Optimising rapid prenatal exome sequencing in the NHS genomic medicine service: the EXPRESS Synopsis

Optimising rapid prenatal exome sequencing in the NHS genomic medicine service: the EXPRESS Synopsis

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Abstract

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

Objective: To evaluate the new pES service to provide evidence that will inform improvements to quality of care and equity of access for parents having prenatal tests.

Design and methods: Our theoretically driven, multi-site, convergent parallel mixed-methods study design combined qualitative analyses of the service, stakeholder perspectives and ethical considerations with quantitative analyses of staff experiences, clinical outcomes and cost effectiveness.

Our final data-set included interviews with parents offered pES (n=48) and professionals (n=63), surveys with professionals (n=159) and data from pES testing referrals between October 2021 and June 2022 (413 referrals and 241 pES tests) linked to National Congenital Anomaly and Rare Disease Registration Service data and the Maternity Services Data Set.

The study had oversight from a Steering Group and a Patient and Public Involvement Advisory Group. The PPIAG contributed to study design, developing study materials and interpreting findings.

Results: Parents and professionals welcomed the introduction of a national pES service. Parents need emotional support across the testing journey, including follow-up care. A newly developed prenatal sequencing animation increased self-reported and objective knowledge of pES. Good communication and close working between genetics, fetal medicine and laboratory teams has supported successful implementation. Challenges for service delivery included increased administrative time and gaps in genomics education, particularly for midwives and fetal medicine clinicians. Local implementation varied in leadership, staffing and approaches to multidisciplinary team working. Ethical issues centred on barriers for equity of access and the intersecting timelines of pES testing and termination of pregnancy laws. Between October 2021 and June 2022 the diagnostic yield for pES was 35% (85/241) with a

median turnaround time of 15 days to the final report. For 85 women who had a diagnosis, 40% had a termination of pregnancy, 18% had a stillbirth, and 42% had a live birth. For women with a no findings result, 18% had a termination of pregnancy, 5% had a stillbirth and 78% had a live birth. The median gestational age at termination was 26 weeks. Total NHS costs for the 413 cases in the study period, with the most common staffing model, was £962,727 (£775,454 to £1,204,027, 95% credibility interval), or £2,331 per case referred and £3,592 per case that proceeded with testing.

Limitations: Our parent interview sample lacked diversity, with most being White/White British and educated to degree level or above. Details on pES service pathways from smaller units have not been captured. Assessment of variation in outcomes was restricted by the relatively small sample size of pES tests in the study period.

Conclusions: This is the first study to explore the implementation of the national pES service in England. Our findings will inform the evolving pES service to ensure equity of access, high standards of care and benefits for all parents.

Future work: Future research should include gathering the views and experiences from parents from diverse backgrounds, evaluating the prenatal sequencing animation in clinical practice and building on EXPRESS to identify and agree optimal care pathways that will ensure equity of access for all parents.

Registration: Research Registry (researchregistry6138).

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Contents

List of tables

List of figures

List of abbreviations

CMA	Chromosomal microarray analysis
CNV	Copy number variant
COG	Clinical oversight group
FM	Fetal medicine

FMU	Fetal medicine unit
GLH	Genomic Laboratory Hub
GMS	Genomic Medicine Service
GMSA	Genomic Medicine Service Alliances
IMD	Index of Multiple Deprivation
IPD	Invasive prenatal diagnosis
MDT	Multi-disciplinary team
MSC	Major Systems Change
MSDS	Maternity Services Data Set
NCARDRS	National Congenital Anomaly and Rare Disease Registration Service
NHS	National Health Service
pES	Prenatal Exome Sequencing
pGS	Prenatal Genome Sequencing
PPIAG	Patient and Public Involvement Advisory Group
VUS	Variants of uncertain significance

Plain language summary

Rapid prenatal exome sequencing is a test that has been offered by the NHS since October 2020. It is offered to pregnant women when ultrasound scans suggest their baby may have a genetic condition. Prenatal exome sequencing can diagnose genetic conditions by looking closely at the genome, which is the body's 'instruction manual'. The exome is the part of the genome where the changes that explain genetic conditions are most often found.

