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Optimising EXome PREnatal Sequencing Services (EXPRESS)

Policy report

EXPRESS
Optimising EXome PREnatal Sequencing Services

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Executive summary

Prenatal exome sequencing for the diagnosis of fetal anomalies was implemented nationally in England in October 2020 by the NHS Genomic Medicine Service.

The optimising EXome PREnatal Sequencing Services (EXPRESS) study explored the implementation of the national prenatal exome sequencing (pES) service. This evaluation was a multi-site, mixed methods evaluation combining qualitative analyses of service, stakeholder perspectives and ethical considerations with quantitative analyses of staff experiences, clinical outcomes and cost effectiveness. Patient and Public Involvement and Engagement (PPIE) was embedded throughout the study.

Key findings

Parents and healthcare professionals (HCPs), that included fetal medicine and clinical genetic consultants, fetal medicine midwives, genetic counsellors and clinical scientists, welcomed the introduction of pES.

The benefits of pES that were highlighted included the value of the additional information for pregnancy management and planning for future pregnancies. pES is offered at an already anxious time and there are challenges for pre- and post-test counselling. Parents reported needing emotional support across the testing journey, including follow-up care regardless of test outcomes. A newly developed animation on prenatal sequencing increased self-reported objective knowledge of pES among parents without previous experience of fetal anomalies.

Good communication and close working between clinical genetics, fetal medicine and laboratory teams has supported successful implementation. On a local level, the personnel involved in implementation varied in terms of leadership, staffing and approaches to multidisciplinary team working.

Challenges for service delivery included increased administrative time and gaps in genomics education, particularly for fetal medicine midwives and clinicians. Ethical issues identified centred on barriers for equity of access and intersecting timeliness of pES laws around termination of pregnancy.

Between October 2021 and June 2022, the diagnostic yield for pES was 35% (85/241), in line with what is reported in the research literature, with a median turnaround time of 15 days to the final report. The cost of delivering the pES service was £2,331 per referred case, with the estimated cost for each diagnosis being £11,326.

Key areas for improvement

Support for parents. Provide points of contact and further support for parents in terms of counselling and resources available before, during and after testing.

HCP engagement and education. Establish educational initiatives to improve the genomic literacy of fetal medicine and obstetric teams, and initiatives to engage and educate local HCPs, particularly those in peripheral units, to raise awareness about the rapid sequencing pathway and eligibility criteria. Develop strategies to increase understanding among clinical geneticists of fetal anomalies and their management.

Workforce. Review workforce requirements to determine numbers of prenatal clinical geneticists, genomically trained fetal medicine midwives and other HCPs needed to deliver an optimal and equitable pES service.

Guidelines. Update national guidelines to define essential core pathway components, including access to expert fetal ultrasound for phenotyping, prenatal genetic expertise and counselling, testing eligibility criteria, and roles and responsibilities of HCPs involved in the pathway. Areas that must be standardised nationally and areas for local flexibility should be highlighted.

Further pathway development. Build on lessons learned to inform the development of optimal care pathways. This includes the use of digital and virtual systems to facilitate communication and sharing of expertise between HCPs involved in these services, which in turn will facilitate equity of access to expertise for parents regardless of where they live.

Support for HCPs. Put in place initiatives, such as dedicated staff, to reduce the administrative burden on HCPs delivering the service.

Pathway audit. Carry out detailed pathway analysis to identify opportunities for streamlining the overall pathway, to allow parents more time to make decisions.

Research opportunities. Further research is required to understand the views of parents from more diverse backgrounds about pES and those who declined pES, and to engage with underserved populations. Additionally, research is required to explore clinical outcomes in the neonatal setting, and on longer term impacts, to identify true costs and benefits.

Exploration and implementation of the recommendations outlined in this report will help ensure the evolving pES service will provide equity of access, high standards of care and benefits for parents across England whilst maximising use of NHS resources.

Contents

Acronyms

CG – clinical genetics

CGS – Clinical Genetics Service

CMA – chromosomal microarray

ES – exome sequencing

FM – fetal medicine

GLH – Genomics Laboratory Hub

GMS – Genomic Medicine Service

HCP – health care professional

MDT – multidisciplinary team

NHS – National Health Service

pES – prenatal exome sequencing

pGS – prenatal genome sequencing

RoD – record of discussion

VUS – variant of uncertain significance

1. Background

The English Genomic Medicine Service

In 2018, NHS England formed the Genomics Medicine Service (GMS), by consolidating the many genetics laboratories around the country into a network of seven regional Genomic Laboratory Hubs (GLHs) to deliver high throughput, rapid genomic testing including genome sequencing [1]. At the same time the National Genomic Test Directory [2], that details all genomic tests available in the NHS GMS with their eligibility criteria and how these tests can be requested, was implemented to enable equity of access to genomic testing across the country. All tests are assigned an R number. The rapid prenatal sequencing service for the diagnosis of fetal anomalies (R21) was added to the Test Directory in England in October 2020 [3].

Fetal genomic testing

Fetal anomalies occur in approximately 2-5% of pregnancies [4]. They cause around 20% of perinatal deaths and contribute to longer term perinatal and paediatric morbidity [5]. Conventional genetic testing for fetuses found to have anomalies on prenatal imaging includes quantitative fluorescence PCR (QF-PCR) for rapid aneuploidy exclusion, and karyotype or chromosomal microarray (CMA) for detection of chromosomal and sub-chromosomal abnormalities [6, 7]. Together, these can provide a diagnosis in up to 40% of cases, but the majority remain undiagnosed [5]. Targeted sequencing of individual genes can be offered in cases where clinical features or family history suggest a specific monogenic disorder. Genome-wide methods using next generation sequencing offer the advantage of interrogation of many genes in a single test.

In the postnatal setting, exome sequencing (ES), which examines the 1-2% of the genome that encodes proteins, is a powerful tool for the diagnosis of children with neurodevelopmental delay [8] and rare diseases [9]. Application for prenatal diagnosis initially lagged behind postnatal application for several reasons:

- Complex analysis precluded return of results in the timeframe of pregnancy.
- Fetal imaging yields incomplete or unknown phenotypes impeding variant interpretation.
- High cost of sequencing.

Over recent years, the development of rapid analytical pipelines has made it possible to return ES results in a timeframe that enables use in clinical management during an ongoing pregnancy [10], and costs of sequencing are falling. Furthermore, two large prospective studies demonstrated the diagnostic utility of ES for prenatal diagnosis of unselected fetuses with structural anomalies, reporting diagnostic rates of 8.5-10% [11, 12]. Additionally, smaller studies have reported diagnostic rates as high as 80% in cases preselected for a likely monogenic aetiology by clinical genetic screening where karyotype and microarray have been uninformative [13]. These advances informed the decision by NHS England to introduce a rapid prenatal sequencing service.

The rapid prenatal sequencing service

In the NHS GMS, parents are offered rapid prenatal ES (pES), when fetal imaging has detected structural anomalies, and a genetic aetiology is strongly suspected but standard genetic testing (karyotyping and chromosomal microarray) has not been diagnostic. All cases are reviewed by a multidisciplinary team (MDT) that includes fetal medicine (FM) experts and clinical geneticists to assess eligibility [3]. Exclusion criteria include phenotypes which suggest specific conditions for which alternative diagnostic tests are available. Where parents have made the decision to end a pregnancy or fetal demise has occurred or is imminent, rapid prenatal sequencing testing is not performed. Initially these cases could be referred for genome sequencing after delivery.

Within each of the seven GLH regions in England there are two or three Clinical Genetics Services (CGSs), 17 in total, who work with their local FM and obstetric specialists to offer prenatal sequencing to parents (Figure 1). The FM and obstetric specialists may work within FM Units at tertiary hospitals or see parents at smaller District General Hospitals. The sequencing and variant interpretation is performed at two GLHs – the Central and South GLH (Birmingham laboratory) and North Thames GLH (Great Ormond Street laboratory) who each receive referrals from around half the country (Figure 1). Each of the seven home GLHs are responsible for the referral, karyotyping and microarray testing, sample collection, sample processing to extract DNA, transfer of DNA to the testing GLH and the local clinical team is responsible for return of results to parents (Figure 2).

