristics, GLH factors) will be examined using regression analysis. Similarly, in each GLH diagnostic yield will be calculated (proportion of women with a clear final diagnosis on the basis of fetal ES) as well as outcomes of fetal ES (proportion of women undergoing ES opting for termination, live birth rate, stillbirth rate and proportion of births with a confirmed anomaly) and factors associated with variation examined.

Case note reviews

Anonymised case note reviews will be conducted in 7-10 FMUs to investigate reasons guiding parent decisions to decline ES. We will consider clinical indications for testing, demographics, pregnancy outcomes and post-natal testing. Anonymised case note reviews will also be used to consider any variations in referral among ethnic or socioeconomic groups. Case note reviews will be conducted in fetal medicine units where variation has been identified and in areas where we know cultural diversity and consanguinity is more common. Case note reviews will be conducted over a defined period of up to 3 months to see if we can establish any underlying reasons for variation, such as lower offer rates or lower uptake rates among different ethnic groups or among women in different IMD quintiles. We will develop recommendations for service improvements to ensure equity.

WS3 Formative Output: Detailed information on factors influencing service outcomes to inform optimised care pathway development and the economic evaluation.

Workstream 4. Ethical analysis

We will identify, characterise, and analyse practical ethical issues arising in the delivery of fetal ES in order to inform and promote the achievement of high ethical standards in the Genomic Medicine Service. The successful delivery of fetal ES will require the identification, analysis and management of a number of ethical problems. These are likely to include, but will not be limited to, the following:

- Enabling adequate levels of informed consent for this complex testing
- Equity of access
- Decisions about reporting in the context of increased uncertainty and complex probabilities
- Questions relating to the sharing of data: for clinical and/or research purposes

- Clarification of the nature and scope of the duties of care of health professionals and laboratory staff when offering this complex testing to pregnant women

We will conduct a systematic scoping review of the relevant literature, professional guidelines, and reports of advisory bodies on the prenatal uses of genomics and genetics. This will provide an initial mapping of the likely ethical issues and themes for further investigation. Themes will be incorporated into interviews and focus groups with parents and professionals (see above) and results will be combined to inform a comprehensive analysis of core ethical concepts and considerations to aid development of a draft ethics framework, which will be revisited and revised in light of further findings from other arms of the study and two ethics workshops.

Workshop 1 (study year 1): We will bring together clinical and laboratory staff from across the seven GLHs and associated clinical services, the PPIAG and patient groups, to gather evidence about ethical issues arising in practice, and to explore perspectives on the nature and scope of professional responsibilities in the provision of fetal ES. The workshop will be an opportunity to discuss ethical issues, share good practice, and identify practical ethical problems. We will map key issues, explore themes in-depth and seek views on requirements for an effective ethics framework. Early and developing framework drafts will be tested with this group and other relevant experts over subsequent months.

Workshop 2 (Study year 3): We will bring together a wider range of key stakeholders, including: patient groups, parents offered fetal ES, clinical geneticists, genetic counsellors, fetal medicine specialists, midwives and laboratory staff and representatives of relevant national societies, e.g. British Maternal and Fetal Medicine Society, British Society of Genomic Medicine, the Genomic Medicine Service oversight board. We will encourage adoption and wider use of the ethics framework, promote wider awareness and discussion of the ethical aspects of prenatal genomics and consider implications for the training of health professionals and the development of models of timely ethics support and advice.

WS4 Summative Output: A framework setting out ethical requirements for an optimal fetal ES service.