Our research has looked at testing across England to find out what information and support parents need, whether all parents can access the test, the usefulness of results and what further training healthcare professionals might need. An advisory group, with representatives of patient support organisations and parents with relevant experiences, contributed to designing the study, developing study materials and interpreting findings.

We spoke with 48 parents. Parents were grateful to be offered testing, but needed expert support and counselling as there is a lot of information to take in at a very stressful time. They needed emotional support across their testing journey, including access to support after being told their results.

We developed an animation that described prenatal exome sequencing, tested it with 428 parents, and found that it improved parents' understanding of the test.

Interviews (63) and surveys (159) with professionals found that prenatal exome sequencing was useful for guiding pregnancy care. Good communication between clinical teams helped the testing service to run smoothly. Offering testing increased staff workload and some professionals need more education around genetics. Looking at information over nine months, 241 tests were conducted and 85 (35%) provided a diagnosis.

Our findings will help professionals support parents and ensure that they receive high quality care. Summaries of findings will be shared with professionals, policy makers and the social media networks of support organisations.

1 Introduction

Following reports of the potential benefits of prenatal exome sequencing (pES),[1-3] rapid pES for the diagnosis of fetal anomalies was implemented nationally in England in October 2020 by the NHS Genomic Medicine Service (GMS). pES has not previously been offered routinely in a national healthcare system. The Optimising EXome PRenatal Sequencing Services (EXPRESS) study was a mixed-methods evaluation of the national pES service. The study had oversight from a Steering Group and a Patient and Public Involvement Advisory Group (PPIAG). At the outset of EXPRESS we published a study protocol[4] and registered our research plans (researchregistry6138). The EXPRESS study website is: www.express-study.co.uk. In this synopsis we bring together the findings of our evaluation. Details of methods and findings are reported fully in our existing and planned outputs (Table 1).

Table 1 List of publications from the EXPRESS study

Citation
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 SL, Han Wu W, Chitty LS. Optimising Exome Prenatal Sequencing Services (EXPRESS): a study protocol to evaluate rapid prenatal exome sequencing in the NHS Genomic Medicine Service. NIHR Open Research. 2022 2:10. doi:10.3310/nihropenres.13247.2.
Peter M, McInnes-Dean H, Fisher J, Tapon D, Chitty LS, Hill M. What's out there for parents? A systematic review of online information about prenatal microarray and exome sequencing. Prenatal Diagnosis. 2022 42:97-108. doi:10.1002/pd.6066.
Hunter A, Lewis C, Hill M, Chitty LS, Leeson-Beevers K, McInnes-Dean H, Harvey K, Pichini A, Ormondroyd E, Thomson K. Public and patient involvement in research to support genome services development in the UK. Journal of Translational Genetics and Genomics. 2023 7:17-26. doi:10.20517/jtgg.2022.19
McInnes-Dean H, Mellis R, Daniel M, Walton H, Baple EL, Bertoli M, Fisher J, Gajewska-Knapik K, Holder-Espinasse M, Lafarge C, Leeson-Beevers K, McEwan A, Pandya P, Parker M, Peet S, Roberts L, Sankaran S, Smith A, Tapon D, Wu WH, Wynn SL, Chitty LS, Hill M,

Peter M. 'Something that helped the whole picture': Experiences of parents offered rapid prenatal exome sequencing in routine clinical care in the English National Health Service. Prenatal Diagnosis. 2024 44:465-479. doi:10.1002/pd.6537.

Peter M, Mellis R, McInnes-Dean H, Daniel M, Walton H, Fisher J, Leeson-Beevers K, Allen S, Baple EL, 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 SM, Smith A, Stewart A, Tapon D, Vasudevan P, Williams D, Wu WH, Chitty LS, Hill M. Delivery of a national prenatal exome sequencing service in England: A mixed methods study exploring healthcare professionals' views and experiences. Frontiers in Genetics. 2024 15:1401705. doi:10.3389/fgene.2024.1401705.