Figure 1: Summary of testing and home GLHs and their linked clinical genetics services. Adapted from Walton et al. 2024 [19].

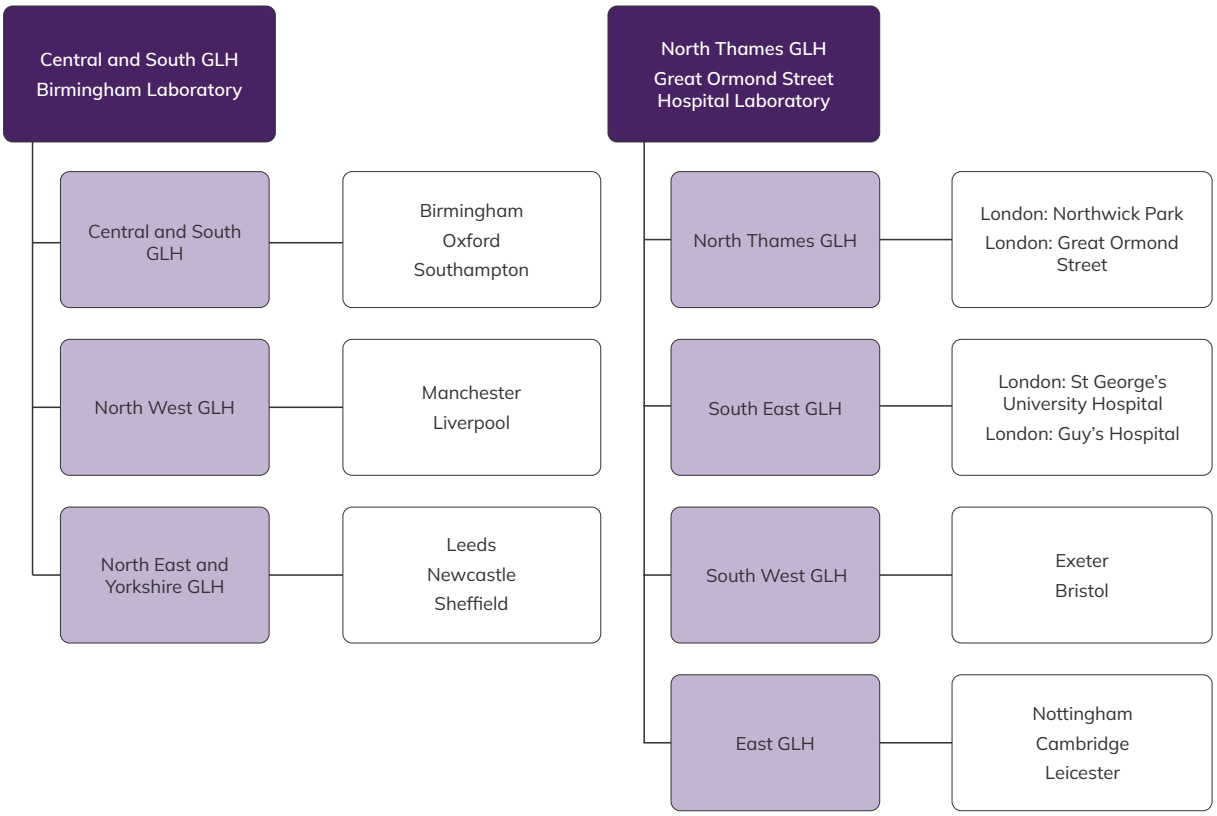
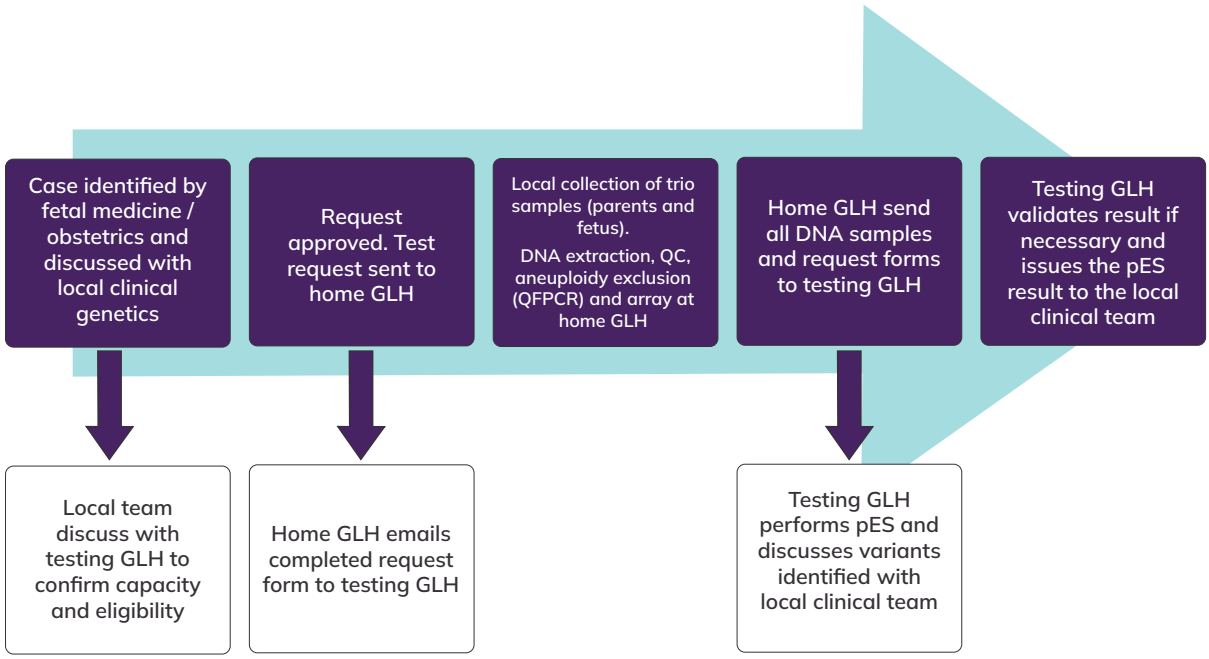


Figure 2: Summary of the prenatal sequencing service pathway. Adapted from the prenatal sequencing clinical guidance [14].



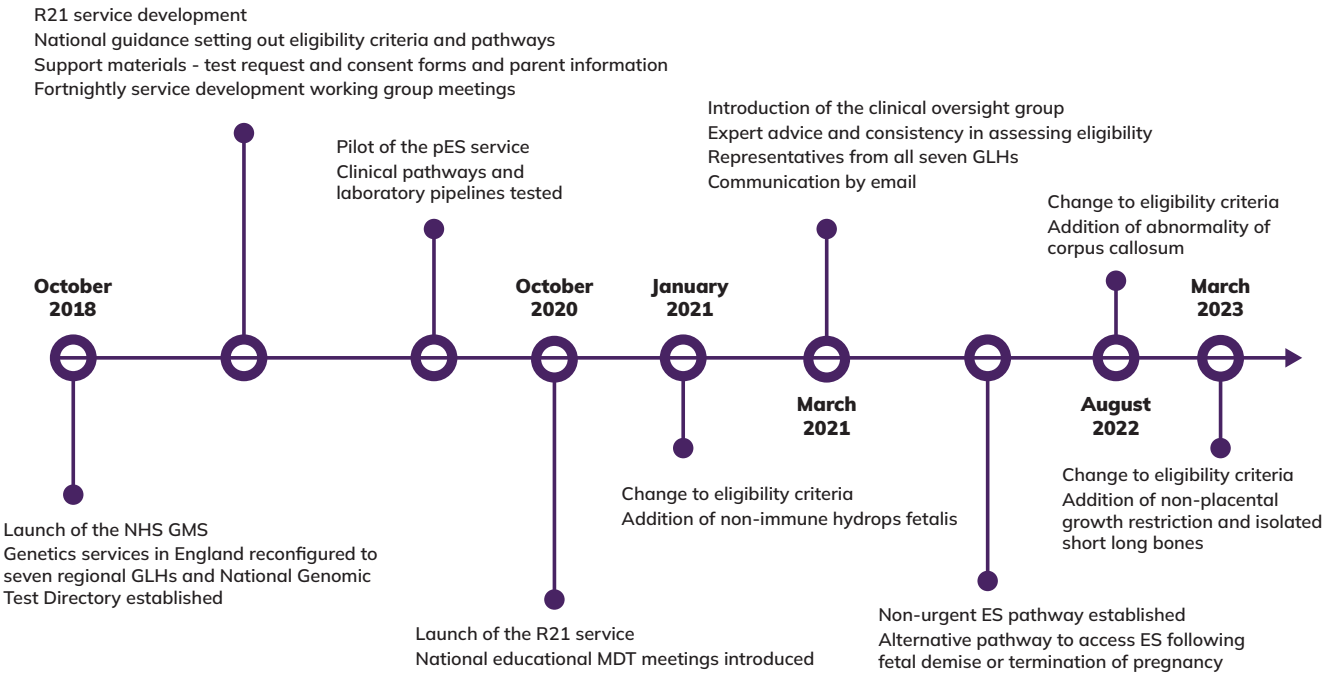
National guidelines for delivery of the rapid prenatal sequencing service set out the key elements of service provision, including (Figure 2) [14]:

- Referral follows discussions between the mother's local obstetric and/or FM management team and a clinical geneticist from the local CGS.
- Due to the urgent nature of this testing, there must be discussion between the referring (home) GLH and the testing GLH to ensure eligibility of the referral.
- The local GLH is responsible for rapid aneuploidy exclusion (QF-PCR) and CMA analysis, but the latter can be done in parallel with pES to prevent delays in reporting pES results. pES can be stopped if CMA indicates a causative result.
- A record of discussion (RoD) form (see NHSE guidance and Appendix 7.3) is used to record parents' choices – including participation in research [3].
- All familial samples, fetal size charts and imaging reports are provided with a test request form and record of discussion (RoD) form to the testing GLH with any relevant clinical details.
- Trio testing (both parents and the fetus) is preferred to aid rapid interpretation, but duo or singleton testing is permitted if parental samples are not available.
- The data is analysed using a nationally agreed panel of genes (the fetal anomaly panel in PanelApp) known to cause structural anomalies that can be detected prenatally or in the early newborn period. [15, 16]

The rapid prenatal sequencing service has continuously evolved since implementation, and several key changes have been introduced since the launch of the service in 2020:

- There is ongoing review of eligibility criteria and through this process several additions have been made to eligibility criteria to reflect the changing evidence landscape (Figure 3).
- In March 2021, a national Clinical Oversight Group was established that includes representatives from each of the seven GMS regions. Healthcare professionals (HCPs) may appeal to the oversight group, who act as an independent arbitrator for test eligibility in 'borderline' or complex cases, when a referral for prenatal sequencing is declined or deemed unclear by the testing laboratory.
- The fetal anomaly gene panel is reviewed by a working group every six months. Potential genes for inclusion are identified using systematic searches. Genes with sufficient evidence of association with a prenatal or early postnatal phenotype that could be detectable prenatally are approved for inclusion in the next version of the panel.
- In 2021 a non-urgent fetal sequencing pathway (R412) was introduced for eligible cases where there was fetal demise or termination of pregnancy to enable more timely return of results [17].

Figure 3: Development of the rapid prenatal sequencing service in England. Key: GMS = Genomic Medicine service, RoD = record of discussion, MDT = multidisciplinary team. Adapted from Walton et al. 2024 [18].



2. The optimising EXome PREnatal Sequencing Services (EXPRESS) study

Project aim

The aim of EXPRESS was to evaluate the national delivery of the rapid prenatal sequencing service and make recommendations for change if necessary to ensure delivery of an equitable, high quality, acceptable, ethical, robust and cost-effective care pathway for parents undergoing prenatal diagnosis in fetuses with anomalies likely to have a genetic cause [19].

Project objectives

This study comprised five interrelated workstreams, designed to address specific objectives:

1. Determine the clinical care pathways for pES in each of the seven GLHs (workstream 1).
2. Establish whether pES is understandable and acceptable to key stakeholders, including parents (workstream 2) and HCPs (workstream 1).
3. Identify education and information needs and how they are best addressed for parents (workstream 2) and HCPs (workstream 1).
4. Establish the outcomes (diagnostic yield, referral rates, final diagnoses) of the pES programme, compare these between regions, and identify any factors (individual or service-related) associated with variation in outcomes (workstream 3).
5. Identify any new ethical issues arising from offering the pES programme in the NHS and explore how HPCs can best be supported in addressing them (workstream 4).
6. Formally evaluate the cost and cost-effectiveness of implementing the optimal pES pathway (workstream 5).
7. Determine the key features that constitute the optimal pES pathway from a service delivery, parent and professional perspective (all workstreams – Integration of findings).

A list of publications arising from the EXPRESS study can be found in Appendix 7.1.

Project oversight

This study was overseen by a steering committee comprising academics, HCPs and patient representatives and a Patient and Public Involvement and Engagement (PPIE) Advisory Group comprising representatives of patient groups and a researcher with relevant experiences (Appendix 7.2).

PPIE was embedded in all aspects of the study [20]. The PPIE Advisory Group gave feedback on parent-facing documents to ensure suitability of participant information sheets and topic guides, and advised on approaches to recruitment of parents for qualitative interviews. They also contributed to the study development, interpretation of findings, reports, publications and the development of recommendations.

Project methods

Various sources of data were analysed in this project and used to inform the project objectives. The research team conducted interviews with HCPs and parents, and surveys with HCPs. Other sources of data analysed for this study include: GLH testing data and pregnancy outcomes; the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) data; maternity service data; and incremental costs of the pES test pathway over standard of care. The analytical methodology varied depending on the workstream, using a combination of qualitative and quantitative approaches as described in the associated publications (see Appendix 7.1).

Project evolution

The COVID-19 pandemic impacted on pES service implementation, initially planned for March 2020. The EXPRESS project was similarly pushed back so that the start date could coincide with the launch of the pES service in October 2020. The EXPRESS team adapted to pandemic restrictions, for example altering data collection methods when it was not possible to carry out site visits to inform case studies and conducting interviews remotely. There were two major changes to the original research plan.

- The time period for collecting data in workstream 4 and workstream 5 was shortened due to the delayed start in the pES service and the need to allow time for the service to settle in.
- In addition, the number of sites in workstream 1 was revised. Initially, the study planned to look at pES service delivery at the level of the seven GLHs. This was altered to studying service delivery at each of the individual 17 CGSs, once it was determined that there were differences between each CGS within the GLH regions (Figure 1).

3. Results

The EXPRESS study has been completed and full details of the results are available in associated publications (Appendix 7.1). In this report, we have reviewed the work done to provide a summary of the key findings and recommendations.

3.1. Implementation of the prenatal exome sequencing service

Objective 1: Determine the clinical care pathways for prenatal ES in each of the seven GLHs (workstream 1).

National delivery of a service is expected to result in some level of variation depending on local approaches to implementation and the specifics of local pathways. In this workstream, the EXPRESS team aimed to understand how pES had been implemented at a local level.

While the seven GLHs oversee pES service delivery, 17 CGS coordinate local pathways. As a result, 17 local pathways were analysed, with study sites comprising each of the 17 CGS, their associated FM and obstetrics teams and the GLH for their region.

Results from this objective are available in the associated publication describing the implementation of rapid pES [18].

Variation in the delivery of local prenatal sequencing services

The project team conducted interviews and surveys with HCPs from all 17 study sites and used this data to explore implementation and map local pES pathways.

While there were similar pathway components across sites, the models of implementation varied. The EXPRESS team identified seven models of service delivery, based on two overarching factors that underpin service delivery: a) whether FM, clinical genetics (CG) or both led the service, defined as who initiates pES referral and takes consent and b) the core staff involved in local service delivery. The models used were found to differ within and between GLH regions.

Key findings

- CG most often led the pES service. However, later interviews suggested that some of these sites were shifting to more active FM involvement when initiating the pES care pathway.
- Minimum staffing comprised a FM clinician, a clinical geneticist and the clinical scientists, however some care pathways also included FM midwives and/or genetic counsellors.
- Different HCPs could be involved at different stages along the pES pathway. For example, while FM staff typically identified the fetus and parents who may be eligible for testing, CG staff (including clinical geneticists and genetic counsellors) most often interacted with the testing laboratory, took consent, organised sample collection and returned results.