Workstream 5. Economic analysis

Phase 1. Cost of fetal ES versus standard testing

We will undertake a detailed micro-costing exercise to evaluate the unit costs of fetal ES and other tests at each GLH. This will provide evidence on the likely affordability of fetal ES for use in routine care. Micro-costing is a highly detailed costing approach that identifies all the underlying resources required for an intervention/activity, such as equipment, consumables, and staff time, and then calculates costs for these resources. We will follow a previously used approach to costing genetic tests.[39] The standard operating procedures for each test will be used to develop costing questionnaires to collect the resource use information. The questionnaires will cover each stage in the experimental protocol from sample preparation to data interpretation and reporting. Resource use information on staff time, consumables, and equipment will be derived from the questionnaires. The analysis will account for the expected cost of any errors or failures during the testing processes. For capital equipment items, the cost will be spread over the item's predicted lifetime and depreciated using equivalent annual costing. The cost of staff and consumables will be taken from market prices. The cost per test will be based on the measured annual throughput of the sequencing platforms. For standard testing we will adopt a two-stage approach. As these tests are currently established in routine care we will ascertain if each GLH has carried out their own micro-costing analysis for reimbursement purposes – in previous similar studies we have found this to be the case. If so, we will use these costs for our analysis, ensuring that the cost components included are commensurate across GLHs. If this is not the case, then we will undertake our own micro-costing exercise at each GLH where costs of standard tests are not available, utilising the same approach as described above for ES. Due to the sensitivity of these data the results for each individual GLH will remain anonymous and we will present mean and (anonymised) ranges only.

Phase 2. Costs and consequences of the optimal fetal ES pathway

We will undertake cost and cost consequences analyses of the different delivery pathways at each of the 7 GLHs, plus the identified optimal fetal ES pathway. In previous research we have argued that quality-adjusted life years are not appropriate to use in economic evaluations of prenatal testing for fetal anomalies, and therefore we will not use them here (nor undertake a cost-utility analysis). Costs will be estimated from the perspectives of both the NHS and families, with the time horizon being the duration of pregnancy. Using an approach we have used in similar studies,[40, 41] the analysis will proceed in the following stages:

1. We will delineate the pathways for prenatal diagnosis of fetal anomalies using fetal ES, from referral for testing until birth outcome. This will be done for each of the 7 GLHs and the optimal pathway, and will be based on data collected during WS1.

2. Using the linked NGIS/FMU/National Congenital Anomaly and Rare Disease Registration Service data collected during WS3 we will plot the movement of pregnant women through each of the pathways. We will extract information on the numbers of women undergoing different tests, the numbers and type of fetal anomalies identified, the number of follow-up contacts related to testing, and pregnancy outcomes.
3. We will identify the unit costs associated with the main cost components of the identified pathways. These will be obtained from the micro-costing, supplemented with other unit costs from the GLHs, and published and other routinely available sources.
4. We will calculate the NHS costs associated with each pathway, by applying the unit costs associated with each item in the pathway from stage 3 with the numbers of women incurring that cost based on the data at stage 2.
5. We will calculate the costs to parents and families from the different pathways using parent questionnaires developed following parent interviews in WS2.
6. We will undertake a cost consequences analysis comparing the NHS and family costs of each pathway against the consequences, as delineated in WS3 (e.g., diagnostic yield, birth outcome).
7. We will use our analysis to assess the expected budget impact to the NHS of introducing fetal ES, based on the mean costs per woman tested and projections of the expected numbers of women tested by fetal ES nationally.
8. We will identify the main sources of uncertainty in our analyses and undertake sensitivity to explore the impacts of this uncertainty.

WS5 Summative Outputs: 1) A report on the cost of fetal ES giving evidence on the likely affordability of its use in routine care. 2) A budget impact and cost consequences model of the optimal fetal ES pathway that can be used for policy decisions.

Workstream 6. Integration of study findings, policy impact and dissemination

Integration of study findings

We will triangulate data collected in the qualitative analyses of the service (WS1) and stakeholder perspectives (WS1 and WS2), the ethical analysis (WS4), the quantitative analyses of clinical outcomes (WS3) and the economics analysis (WS5) to identify the main features of the fetal ES service nationally and points of local variation. Through this process we will define current service provision, identify the

facilitators and barriers to optimal service delivery and highlight key lessons to inform future models of service provision and will produce recommendations for best practice.