Walton H, Daniel M, Peter M, Mellis R, Allen S, Fulop NJ, Chitty LS, Hill M. Evaluating the implementation of the rapid prenatal exome sequencing (pES) service in England. Public Health Genomics. 2025 28:34-52. doi:10.1159/000543104.

Peter M, Hill M, Fisher J, Daniel M, McInnes-Dean H, Mellis R, Walton H, Lafarge C, Leeson-Beevers K, Peet S, Tapon D, Wynn SL, Chitty LS and Parker M. Equity and timeliness as factors in the effectiveness of an ethical prenatal sequencing service: reflections from parents and professionals. Eur J Hum Genet. 2025 33:360-367. Doi:10.1038/s41431-024-01700-0.

Ramakrishnan R, Mallinson C, Hardy S, Broughan J, Blythe M, Melis G, Franklin C, Hill M, Mellis R, Wu WH, Allen A, Chitty LS, Knight M, EXPRESS Clinical Outcomes Group. Implementation of a national rapid prenatal exome sequencing service in England: Evaluation of service outcomes and factors associated with regional variation. Front Genet. 2024 6;15:1485306. doi: 10.3389/fgene.2024.1485306

Daniel M, McInnes-Dean H, Wu WH, Fisher J, Lafarge C, Leeson-Beevers K, Lewis C, Mellis R, Peet S, Tapon D, Wynn SL, Chitty LS, Hill M, Peter M. Development and survey evaluation of an animation for parents about prenatal sequencing: Can an animation improve parents' knowledge and how does it compare to written information? Prenat Diagn. 2025 Apr 2. doi:10.1002/pd.6792. Online ahead of print.

Smith E, Hill M, Wu WH, Peter M, Mellis R, Allen, S. Mallinson C, Hardy S, Chitty LS and Morris S. Implementation of a national prenatal exome sequencing service in England: an economic evaluation. BJOG. 2025 132(4):483-491. doi:10.1111/1471-0528.18020.

1.1 Context and Rationale

It is now well established that pES can increase the likelihood of finding a diagnosis during pregnancy when a structural anomaly has been identified on ultrasound and other prenatal tests, such as karyotype, chromosomal microarray are uninformative.[1, 2, 5] In unselected pregnancies with a structural anomaly, pES can improve the diagnostic yield by 8-10%.[1, 2] Factors such as limiting testing to specific phenotypes, opting for trio (fetus and both genetic parents) versus singleton (fetus only) sequencing, and selecting cases with a greater likelihood of a genetic basis through multi-disciplinary review further increases diagnostic yield.[5, 6] The clinical utility of pES has been demonstrated[3, 7, 8] and there is growing evidence that results from pES are being used to guide counselling about prognosis, direct clinical management during pregnancy, birth and the neonatal period, inform parental decision making about whether to continue the pregnancy, and provide recurrence risks for future pregnancies.[9-11]

In recent years the English NHS has advanced rapidly towards the goal of delivering 'the most advanced genomic healthcare system in the world'.[12] With the launch of the NHS GMS in 2018, the NHS in England became the first national healthcare system to embed genomic medicine into routine clinical care.[13] Testing is delivered through seven regional Genomic Laboratory Hubs (GLHs) and Genomic Medicine Service Alliances (GMSAs). The GLHs and GMSAs work closely with a network of 17 Clinical Genetic Services that provide specialist support to clinicians and patients in their region. All genomic tests available through the NHS are listed in the National Genomic Test Directory with a specific "R number".[14] pES for the diagnosis of fetal anomalies is listed as R21 in the National Genomic Test Directory.