- The nature of results could change how they were returned to parents, and the involvement of FM, CG or both. Returning more complicated results would typically be undertaken by clinical geneticists. Joint clinics involving FM and clinical geneticists and/or genetic counsellors were also used for returning these results by some services. Who returned 'no finding' results was more variable, with FM clinicians and genetic counsellors more often involved. At one tertiary FM unit, FM midwives also returned 'no finding' results.
- Good communication and a close working relationship between FM and CG and the GLHs was vital for effective service delivery. Communication and close working could be facilitated in a number of different ways: regular MDTs, ad hoc discussion, joint appointments, and having a prenatal clinical geneticist embedded in the FM unit. Good communication and clear pathways were important for reducing delays across the testing pathway.

Factors influencing service variation

The pES pathway involves complex logistics in terms of staffing, testing processes, communication, and timing of referrals and administration. This makes it likely that local and regional factors would influence test delivery. Successful implementation of any new service pathway will require a balance between adherence to and adaptation of established processes and procedures. EXPRESS identified several factors that influenced local implementation.

Key findings

- Cross-disciplinary working between FM units and CG is key to the success of a national pES service.
- Pre-existing working relationships between FM, laboratory, and CG teams facilitated smooth implementation. Other FM units and CGS made significant efforts to develop close working relationships and are now working well together.
- Working within an MDT was highly valued as a key forum to discuss eligibility and results interpretation and gather expert views of fetal phenotyping of complex cases. MDT meetings were also important for service updates, education and knowledge exchange. Across sites, approaches to MDT meetings varied in terms of frequency, format and staff involved.
- Where a clinical geneticist or genetic counsellor was physically embedded in FMUs or were closely located, it was highly valued by FM and CG staff and facilitated MDT working.
- Sufficient staffing across CG teams, FM teams and support teams, and infrastructure for collaborative working, supported implementation.

- Differences in preparedness to deliver the service were identified. Some sites had previously offered pES in research or clinical settings or drew on their experience of offering CMA. Sites with limited previous experience, in particular peripheral units, required greater efforts in order to establish appropriate pathways.
- HCPs viewed limitations in IT infrastructure as a barrier. This added to the burden of administrative tasks.
- Confidence, enthusiasm, and interest of FM staff in genomics positively impacted implementation.
- Engagement of peripheral units varied, with delays in referrals and difficulty in obtaining expert phenotyping reported.

3.2. Experiences of healthcare professionals and parents

Objective 2: Establish whether prenatal ES is understandable and acceptable to key stakeholders, including parents (workstream 2) and healthcare professionals (workstream 1).

Objective 3: Identify education and information needs and how they are best addressed for parents (workstream 2) and healthcare professionals (workstream 1).

The research team conducted interviews and surveys with HCPs and interviews with parents to gather their views on the pES service.

Results from these objectives are available in the associated publication describing the views and experiences of HCPs and parents of the pES test pathway [21-24].

Experiences of healthcare professionals

HCPs from FM, CG and laboratory backgrounds are integral to the delivery of the rapid pES service. The EXPRESS team captured their experiences and reflections on the launch and evolution of this service, in terms of the initial implementation, impact on their workload and ongoing education or training needs.

Service delivery

The availability of rapid pES was viewed positively by HCPs. This test increased the likelihood of making a diagnosis, and this may provide clarity and actionable information to support parental decision making and subsequent management. In terms of the service, HCPs praised the rapid turnaround times, responsiveness of local team members and the agility of the service.

However, some differing views were held around the stringency of the eligibility criteria, with some HCPs feeling that these criteria should be broader with greater flexibility so that testing would be available to more parents. Some HCPs also felt the gene panel was too selective and may result in missed diagnoses. On the other hand, other HCPs agreed with

the limitations imposed, especially at the outset of the service when processes were being established. Additionally, some HCPs found that reporting more complex variants, such as variants of uncertain significance and incidental findings, could be challenging. Parents are informed of the small risk of these types of results during pre-test counselling but may not appreciate the implications as information is shared at a time when they are anxious and focused on the baby.

At the time the pES service was launched, reconfiguration of genetic laboratory services into a unified national GMS was still being embedded. There were initial concerns around how the reorganisation would affect the pES service and working relationships between FM and CG and laboratory departments. While the need to establish new relationships did affect pES implementation, FM and CG departments generally felt they were working together well.

Capacity and resources

Appropriate administrative support is integral to coordination of test pathways. The RoD captures the discussion with parents about sequencing, including consent, likelihood and type of results that may ensue. Half of HCPs surveyed had experience of completing a RoD, although HPCs were more likely to respond yes. Consent was seen as challenging, in particular, when balancing the right amount of information for parents to make an informed decision at a time when they were very stressed. Expert pre-test counselling requires a good understanding of pES and the limitations of this test to support parental decision-making during this challenging time. HCPs who were less familiar with genomics and sequencing found pre-test counselling and completion of the RoD challenging. However, some HCPs found the RoD helpful, as going through it ensured that all key points were discussed with parents.

In addition to an increase in clinical time required for discussing pES and taking consent, pES has also led to a reported increase in time spent on administrative tasks, particularly for genetics HCPs. This was felt to be challenging in terms of managing clinic time, but there was also an added 'invisible labour' from time spent liaising with other departments, sharing information or tracking samples. There is a careful balance needed between ensuring parents are adequately consulted on the test while ensuring adequate capacity to support parents along the test pathway.

Awareness and education needs

The survey identified gaps in some HCPs understanding of the eligibility criteria. In particular, FM HCPs overall had less awareness of the eligibility criteria, which could potentially lead to inequalities in access to testing if eligible parents were not being identified and referred in the same way across the country.

HCPs highlighted that further training would be valuable. In fetal medicine they were more likely to highlight the need for additional training around basic principles of genetics. Whilst CG HCPs felt they would benefit from learning more about identifying and managing genetic conditions in the prenatal period. More widely, there is a shortage of CG HCPs with specialist knowledge of prenatal conditions and their management.

Where FM midwives had taken an interest in pES and genomics, their skills were seen as integral to delivery of the pES test and support of parents. While the pES service is likely to remain largely led by CG, HCPs thought that in the future the service should be led by FM with CG oversight. A role for FM midwives confident in genomics and/or genetic counsellors to support parents undergoing pES across their testing journey was identified.

There are existing opportunities for genomics training for FM HCPs (e.g. sessions led by CG colleagues or online education through NHS England), however, in some regions, uptake has been poor, particularly amongst midwives. This is principally because of time pressures and some HCPs not seeing pES as part of their role. Training for all FM HCPs which includes case examples, i.e. cases referred to the pES test pathway, may promote awareness and understanding of this service, and the value it brings for parents.

Key findings

- The availability of rapid pES was viewed positively by HCPs.
- HCPs wanted to provide parents with enough information to support decision-making without overloading parents at a challenging time.
- Views on eligibility criteria and referral processes varied, with some HCPs seeing them as too restrictive.
- The introduction of the Clinical Oversight Group to act as an independent arbitrator for pES in 'borderline' or complex cases was welcomed by HCPs.
- There were mixed opinions on how restrictive the gene list used for analysis should be to balance finding a diagnosis against uncertain results, for example detecting variants of uncertain significance (VUS) or incidental findings.
- Additional administrative support for clinical teams could reduce the burden of administrative tasks, for example, time they spend on tracking samples and sharing information between laboratories and clinical teams.
- Training of HCPs around the eligibility criteria is important to prevent parents being told about the test only to be informed they are not eligible. Particularly in peripheral obstetric units there may be a of lack awareness of clinical indications for pES, and upskilling is necessary to promote delivery of national pES service and equitable access for all parents.
- There are gaps in genomics knowledge among FM clinicians and too few CG clinicians with specialist prenatal knowledge and experience to support the service.
- There is a role for FM midwives trained in genomics in supporting parents across the pES pathway.
- Education and information needs for HCPs include:
    - More engagement activities with FM and obstetric HCPs are needed to increase awareness and willingness of HCPs to take part in service delivery, this includes FM midwives. Genomics training using case examples may support better awareness and understanding among HCPs.