The findings from all WSs will inform two workshops (one South, one North) with key stakeholders, designed in collaboration with experts from across the WSs to present study findings with the aim of exploring with stakeholders what 'best practice' looks like across the seven GLHs and in fetal ES services more generally.

Policy Impact and Dissemination

We will focus on engagement and communication with patients, the public, service providers, managers and commissioners and will draw on work done in all WSs. Dissemination will be both formative, as we will feed back findings as the study proceeds, and summative. To facilitate formative feedback to the service, we will produce a quarterly progress report timed to coincide with the meetings of the NHS Genomics Laboratory Hub Partnership Board which includes the operational and medical leads from the seven GLHs as well as representatives from NHSE and Genomics England. The progress report will also be disseminated through other professional bodies, such as the Joint Committee on Genomics in Medicine and through lay groups such as ARC and Genetic Alliance UK. We will also seek to present our findings to these groups at appropriate meetings as the study progresses. In addition to peer reviewed publications and conference and meeting presentations, a final report on the integration of study data described above will:

- Review and describe current service provision
- Identify the facilitators and barriers to optimal service delivery
- Identify unintended consequences resulting from implementation of this new diagnostic test
- Capture professional perspectives on key lessons arising from implementation
- Consider future models of service provision
- Provide recommendations for best practice
- Provide recommendations for education and information for parents and health professionals

The PPIAG will advise how best to disseminate the research to parents and families and will write user-friendly summaries for these groups.

WS6 Formative Output: Regular progress updates communicated though reports, briefings and policy documents targeting lay organisations, healthcare providers, policy makers and commissioners.

WS6 Summative Output: A final report with recommendations and guidance for best practice.

Outputs

Our evaluation of the fetal ES service will deliver lessons for the developing service that will be of value to those who commission, organise and manage fetal ES services and will reduce unnecessary variations in care. The research has significant potential to influence policy, by informing the implementation of the service as it is established. Informing the development of a fetal ES service that delivers equity of access and high standards of care across England will also bring benefits for parents and families.

This research will generate the following outcomes;

- Understanding of how fetal ES is delivered across England in the new Genomic Medicine Service
- Recommendations for an optimised, cost-effective care pathway in routine clinical practice
- Recommendations for meeting the information, counselling and support needs of parents
- Recommendations for education specific to fetal medicine, maternity and genetic services
- An ethics framework to inform good practice and act as a decision aid for clinicians, laboratory staff, and service providers
- Guidance for commissioners and policy makers based on lessons learnt on what practices work well (and why) in the fetal ES service
- Signposts for future research and evaluation needs
- Implications for the wider Genomic Medicine Service

Dissemination

Members of the research team will visit each GLH at the start of the study to speak about the study and raise awareness amongst professionals. We will offer a discussion forum in each GLH and invite clinical geneticists, counsellors, clinical scientists, midwives, fetal medicine specialists and obstetricians from across the GLH catchment area. Dissemination will occur throughout the study. To provide formative feedback for the development of the service we will produce quarterly progress reports that will be shared at a national level as part of the NHS Genomics Laboratory Hub Partnership Board which includes the operational and medical leads from the seven GLHs as well as representatives from NHSE and Genomics England. We will build a contact list of stakeholders and will communicate the quarterly progress reports widely by email. We will also update professional bodies such as the Joint Committee on Genomics in Medicine and will work with Public Health England, responsible for delivering the fetal anomaly screening programme, to give regular updates at their national midwife training days. Dissemination will also come through peer reviewed publications,

presentations at national and international conferences, health professional workshops, social media and meetings primarily aimed at parents and families affected by fetal anomalies. Through ARC, dissemination will reach the relevant patient population to raise awareness of fetal ES. Key findings will be shared through ARC's social media channels and newsletter and presentation at ARC's conference and annual Information and Support Day, to which parents and families are invited. We will also disseminate findings through other relevant patient groups such as the National Childbirth Trust (NCT) and Genetic Alliance UK, and for the harder to reach groups through Breaking Down Barriers. The PPIAG will help to write plain language summaries for parents and parent support groups.