The rapid pES service was launched in October 2020. pES is offered to parents when anomalies identified on fetal imaging are considered likely to have a genetic aetiology and a diagnosis could impact pregnancy, labour or neonatal management, as determined by a multidisciplinary team that includes fetal medicine experts and clinical geneticists.[13] Testing is preferably performed as trio sequencing (fetus and both genetic parents) with analysis currently using a panel of more than 1300 genes. The preliminary results should be returned within two weeks, with the final report within three weeks. Incidental findings with

implications for child or parental health, or future reproductive choices are reported, but additional findings, for example cancer susceptibility genes, are not looked for. Variants of uncertain significance (VUS) are reported in some circumstances when multidisciplinary team review considers minimal additional information during pregnancy or after birth would allow reclassification to pathogenic. An overview of the general pathway for delivering pES is provided in Figure 1.

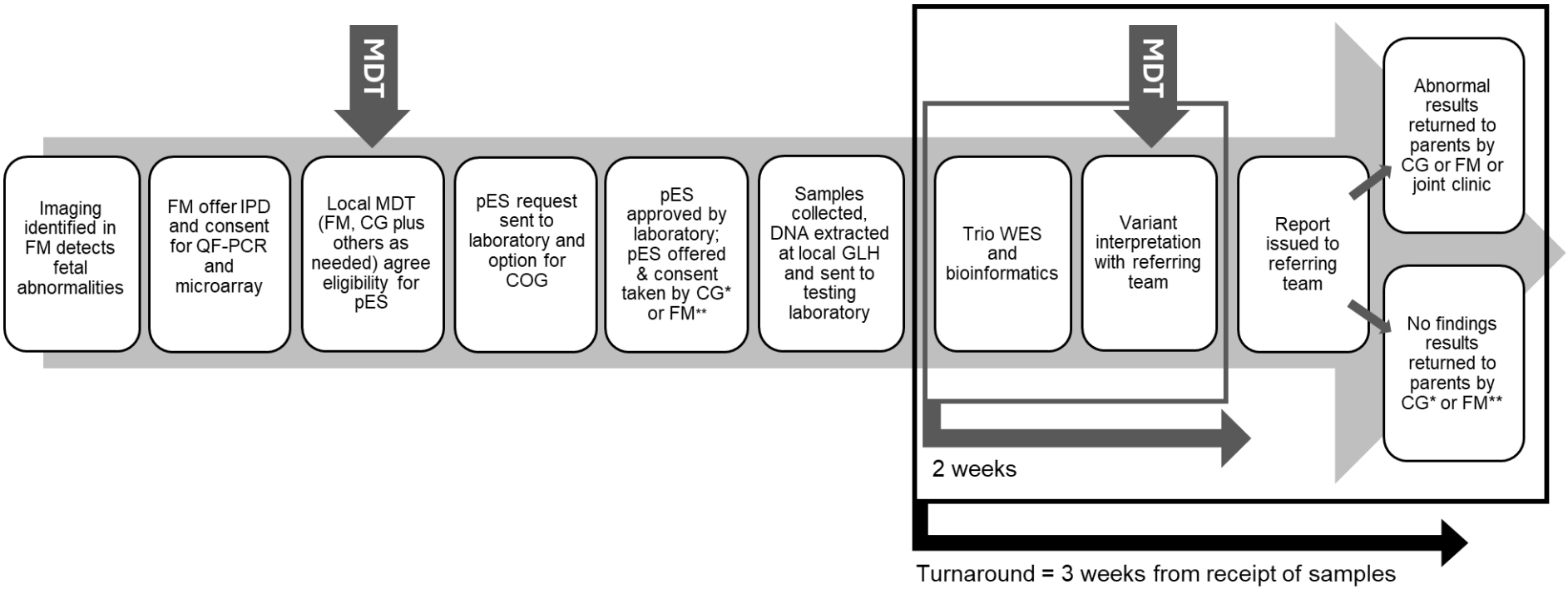

Figure 1 Overview of the pES pathway. Adapted from Peter et al.[15] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The Figure includes minor additions and formatting changes to the original. MDT = Multi-disciplinary team, FM = Fetal medicine, IPD = Invasive prenatal diagnosis, QF-PCR = quantitative fluorescent-polymerase chain reaction, CG = Clinical genetics, COG = Clinical oversight group, GLH = Genomic laboratory hub, WES = Whole exome sequencing; * = may include genetic counsellors; ** = may include midwives