- FM staff requested further genomics education to increase confidence when referring parents to the service and to become more involved in service delivery, i.e. taking consent and returning results.
- There is currently a shortage of prenatal genetic expertise amongst CG staff, and multiple approaches are needed to address this gap.

Experiences of parents

EXPRESS explored the views and experiences of parents who had undergone pES as part of the clinical service through semi-structured interviews. These insights can inform what elements of the service work well for parents and where improvements may be made.

Searching for answers

Parents were generally positive about the opportunity to be offered pES as the test provided an additional pathway to find more information about the prognosis for the baby. For parents, pES results could also help inform their decision to continue or terminate a pregnancy or help in planning clinical care at birth and in the neonatal period.

pES is offered at an emotionally charged time. Parents are anxious following identification of fetal anomalies and resultant multiple testing and clinical appointments. The detailed pre-test counselling was sometimes perceived by parents as an overload of information. Parents may also feel time-pressured by pregnancy and the 24-week change in termination law that restricts access to termination of pregnancy (see section 3.3) and, as a result, decisions can feel rushed.

A diagnosis from pES can provide additional information to parents when deciding whether to continue or end a pregnancy. For parents who continue the pregnancy, diagnosis can also avoid distress and delay in diagnosing a genetic condition after birth, as well as informing birth management and follow-up care. A 'no finding' result can lead to mixed feelings for parents. For some, these results provided relief and reassurance, while others expressed disappointment at the ongoing uncertainty. HCPs felt some parents may be overly reassured following a 'no finding' result. When parents do not have a good understanding of the limitations of the test, they may not consider the full picture of findings from other tests such as scans. This is especially important as current eligibility means that all fetuses tested have significant anomalies. Personalised counselling for parents is crucial.

Supporting parents through pES test pathway

Parents were positive about the support and care they received from HCPs. In particular, FM midwives were seen as a great source of emotional support. HCPs were aware that parents seek information outside of clinic appointments and parents felt they would benefit from more signposting to appropriate information. Several HCPs commented that pre-test counselling can be challenging because parents have varying levels of educational attainment or may

better understand their testing options if information is available in their native language or in alternate formats. Parents who contacted the charity Antenatal Research and Choices valued the additional emotional support and information. After results were returned, parents did feel that, while they felt well supported during the testing process, there was a lack of follow-up and ongoing psychological support.

In response to these views the EXPRESS team, working together with parents, the PPIE Advisory Group and HCPs, developed an animation designed to be accessible to parents and for use as a clinical aid to support pre-test discussions [25]. An independent evaluation of this animation found that it improved parents' self-perceived understanding, although they still found this information technical. This may reflect that parents recruited had experience of a fetal anomaly but had not necessarily undergone pES [24].

Key findings

- Parents welcomed the opportunity to access pES.
- pES influenced parental decision making to continue or end pregnancy.
- Expert pre-test counselling by clinicians with a good understanding of pES and the limitations of testing is necessary to support parental decision-making.
- Parents and HCPs expressed that parents would benefit from access to a named HCP to answer queries and provide support while parents undergo testing. Signposting to accurate information resources and specialist parent support services, such as Antenatal Results and Choices, would also be valued.
- FM midwives were identified by parents as a key source of emotional support throughout their journey with pES.
- Expert follow-up and discussion is needed regardless of the pES result to explain 'no finding' results as well as diagnostic findings.
- There was concern that parents may interpret a 'no finding' result as a good outcome. Therefore, HCPs need to address the limitations of pES and discuss pES results within the context of a full diagnostic picture. This will ensure that parents understand that a 'no finding' result does not rule out the presence of a genetic condition or a poor prognosis based on sonographic findings.
- The majority of parents interviewed in this study reported being white British and educated to degree level or above.
- Educational needs of parents:
  - Careful pre-test counselling is needed that explains the benefits, limitations and possible results from pES.
  - Parents' understanding of their testing options would be supported by information being available in their native language or in alternate formats.
  - The animation developed as part of EXPRESS improved understanding of prenatal sequencing for parents.

3.3. Ethical observations of delivering the prenatal sequencing exome service

Objective 4: Identify any new ethical issues arising from offering the prenatal ES programme in the NHS and explore how healthcare professionals can best be supported in addressing them (workstream 4).

Results from these objectives are available in the associated publication describing the outcomes from ethical analysis of the pES test pathway [26].

Many of the ethical issues arising from using genomic testing in the prenatal period are well known. The EXPRESS study focussed on ethical issues that arose as a result of offering pES as a national service in England. This workstream drew on data obtained from parents and from HCP interviews and questionnaires. The key themes arising were the potential inequity of parental access to all aspects of service and the timeliness of the test and results to inform pregnancy decision making.

Equity of access

National implementation of a service aims to ensure equity of access across the country. However, differences in service delivery can lead to disparities in access. Several factors were identified that may impact on equity of access to pES.

Some HCPs considered the eligibility criteria to be too narrow, thereby limiting eligibility to cases with selected anomalies. Others recognised that a selective approach was necessary to manage likely resource limitations, and because including a wider range of conditions could lead to more uncertain results for parents.

HCPs have varying levels of knowledge of pES and this can lead to variation in clinical decision making. For example, HCPs in peripheral obstetric units may have less awareness of pES test availability and so may not refer or refer late or inappropriately.

Local referrals may also be affected by resource issues, for example, availability of expert fetal imaging for phenotyping or access to expert prenatal genetic counselling. Referral for pES could be influenced by worries of the implications of not offering testing. Some HCPs were concerned parents may sue where pES was not offered or refused, and a genetic condition discovered after birth. As a result, HCPS may change referral decisions, resulting in significant variations in parental access to pES.

There are also existing health inequities that may prevent parents accessing pES. These may be financial or geographical, preventing parents from attending in person appointments at tertiary centres when there is a lack of local expertise.

The nature of the pES service requires the discussion of nuanced and complex information. HCPs felt that inequities could arise for parents with learning difficulties, limited education or whose first language is not English. For example, while HCPS reported that some language interpreters were very good, others mentioned that interpreters may express limited or inaccurate information, which could lead to miscommunication.

Time critical information and decision making

Pregnancy is a time sensitive period, particularly following identification of fetal anomalies. For HCPs, this can add pressure to this rapid service, while also trying to ensure parents are adequately informed and understand the test. Referrals for pES were most often made following the identification of fetal structural anomalies at routine scans, typically around 20 weeks. This is close to 24-weeks which is when the law in England changes and termination is only permitted where there is substantial risk of serious handicap in the child. A number of other factors also impacted the timeliness of the pES result, including late referral, delays in obtaining parental samples, waiting for the array result before referral, and additional investigations prior to or following pES to make the diagnosis. Furthermore, some anomalies do not manifest until later in pregnancy. There is a clear relationship between the termination law change at 24 weeks and decision-making needs of parents and this was reported to be stressful for both parents, who feel pressured to make decisions quickly, and the HCPs supporting them.

Some parents and HCPs placed special importance on the pES result, and this can impact on how parents perceive test results and the need to wait to make decisions. pES results need to be contextualised with other clinical findings. Parents and some HCPs may be overly positive about a 'no-finding' result, however, as pES is only offered in the presence of fetal anomalies, there will be health issues for the baby irrespective of the pES finding.

Access to rapid pES is restricted if parents have decided to terminate the pregnancy before the offer of pES. This could be viewed by parents as distressing and unjust, however, the health system needs to consider resource use and the needs of all parents. To address this, an alternate non-urgent pES test pathway was made available in 2021 for parents who decide to terminate or where fetal demise has occurred [17].

There is the potential for some of these ethical challenges to be mutually reinforcing. There are known inequities in accessing health services and the nature of referrals at the 20-week fetal anomaly scan can make it harder to achieve timely return of results.