Impact

Evaluating the new fetal ES Service as it is rolled out across the country will directly benefit the NHS and patients by identifying best practices, minimising potential harms, and ensuring fetal ES is implemented in a responsible and equitable manner. The overarching impact of this research will be a better fetal ES service that delivers equity of access and high standards of care across England. The associated improvement in prenatal diagnostic yield will deliver clinical benefits for parents through better information regarding their baby's health, facilitating informed decision making and improvements in pregnancy and postnatal management.

Optimised clinical use of fetal ES will allow more parents to receive an accurate genetic diagnosis in pregnancy, providing valuable information about the cause and prognosis of their baby's problems. This information may benefit them by guiding management of the pregnancy, delivery and treatment, resulting in improved outcomes for the child and family. A confirmed diagnosis may also provide psychological benefit by allowing parents to terminate a pregnancy with certainty or to prepare for the birth of an unwell child. Conversely, where the diagnosis proves less severe than predicted this can provide reassurance and allow safe continuation of pregnancy.

Findings will benefit healthcare professionals in fetal medicine and genetics by understanding their views and training needs and making recommendations for educational materials that will equip clinicians to confidently use fetal ES in a manner that maximises benefit to their patients. Health care services in other countries may also benefit from recommendations for an optimised clinical care pathway for fetal ES and detailed information on clinical utility. This information and the identification of any challenges in the system may be of use to others as they implement and refine their own fetal ES pathways.

Research timetable

Tasks	Months
Project set-up (ethical approval / recruitment of steering and PPI advisory committees / engagement with GLHs)	-5 to 3
Determine clinical care pathways across the GLHs (WS1)	1 to 36
Phase 1: Goals and challenges for the current service	1 to 8
Phase 2: Establish emergent care pathways and services	4 to 18
Phase 3: In depth case studies	24 to 33
Phase 4: Develop optimal care pathway	18 to 36
Parental experiences of fetal ES (WS2)	3 to 24
Factors associated with variation in outcomes across the GLHs (WS3)	6 to 30
Ethical analysis (WS4)	1 to 30
Economic analysis (WS5)	12 to 36
Integration of WS findings, policy impact and dissemination (WS6)	30 to 36
Progress reports with formative feedback for policy makers	6, 12, 18, 24, 30
Final report	33 to 36

Project management

Research Team

A project manager will coordinate all project activities and oversee engagement and data collection at each GLH. The full research team will meet bi-monthly (teleconference / videoconference plus face-to-face meetings) to monitor overall progress, data collection, analysis, dissemination and stakeholder engagement. These meetings will be important to facilitate interactions across all WSs so that interdependencies and linkages between each WS can be developed. Smaller teams working together on individual WSs will meet more frequently.

Steering Committee

The study steering committee will have an independent chair and draw together representatives of relevant professional bodies, academics with expertise in qualitative and quantitative methods and patient and public representatives. The aim of the study steering committee will be to provide support and oversight. They will meet face-to-face annually (with teleconference and videoconference options), with interim email updates and additional teleconference discussions where necessary.

PPI Advisory Group

A PPIAG, led by JF, will include 5-6 members, including a parents with direct experience of the prenatal diagnosis of rare diseases and members that can represent parents more broadly. EL-B will bring the views of ethnic minority groups. The PPIAG will meet twice a year during the project and will be consulted by email for input into specific documents or processes. The PPIAG will help with study design (including sensitive approaches to parents), development of research materials (e.g. survey, interview / focus group topic guides, participant information), result interpretation and dissemination of findings. Appropriate training and support will be provided for all PPIAG members via the PPI/Engagement Officer at CLAHRC North Thames.