The introduction of an innovative technology such as pES into an already complex healthcare system is likely to bring multiple challenges, and professional bodies have highlighted the many practical issues to consider when implementing pES services.[16-18] In addition, while research gathering parent or professional views has generally found support for offering pES, these studies have also highlighted concerns over the potential for increased parental anxiety, challenges ensuring informed consent, uncertain results and costs.[19-24] Previous research has also demonstrated that implementation of innovations and/or new health services,[25-28] including genomic services,[29, 30] can vary substantially when implemented in different local contexts due to the need to make changes at system, organisational and individual levels.[30] The EXPRESS study has been a unique opportunity to evaluate the pES service alongside implementation and give feedback to the service to support high quality care for parents and facilitate delivery of an equitable and efficient national service.

1.2 Aims and Objectives

The aim of EXPRESS was to conduct a formative and summative mixed-methods evaluation of the new rapid pES service to deliver feedback that will inform national delivery of an equitable, acceptable, ethical, robust and cost-effective care pathway to inform improvements to quality of care for parents undergoing prenatal diagnosis in fetuses with anomalies likely to have a genetic aetiology.

Our objectives were to:

A. Determine the clinical care pathways for pES in each of the seven GLHs (Workstream 1).
B. Establish whether pES is understandable and acceptable to key stakeholders including parents (Workstream 2) and professionals (Workstream 1).
C. Identify education and information needs and how they are best addressed for parents (Workstream 2) and health professionals (Workstream 1).
D. Establish the service (diagnostic yield, referral rates, and sources of referral) and pregnancy outcomes of the pES service (Workstream 3), compare these between GLHs,

and identify individual or service-related factors associated with variation in outcomes (All Workstreams).

E. Identify any ethical issues arising from offering pES in the NHS and explore how professionals can best be supported in addressing them (Workstream 4).
F. Evaluate the cost and cost-effectiveness of implementing the optimal pES pathway (Workstream 5).
G. Determine the key features that constitute the optimal pES pathway from a service delivery, patient and professional perspective (All Workstreams).

Please not that our Aims and Objectives were previously described in our published study protocol.[4] The text has been reproduced from Hill et al.[4] The text above includes minor additions and formatting changes to the original text

2 Methods

EXPRESS comprised five interrelated workstreams, as described in our study protocol[4] and detailed in Figure 2. The objectives and methods of each workstream are outlined below.