Key findings

- Some issues that have been raised with the potential to affect equitable access to pES services may be addressed through improved awareness and education of some HCPs.
- To reduce time pressures on parent decision making, pES needs to be considered in the context of wider innovations in fetal anomaly screening which may provide opportunities for earlier assessment, more streamlined sample collection and expedited referral for access to pES.
- The value of the pES result needs to be considered in the context of the structural fetal anomalies identified to avoid over emphasis and need to wait for the pES result, as prognosis will also be dependent on findings from other tests such as scans or MRIs.
- Findings from this study should be used to inform next steps towards developing an ethical framework for pES delivery.

3.4. Service outcomes

Objective 5: Establish the outcomes (diagnostic yield, referral rates, final diagnoses) of the prenatal ES programme, compare these between regions, and identify any factors (individual or service-related) associated with variation in outcomes (workstream 3).

Results from these objectives are available in the associated publication describing the outcomes of the pES test pathway associated with variation in outcomes [27].

Implementation of a national service, such as pES, was anticipated to lead to regional differences in service outcomes, such as diagnostic yield, referral rate and sources of referral. EXPRESS aimed to identify any regional differences and use these insights to inform improvements where appropriate to ensure an equitable service.

Clinical outcomes of the pES service were examined across a nine-month period (01 October 2021 to 30 June 2022). pES data from the two testing laboratories were linked to NCARDRS and the Maternity Services Data Set. This enabled comparison of women receiving pES to all women having babies (including stillbirths) during the same time period. In total, 409 women were referred for pES, which was 8.6 per 10,000 maternities in the nine-month study period. The acceptance rate by the testing laboratories was 75.3% (308) of which 58.9% (241) of tests proceeded. Testing was declined or did not proceed for a number of reasons, including parents opting for pregnancy termination, fetal demise, other tests yielding a diagnosis and parents declining invasive testing or sequencing. The characteristics of women referred for testing did not differ substantially from the populations who gave birth in the GLH areas.

Diagnostic yield

The diagnostic yield of the pES service was 35%, ranging from 28.6% to 45.5% across GLHs. A yield of 35% was in line with diagnostic yields reported in the literature, where cases were pre-selected by clinical genetic review for likelihood of a monogenic condition [28]. Most factors are fixed across the national pES service, and this variation is more likely to be due to local differences in how eligibility criteria were being applied. However, this analysis was based on small numbers of referrals, limiting any inferences that may be made.

The median turn-around time, which is the time from sample receipt in the laboratory to return of final results, was 16 days for a diagnosis and 14 days for a ‘no finding’ result.

Pregnancy outcomes

Overall, for women who had pES, 65% had live births, 9% had a stillbirth and 25.5% underwent termination of pregnancy.

Outcomes of pregnancy differed for parents with and without a diagnosis. In women who received a diagnosis, 39.8% underwent termination, 18.1% had a still birth and 42.2% had a live birth compared to women who did not receive a diagnosis (17.8% underwent termination, 4.6% had a still birth and 77.6% had a live birth).

The characteristics and outcomes of women who received a diagnosis differed by age, ethnicity and level of deprivation. A diagnosis had a significant impact on the decision to terminate, with 39.8% of women with a diagnosis choosing to terminate compared to 17.8% of those with 'no finding'. Ethnicity and complex social factors were important factors for confirmed diagnosis and pregnancy outcomes. A higher proportion of women from an Asian background or with complex social factors received a diagnosis and a higher proportion of women with complex social factors underwent termination. Data on consanguinity and autosomal recessive conditions was not available, preventing analysis on these variables.

A high proportion of women with a diagnosis did continue with their pregnancies and had a live birth (42.2%). This finding highlights that pES can be associated with a decision to continue the pregnancy. Data was not available for pregnancy outcomes and the neonatal period preventing analysis of neonatal outcomes following pES test results.

Among women who had a termination, median gestational age at final report was 24.9 weeks and at termination was 26.2 weeks. This is because most referrals for pES are made following routine fetal anomaly scans at 18-20 weeks. Late termination has additional legal considerations, and this may result in additional stress for parents and HCPs waiting for pES results and may restrict parental choices regarding pregnancy management.

Streamlining may be possible across the pES test pathway which has a number of steps including pre-test counselling, sample transfer, laboratory testing, returning results and pregnancy decision making. Additionally, the nature of the result can affect turnaround time including the need for clinical validation before reporting, challenges of variant interpretation requiring close communication between the laboratory and referring HCPs, and the evolving phenotypes or requirement for additional examinations of the fetus or parents.

Service variability

The EXPRESS study explored the different models of service delivery identified in workstream 1 to determine impact on service outcomes. No significant differences were observed between the 17 CGS test pathways. However, this analysis was based on a small sample size and a larger number of referrals may be needed to identify any differences.

Key findings

- To ensure equity of access for parents, further education for HCPs and review of local processes is needed to ensure the eligibility criteria are applied in a similar way across all regions.
- Small numbers of referrals included in this study period limited comparison between GLH regions but did show a trend towards difference in diagnostic rates. In particular the EXPRESS team was unable to determine if eligible parents are not being referred in some regions, and reasons behind parents declining referral.

- It would be beneficial to parents to return results earlier in pregnancy to avoid the results being returned after 24 weeks. Future research is needed to better understand the factors that affect referral and sample collection from the perspective of parents and HCPs. For example, journey mapping can be used to determine a wider range of factors that affect timelines to enable interventions to improve the gestational age at diagnosis by shortening the overall testing pathway. This could include streamlining processes that will reduce the time for samples to reach the testing laboratories.
- Terminations are occurring late in pregnancy and guidance is needed to prepare and support parents who have late terminations.
- Data was not available for pregnancy outcomes and the neonatal period limiting analysis of pES outcomes and any potential impact on neonatal mortality and morbidity.

3.5. Health economics

Objective 6: Formally evaluate the cost and cost-effectiveness of implementing the optimal pES pathway (workstream 5).

Delivery of a national service must consider the associated costs and benefits for the NHS as well as parents. EXPRESS evaluated the cost and cost-effectiveness of implementing pES to date across the various pathways to inform optimal cost-effective service delivery. This analysis was based on data collected in workstream 4 (section 3.4, above).

Results from these objectives are available in the associated publication describing the costs and cost-effectiveness of the pES test pathway [29].

Costs of delivering the pES service

The EXPRESS study found that the mean incremental cost of delivering the pES service was £2,331 per referred case; £3,592 for a proceeded case (pES carried out) and £564 for a non-proceeded case (pES not carried out). The laboratory cost of the pES test was £2,931 per proceeded case and, as a result, accounted for the majority of the overall cost (76%). This also explains the proportionately lower costs associated with cases that did not proceed. The total annual incremental cost of the pES service to the NHS was £1,768,193.

The EXPRESS study considered these headline costs in the context of pregnancy outcomes to determine cost-benefit. Over the period of study, given that the diagnostic yield was 35.3% (85 cases), the cost of pES testing per additional diagnosis, in addition to standard of care, was £11,326.

A diagnosis is not the only outcome of a pES test that can change clinical management. For cases that received a diagnosis, 82% reported a change in management, increasing the cost per outcome to £13,753. Where a 'no finding' result was returned, clinical management changed in 51% of cases. Therefore, overall, pES results changed case management for 63% of cases and the cost per outcome was £6,334. Clinical management of cases was only ascertained for 42% of cases, so this may be an overestimation.

Service model and cost effectiveness

Given the variation in service delivery identified across the 17 pathways, the EXPRESS team evaluated how this influenced the costs associated with delivering pES testing and found that the model of service delivery had a minimal impact on cost effectiveness. This is because the pES laboratory cost itself made the largest contribution to cost. There was some variation in terms of higher costs being associated with models that used a greater proportion of clinician level time. However, this was slightly offset by a lower amount of time used for existing appointments and fewer additional appointments. When a midwife was part of the core delivery team, costs were lower.

A potentially evolving service

With the increasing use of genome rather than exome sequencing in the NHS for postnatal indications, EXPRESS calculated the maximum cost of the prenatal genome sequencing (pGS) test at which the pGS pathway would be no more expensive than the pES pathway to the NHS. To do this, some assumptions were made as to how the service could change. In the current test pathway, the home GLH performs prenatal CMA analysis, however, in this study period, only four cases were declined testing or discontinued based on a CMA result. CMA analysis can be reliably performed using WGS data. If CMA analysis were replaced in every case using pGS, the cost of the pGS test could be up to £3,283 for the pGS pathway to be no more expensive than the pES pathway. Other savings, such as not having to re-sequence after delivery for reanalysis, have not been taken into consideration.