Critical distance

It is important to acknowledge that our research team includes several clinicians and laboratory scientists with a professional role in the Genomic Medicine Service. LSC is the acting clinical lead of the North London GLH. She has driven the research on rapid fetal ES that has led to this test being included in the Genomic Medicine Service's test directory. Her role as co-PI is divested from her expertise in fetal ES and existing networks with fetal medicine and genetics. Similarly, SE is the Scientific Director of the South West GLH and DM the rare disease lead at Wessex and West Midlands GLH. Their expertise will be crucial in the set-up and running of the study. MH (Co-PI), NJF, SM and the other researchers leading data collection and analysis are professionally independent of the Genomic Medicine Service. NJF and SM have extensive experience in the evaluation and appraisal of healthcare services and they will be responsible for ensuring that a "critical distance" is maintained throughout our evaluation. Critical distance will be further strengthened by the oversight of a study steering committee and a PPIAG.

Patient and public involvement

Patient and public involvement is crucial to our research and will be embedded in all stages of the study. We have two patient advocates in our research team. JF is a patient advocate and Director of the support charity Antenatal Results and Choices (ARC), the only national charity helping parents and healthcare professionals through antenatal screening and diagnosis and its consequences. KL-B leads the Breaking Down Barriers project. She will advise the research team on how best to reach out to and include minority ethnic groups. The study steering committee will include parents and representatives from relevant patient support groups. Jane Fisher will lead the Patient and Public Involvement Advisory Group (PPIAG). The PPIAG will bring the parental perspective to the study ensuring that PPI priorities and needs remain the focal point. The PPIAG will input into all aspects of the project including: development of study design, participant information sheets', interview topic guides and

survey questions, how to approach parents, analysis and interpretation of findings and preparation of publications and other dissemination materials. They will also be asked to contribute to the consultations to identify practical ethical issues in delivering a fetal ES service (WS4). The PPIAG will meet twice a year and be sent emails at regular intervals to update them on study progress and to request the review of study design and documents.

References

1. Best S, Wou K, Vora N, Van der Veyver IB, Wapner R, Chitty LS. Promises, pitfalls and practicalities of prenatal whole exome sequencing. *Prenatal Diagnosis*. 2018;**38**:10-9.

2. Chandler N, Best S, Hayward J, Faravelli F, Mansour S, Kivuva E, Tapon D, Male A, Chitty LS. Rapid prenatal diagnosis using exome sequencing: A cohort study to assess feasibility and potential impact on prenatal counselling and pregnancy management. *Genetics in Medicine*. 2018;**20**:430-1437.

3. Calzolari E, Barisic I, Loane M, Morris J, Wellesley D, Dolk H, Addor MC, Arriola L, Bianchi F, Neville AJ, Budd JL, Klungsoyr K, Khoshnood B, McDonnell B, Nelen V, Queisser-Luft A, Rankin J, Rissmann A, Rounding C, Tucker D, Verellen-Dumoulin C, de Walle H, Garne E. Epidemiology of multiple congenital anomalies in Europe: a EUROCAT population-based registry study. *Birth Defects Research Part A, Clinical and Molecular Teratology*. 2014;**100**:270-6.

4. Mathews TJ, MacDorman F, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. National Vital Statistics Reports [Internet]. 2015 08/03/2017; 64(9):[1-30 pp.]. Available from: https://www.cdc.gov/ncbddd/birthdefects/data.html.

5. Boyd PA, Tonks AM, Rankin J, Rounding C, Wellesley D, Draper ES. Monitoring the prenatal detection of structural fetal congenital anomalies in England and Wales: register-based study. *Journal of Medical Screening*. 2011;**18**:2-7.

6. Normand EA, Braxton A, Nassef S, Ward PA, Vetrini F, He W, Patel V, Qu C, Westerfield LE, Stover S, Dharmadhikari AV, Muzny DM, Gibbs RA, Dai H, Meng L, Wang X, Xiao R, Liu P, Bi W, Xia F, Walkiewicz M, Van den Veyver IB, Eng CM, Yang Y. Clinical exome sequencing for fetuses with ultrasound abnormalities and a suspected Mendelian disorder. *Genome Medicine*. 2018;**10**:74.

7. Horn R, Parker M. Opening Pandora's box?: ethical issues in prenatal whole genome and exome sequencing. *Prenatal Diagnosis*. 2018;**38**:20-5.

8. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. *Prenatal Diagnosis*. 2018;**38**:6-9.

9. Yates CL, Monaghan KG, Copenheaver D, Retterer K, Scuffins J, Kucera CR, Friedman B, Richard G, Juusola J. Whole-exome sequencing on deceased fetuses with ultrasound anomalies: expanding our knowledge of genetic disease during fetal development. *Genetics in Medicine*. 2017;**19**:1171-8.

10. Fu F, Li R, Li Y, Nie ZQ, Lei T, Wang D, Yang X, Han J, Pan M, Zhen L, Ou Y, Li J, Li FT, Jing X, Li D, Liao C. Whole exome sequencing as a diagnostic adjunct to clinical testing in fetuses with structural abnormalities. *Ultrasound in Obstetrics & Gynecology*. 2018;**51**:493-502.

11. Daum H, Meiner V, Elpeleg O, Harel T. Fetal exome sequencing: yield and limitations in a single tertiary center. *Ultrasound in Obstetrics & Gynecology*. 2018.

12. Petrovski S, Aggarwal V, Giordano JL, Stosic M, Wou K, Bier L, Spiegel E, Brennan K, Stong N, Jobanputra V, Ren Z, Zhu X, Mebane C, Nahum O, Wang Q, Kamalakaran S, Malone C, Anyane-Yeboa K, Miller R, Levy B, Goldstein DB, Wapner RJ. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. *Lancet*. 2019;pii: S0140-6736(18)32042-7.

13. Kalynchuk EJ, Althouse A, Parker LS, Saller DN, Jr., Rajkovic A. Prenatal whole-exome sequencing: parental attitudes. *Prenatal Diagnosis*. 2015;**35**:1030-6.

14. Quinlan-Jones E, Hillman SC, Kilby MD, Greenfield SM. Parental experiences of prenatal whole exome sequencing (WES) in cases of ultrasound diagnosed fetal structural anomaly. *Prenatal Diagnosis*. 2017;**37**:1225-31.

15. Vora NL, Powell B, Brandt A, Strande N, Hardisty E, Gilmore K, Foreman AKM, Wilhelmsen K, Bizon C, Reilly J, Owen P, Powell CM, Skinner D, Rini C, Lyerly AD, Boggess KA, Weck K, Berg JS, Evans JP. Prenatal exome sequencing in anomalous fetuses: new opportunities and challenges. *Genetics in Medicine*. 2017;**19**:1207-16.

16. Bayefsky MJ, White A, Wakim P, Hull SC, Wasserman D, Chen S, Berkman BE. Views of American OB/GYNs on the ethics of prenatal whole-genome sequencing. *Prenatal Diagnosis*. 2016;**36**:1250-6.

17. Quinlan-Jones E, Kilby MD, Greenfield S, Parker M, McMullan D, Hurles ME, Hillman SC. Prenatal whole exome sequencing: the views of clinicians, scientists, genetic counsellors and patient representatives. *Prenatal Diagnosis*. 2016;**36**:935-41.

18. Desai P, Haber H, Bulafka J, Russell A, Clifton R, Zachary J, Lee S, Feng T, Wapner R, Monk C, Chung WK. Impacts of variants of uncertain significance on parental perceptions of children after prenatal chromosome microarray testing. *Prenatal Diagnosis*. 2018;**38**:740-747.

19. Salway S, Yazici E, Khan N, Ali P, Elmslie F, Thompson J, Qureshi N. How should health policy and practice respond to the increased genetic risk associated with close relative marriage? Results of a UK Delphi consensus building exercise. *BMJ Open*. 2019;**9**:e028928.

20. Fulop N, Boaden R, Hunter R, McKevitt C, Morris S, Pursani N, Ramsay AI, Rudd AG, Tyrrell PJ, C DAW. Innovations in major system reconfiguration in England: a study of the effectiveness, acceptability and processes of implementation of two models of stroke care. *Implementation Science*. 2013;**8**:5.