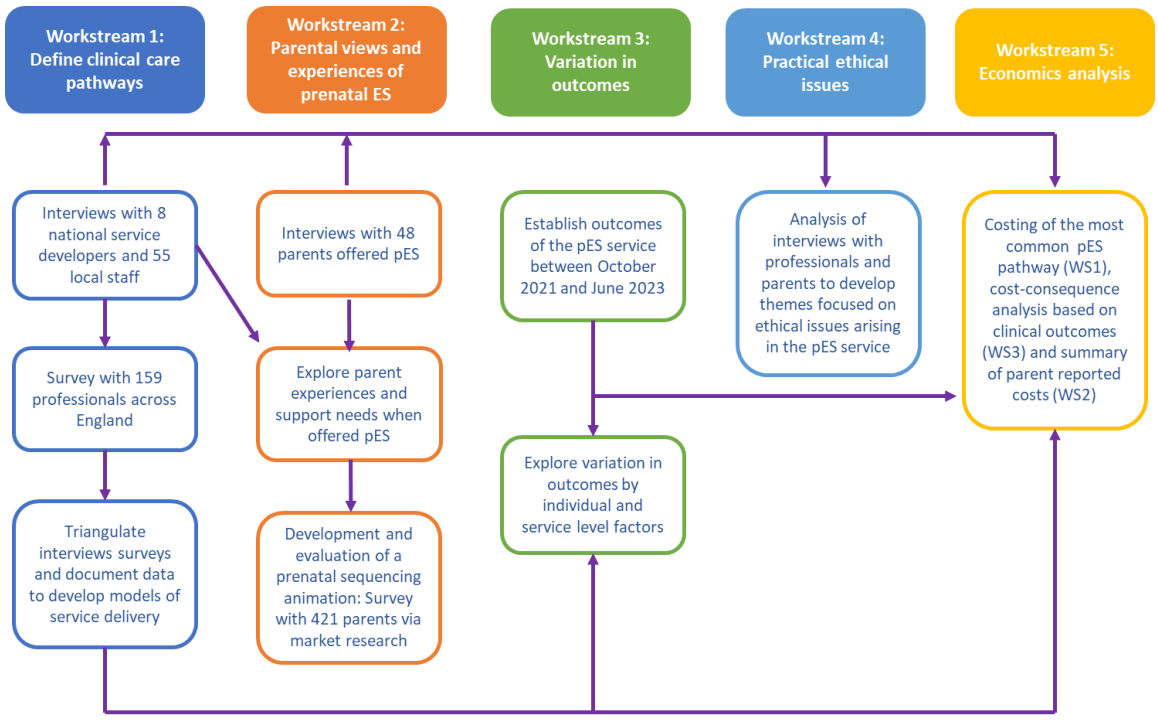

Figure 2 Overview of the EXPRESS study

2.1 Setting

EXPRESS focused on the national implementation of pES within the English GMS. The GMS is a national genomic testing service that is delivered through a network of seven GLHs. Each GLH coordinates services for a particular geographical region in England (Appendix 2 – Figure 8). Laboratory testing is performed at two GLHs (North Thames GLH and Central and South GLH). There are 17 clinical genetics services in England (two or three per GLH) who work with their local fetal medicine and obstetric specialists to deliver the pES service. The fetal medicine and obstetric specialists may work within fetal medicine units (FMUs) at tertiary hospitals or see patients at smaller District General Hospitals.

We had initially planned to evaluate how the pES service had been implemented from the perspective of the seven GLHs, however, when data collection commenced it became clear that care-pathways had been decided at the level of the 17 genetics services rather than the overarching GLHs. We therefore adapted our study to look at implementation from the perspective of 17 sites.

2.2 Study design and theoretical framework

EXPRESS is a multi-site, mixed-methods evaluation of how pES has been implemented in the NHS GMS. Mixed methods approaches are frequently used to characterise complex healthcare systems as comparing the results of multiple data sets provides a more complete understanding of the topic.[31] A convergent mixed methods design with data collection conducted in parallel was used.[32, 33] Our study design incorporates the Major System Change (MSC) framework, which was developed to evaluate the implementation of innovative new services in the NHS.[34-36] The framework addresses the "how and why" of system innovation and "what works and at what cost" by considering key processes in implementing a new service across five domains: decision to change, decision on which model to implement, implementation approaches, implementation outcomes and intervention outcomes (e.g. evidence based care, clinical outcomes, parent experiences and costs and consequences).[34, 36] To consider the relationship between implementation outcomes and intervention outcomes against the MSC framework, data was triangulated for analysis and comparison (Section 3.9). See Figure 3 for an overview of the data used to explore the MSC framework domains.