Financial costs to parents

Receiving healthcare comes with costs associated with travel to appointments as well as time taken away from work or childcare. The EXPRESS team explored these costs for parents in interviews undertaken in workstream 2. The location and ease of travel to the hospital for appointments, as well as flexibility in parents' working arrangements, may affect their ability to make an appointment. Parents interviewed by the EXPRESS team were not able to specifically attribute costs to pES. Parents with pregnancies complicated by fetal anomalies experienced frequent visits to hospitals for scans and monitoring. Typically, the pre-test discussion took place in person while attending hospital for a scan, with blood samples taken at the same time. Results were often returned remotely with no additional cost implications. Overall, it appears that costs for parents specifically for pES is minimal. However, this may be reflective of the parents interviewed in this study and may not reflect the experience of all parents offered pES.

Key findings

- The laboratory cost of pES contributes most to the overall cost of the pES test pathway and the model of service delivery has limited effect on the costs. Therefore, it was not possible to identify an optimal model of service delivery based on cost alone.
- Diagnostic yield and changed clinical management are important metrics when determining the cost-effectiveness of pES. Both diagnostic findings and 'no finding' from pES can result in a change in management.

- Future research should explore the clinical implications of pES in preventing the diagnostic odyssey and implications for savings from diagnosis-informed neonatal management.
- For parents, pES does not usually result in any additional costs as they are already attending hospital for additional appointments and tests.

3.6. Developing an optimal prenatal sequencing pathway

Objective 7: Determining the key features that constitute the optimal prenatal ES pathway.

A key aim of the EXPRESS project was to identify the optimal prenatal ES pathway to form the foundation of any future recommendations on service delivery.

An optimal care pathway would maximise the benefits for parents while optimising use of NHS resources. However, the cost of delivery was found not to vary substantially between the different current models of delivery. This is mostly because the cost of the pES laboratory testing is the major contributor to overall cost and, as a result, variation in the types of HCP involved did not greatly impact costs. Other key outcomes could be used to answer the question of what constitutes optimal service delivery. These outcomes should consider the whole test pathway, from referral through to outcomes of pregnancy and for the fetus.

Assessment of clinical outcomes in the EXPRESS study was limited by the small sample size, particularly when comparing GLH regions, and there were limitations in the data available on pregnancy outcomes. A larger referral sample size will clarify any true differences in models of service delivery and what this might relate to. However, it was clear that not all families have timely access to the expert fetal medicine and clinical genetic expertise required for an optimal service.

4. Future outlook and recommendations

The EXPRESS study has identified a number of recommendations for current service delivery and key research questions that will inform the test pathway.

4.1. Recommendations for current service delivery

The EXPRESS study identified recommendations, which if taken up, could lead to improvements in service delivery and experiences of parents, while making better use of limited resources for service delivery.

Recommendations to optimise the pES test pathway:

- Promote closer collaboration and communication between FM, CG and laboratory teams through regular joint MDT meetings, joint clinics or embedding CG staff in FM units.
- Improvements to IT systems, for example to support sharing of documentation and monitoring tests status, would streamline pathways with potential to shorten time-to-results.
- Better use of virtual systems to promote communication between specialties and peripheral units is needed and could be delivered via remote MDTs. A national network of MDTs, building on existing good practice in some areas, and run across regions, would enable access to expert care from all relevant experts, including prenatal genomics and expert fetal phenotyping (prenatal imaging) from FM and CG clinicians. This approach may particularly benefit peripheral units who do not have this expertise, or access to it, in their local clinical team, and allows parents access to the required expertise without the need to travel outside their region.
- FM networks should encourage greater participation of peripheral units through MDT and educational meetings across the GLH region and nationally, particularly to improve awareness and understanding of the prenatal sequencing service.
- Further education is needed to improve genomic literacy in FM staff and there is a need for more clinical geneticists with expertise in prenatal genomics. Specific training resources, for example via the NHS England Genomics Education Programme and speciality registrar and specialist midwifery training, could help to meet these needs. Virtual MDTs would also provide an educational forum accessible by HCPs with less exposure to genomics or prenatal genomics expertise.
- Improvements in existing resourcing of pES and additional staff group involvement could reduce the administrative workload for clinicians, i.e. administrative staff or genomics associates, could address limited staff time by reducing the administrative burden on senior staff.

- National guidelines need to be expanded in a number of ways, including:
  - Recognition of the acceptability of local variation and what elements of the pathway should not vary, for example access to expert fetal ultrasound for phenotyping and expert prenatal genetic opinion and counselling.
  - Clear guidance on the review and updates of eligibility criteria.
  - Roles and responsibilities of HCPs in the pES pathway.

Recommendations to improve support for parents undergoing pES:

- Pre-test counselling needs to be detailed and ensure parents have clear expectations of what pES involves with signposting to appropriate support. This should be included in pre-test information provided to parents and through active discussion with a well-informed HCP.
- Parents should be given a clear point of contact to provide ongoing support throughout the testing pathway. This could be delivered by genetic counsellors or fetal medicine midwives trained in genomics.
- Interpretation of results and post-test counselling should be personalised and draw on both pES findings and other information sources including fetal imaging.
- Clear care guidelines are needed for post 24-week terminations, so parents can be appropriately counselled. This should be informed by the experiences of HCPs and included in clinical guidelines by relevant bodies.
- All parents should be provided follow-up care regardless of the test result.
- Parents should have access to information about pES in a range of formats, for example written, audio and visual, physical and electronic, and in different languages as required.

4.2. Recommendations for future research opportunities

There are outstanding questions to be addressed in future research to inform future delivery of the pES service.

Identification and referral of parents

- Limitations in study design prevented analysis that estimated how many parents are being missed, who may be eligible for pES testing and in which units. Future research is needed which will inform targeted policies to address these gaps.
- Although differences in diagnostic yield between GLH regions were identified, sample size in the analysis of clinical outcomes limited analysis of differences in outcomes between regions and future research with larger datasets is needed.
- The majority of parents recruited for interviews self-reported as white/white British and educated to degree-level and predominantly had opted for pES testing. Research is needed to capture the views and experiences of parents from diverse backgrounds and those who declined pES.

- Future research could focus on engaging with underserved populations to inform pathway design. Studies are in development to explore the views of people from different ethnic or cultural backgrounds to gain better insight into the factors that influence their decision making around pES.

Pre-test and consent discussions

- Further evaluation is needed to explore the value of the animation when offered in a clinical setting and when available in a range of different languages to determine if this tool facilitates the pre-test and consent discussions.
- Further attention should be given to other resources which could facilitate pre-test and consent discussions, with particular attention to the needs of FM professionals with less experience of discussing pES.

Testing pathway

- Build on lessons learned from EXPRESS to agree the core components of the optimal pES care pathways ensuring equity of access to the relevant experts, FM and prenatal CG, for all parents regardless of where they live.
- Explore the use of a national network of hybrid MDTs with remote IT access for expert image review discussion and prenatal clinical genetic input to promote equity of access to relevant expertise.
- Equity of referrals should be reviewed by auditing cases seen in FMs or referring obstetric units to determine which are and which are not being considered for pES, with reasons for the decision. This would be useful to identify where there are gaps in awareness of pES or service variations when applying eligibility criteria.
- Audit of entire care pathways to identify areas for streamlining to reduce turn-around times. This would allow parents more time for decisions and to reduce the additional stress of pES results coming at or after 24 weeks.
- Diagnosis during the prenatal period is predicted to avoid the diagnostic odyssey and improve clinical management in the neonatal period leading to cost benefits for parents and the health system. Future research needs to explore how this evidence can be better captured to inform health economic analysis.

Return of results

- Variants of uncertain significance and incidental findings are a key reason for uncertainty for parents having genomic testing. Research is needed to understand the impact of these results on parents, and to inform guidance for HCPs on including these potential findings in consent discussions.