21. Fulop NJ, Ramsay AI, Vindrola-Padros C, Aitchison M, Boaden RJ, Brinton V, Clarke CS, Hines J, Hunter RM, Levermore C, Maddineni SB, Melnychuk M, Moore CM, Mughal MM, Perry C, Pritchard-Jones K, Shackley DC, Vickers J, Morris S. Reorganising specialist cancer surgery for the twenty-first century: a mixed methods evaluation (RESPECT-21). *Implementation Science.* 2016;**11**:155.

22. May C. Towards a general theory of implementation. *Implementation Science*. 2013;**8**:18.

23. May C, Finch T, Mair F, Ballini L, Dowrick C, Eccles M, Gask L, MacFarlane A, Murray E, Rapley T, Rogers A, Treweek S, Wallace P, Anderson G, Burns J, Heaven B. Understanding the implementation of complex interventions in health care: the normalization process model. *BMC Health Services Research*. 2007;**7**:148.

24. McEvoy R, Ballini L, Maltoni S, O'Donnell CA, Mair FS, MacFarlane A. A qualitative systematic review of studies using the normalization process theory to research implementation processes. *Implementation Science*. 2014;**9**:2.

25. Nilsen P. Making sense of implementation theories, models and frameworks. *Implementation Science*. 2015;**10**:53.

26. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;**350**:g7647.

27. Kmet LMLR, Cook LS. Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields Alberta Heritage Foundation for Medical Research. 2004.

28. Parker M. Ethical Problems and Genetics Practice (Cambridge Bioethics and Law). Cambridge: Cambridge University Press. 2012.

29. Hahlweg P, Didi S, Kriston L, Harter M, Nestoriuc Y, Scholl I. Process quality of decision-making in multidisciplinary cancer team meetings: a structured observational study. *BMC Cancer*. 2017;**17**:772.

30. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ (Clinical research ed)*. 2015;**350**:h1258.

31. Eisenhardt KM. Building Theories from Case Study Research. *The Academy of Management Review*. 1989;**14**:532-50.

32. Yin RK. Case Study Research: design and methods (3rd ed.). London: SAGE2003.

33. Yin RK. Validity and generalization in future case study evaluations. *Evaluation*. 2013;**19**:321-32.

34. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology*. 2006;**3**:77-101.

35. Bradley EH, Curry LA, Devers KJ. Qualitative data analysis for health services research: developing taxonomy, themes, and theory. *Health Services Research*. 2007;**42**:1758-72.

36. Mays N, Pope C. Qualitative research in health care. Assessing quality in qualitative research. *BMJ*. 2000;**320**:50-2.

37. Hill M, Compton C, Karunaratna M, Lewis C, Chitty L. Client views and attitudes to non-invasive prenatal diagnosis for sickle cell disease, thalassaemia and cystic fibrosis. *Journal of Genetic Counseling*. 2014;**23**:1012-21.

38. Lewis C, Hill M, Chitty LS. Women's Experiences and Preferences for Service Delivery of Non-Invasive Prenatal Testing for Aneuploidy in a Public Health Setting: A Mixed Methods Study. *PloS One*. 2016;**11**:e0153147.

39. Hamblin A, Wordsworth S, Fermont JM, Page S. Clinical applicability and cost of a 46-gene panel for genomic analysis of solid tumours: Retrospective validation and prospective audit in the UK National Health Service. 2017;**14**:e1002230.

40. Chitty LS, Wright D, Hill M, Verhoef TI, Daley R, Lewis C, Mason S, McKay F, Jenkins L, Howarth A, Cameron L, McEwan A, Fisher J, Kroese M, Morris S. Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. *BMJ*. 2016;**354**:i3426.

41. Morris S, Karlsen S, Chung N, Hill M, Chitty LS. Model-based analysis of costs and outcomes of non-invasive prenatal testing for Down's syndrome using cell free fetal DNA in the UK National Health Service. *PloS One*. 2014;**9**:e93559.