Parental support through the testing journey

- The feasibility and benefit of a dedicated point of contact for parents should be assessed and other options should be explored to ensure parents feel supported at all stages of the test pathway, while considering the existing workload of clinical staff.
- Parents should be signposted to specialist parent support services, such as those provided by Antenatal Research and Choices.

5. Conclusion

The EXPRESS study was a mixed-methods study that explored the implementation of the national pES service in England. PPIE was embedded in all aspects of the study. Parents and HCPs welcomed the introduction of pES and key areas for improvement have been highlighted. These included better support of parents throughout the test pathway regardless of the test result, improved service delivery through education of HCPs, a review of workforce requirements, and better use of technology to remove administrative burden. This will facilitate communication between teams and enable parental access to all expertise required. Implementation of these changes could inform the development of optimal care pathways that will ensure that the evolving pES service will provide equity of access, high standards of care, and benefits for parents across England.

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7. Appendix

7.1. EXPRESS project publications and outputs

Project protocol, engagement and approach to PPIE:

- Hill M., Ellard S., Fisher J., Fulop N., Knight M., Kroese M., Ledger J., Leeson-Beevers K., McEwan A., McMullan D., Mellis R., Morris S., Parker M., Tapon D., Baple E., Blackburn L., Choudry A., Lafarge C., McInnes-Dean H., Peter M., Ramakrishnan R., Roberts L., Searle B., Smith E., Walton H., Wynn S. L., Han Wu W., Chitty L. S. (2022). "Optimising Exome Prenatal Sequencing Services (EXPRESS): a study protocol to evaluate rapid prenatal exome sequencing in the NHS Genomic Medicine Service." NIHR Open Res 2: 10.
- Hunter A., Lewis C., Hill M., Chitty L. S., Leeson-Beevers K., McInnes-Dean H., Harvey K., Pichini A., Ormondroyd E., Thomson K. (2023). "Public and patient involvement in research to support genome services development in the UK." Journal of Translational Genetics and Genomics 7(1): 17-26.

Workstream 1: Implementation defining clinical care pathways

- Walton H., Daniel M., Peter M., McInnes-Dean H., Mellis R., Allen S., Fulop N. J., Chitty L. S., Hill M. (2025). "Evaluating the Implementation of the Rapid Prenatal Exome Sequencing Service in England." Public Health Genomics 28(1): 34-52.
- Peter M., Mellis R., McInnes-Dean H., Daniel M., Walton H., Fisher J., Leeson-Beevers K., Allen S., Baple E. L., Beleza-Meireles A., Bertoli M., Campbell J., Canham N., Cilliers D., Cobben J., Eason J., Harrison V., Holder-Espinasse M., Male A., Mansour S., McEwan A., Park S. M., Smith A., Stewart A., Tapon D., Vasudevan P., Williams D., Wu W. H., Chitty L. S., Hill M. (2024). "Delivery of a national prenatal exome sequencing service in England: a mixed methods study exploring healthcare professionals' views and experiences." Front Genet 15: 1401705.

Workstream 2: Parental views and experiences of pES

- Peter M., McInnes-Dean H., Fisher J., Tapon D., Chitty L. S., Hill M. (2022). "What's out there for parents? A systematic review of online information about prenatal microarray and exome sequencing." Prenat Diagn 42(1): 97-108.
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- Daniel M., McInnes-Dean H., Han Wu W., Fisher J., Lafarge C., Leeson-Beevers K., Lewis C., Peet S., Tapon D., Wynn S. L., Chitty L. S., Hill M. and Peter M. (2025). Can an animation improve parents' knowledge and how does it compare to written information? Development and survey evaluation of an animation for parents about prenatal sequencing. Manuscript under review
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Workstream 3: Service outcomes and factors associated with variation in outcomes

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Workstream 4: Ethical evaluation

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Workstream 5: Health economics evaluation

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7.2. Acknowledgements

7.2.1. EXPRESS study delivery

Thank you to the parents and professionals who took part in an interview or survey.

Thank you to the laboratory teams delivering pES at Central and South GLH and North Thames GLH for their support of the EXPRESS study.

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Holly Walton	Senior Research Fellow	University College London
Wing Han Wu	Research Project Manager	Great Ormond Street Hospital NHS Foundation Trust

7.2.2 EXPRESS study oversight

Study Steering Committee

Professor Jenny Hewison (Chair)	Professor of the Psychology of Healthcare	University of Leeds
Ms Rebecca Al-Ausi	Programme ManagerNHS Fetal Anomaly Screening Programme	NHS Fetal Anomaly Screening
Professor Zarko Alfirevic	Professor	University of Liverpool
Ms Siobhan Alt	Project Lead - Fetal Anomaly Screening Programme	NHS Fetal Anomaly Screening
Professor Sandi Deans	Deputy Director Genomic Unit	NHS England

Dr Frances Elmslie	Consultant Clinical Geneticist & Care Group Lead	St George's University Hospitals NHS Foundation Trust and Clinical Director – South East Genomic Medicine Service Alliance
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Professor Anneke Lucassen	Professor of Genomic Medicine	University of Oxford
Ms Annette McHugh	Fetal Anomaly Screening Programme	NHS Fetal Anomaly Screening
Professor Rosamund Scott	Professor of Medical Law and Ethics	Kings College London
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Ms Jane Fisher (Chair)	Director	Antenatal Results and Choices (ARC)
Professor Caroline Lafarge	Professor of Psychology	University of West London
Ms Kerry Leeson-Beevers	Chief Executive	Alström Syndrome UK, Breaking Down Barriers
Ms Sophie Peet	Director of Engagement and Support	Genetic Alliance UK
Ms Lauren Roberts	Director of Engagement and Support	Genetic Alliance UK
Dr Sarah Wynn	Chief Executive Officer	Unique

7.3. Record of discussion form

Patient Name	
Date of Birth:	
Medical record Number:	
NHS Number:	

NHS
North Thames
Genomic Laboratory Hub

Record of discussions form to summarise clinical consent

This form relates to the person being tested.
All of the statements below remain relevant even if the test relates to someone other than yourself, for example your child or dependent.

I have discussed genetic testing with my health professional and understand that:

Family implications
1.The results of my test may have implications for me and members of my family. I understand that my results may also be used to help the healthcare of members of my family.

Uncertainty
2. The results of my test may have findings that are uncertain and not yet fully understood. To decide whether findings are significant for myself or others, my data may be compared anonymously with other patients' results across the country and internationally. I understand that this could change what my results mean for me and my treatment over time.

Unexpected information
3. The results of my test may also reveal unexpected results that are not related to why I am having this test. These may be found by chance and I may need further tests or investigations to understand their significance.

DNA storage
4. Normal NHS laboratory practice is to store the DNA extracted from my sample even after my current testing is complete. My DNA might be used for future analysis and/or to ensure that other testing (for example that of family members) is of high quality.

Data storage
5. The data from my test will be securely stored so that it can be looked at again in the future if necessary.

Health records
6. Results from my genomic test will be part of my patient record, a copy of which is held in a national system only available to healthcare professionals.

Note of other specific issues discussed
(*e.g. referral to particular research programmes, insurance*):

For any further questions, my healthcare professional can provide information. More information regarding genetic testing and how my data is protected can be found at https://www.nhs.uk/conditions/genetics/.

Please sign on page 2 to confirm your agreement to testing.

Patient Name	
Date of Birth:	
Medical record Number:	
NHS Number:	

NHS
North Thames
Genomic Laboratory Hub

I agree to genetic/genomic investigations*:

_____

**insert details here, e.g. to investigate the cause of my child's developmental delay / family history of cancer /heart disease etc*

Patient/parent signature: _____

Patient/parent name**:** _____

Date**:** _____

Discussion undertaken by: _____

Clinician Signature: _____

Clinician Name: _____

Consultant's name (if different from the above): _____

Date: _____

Genetics Reference Number: _____

☐ Recorded remotely by clinician, no patient signature

1 copy for notes, 1 copy for patient to retain

PHG FOUNDATION

making science work for health

The PHG Foundation is a non-profit think tank with a special focus on how genomics and other emerging health technologies can provide more effective, personalised healthcare and deliver improvements in health for patients and citizens.

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