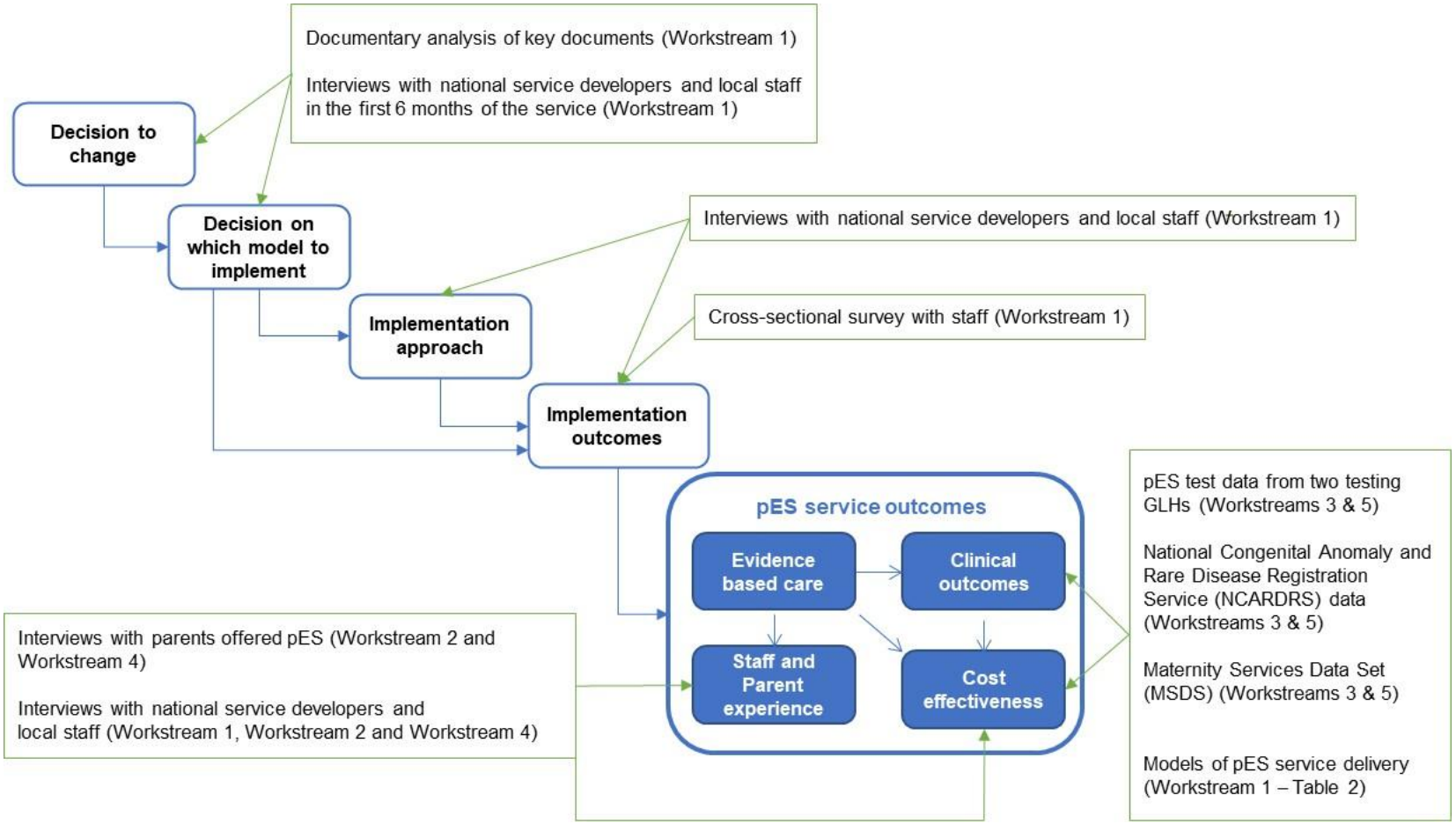

Figure 3 Overview of the Major system change (MSC) framework[35] and data sources used in this study. Figure adapted from Walton et al.[37] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The Figure includes minor additions and formatting changes to the original.

2.3 Workstreams

2.3.1 Workstream 1: Define clinical care pathways and identify facilitators, barriers and unintended consequences

Objectives:

a. Gain a detailed understanding of the pES care pathways across the seven GLHs
b. Examine the implementation processes that emerge in practice
c. Gather professional perspectives of any implementation issues

Interviews with professionals

Interviews targeted professionals working in clinical genetics, fetal medicine and clinical science involved in designing ("national service developers") or in delivering ("local staff") the pES service. Professionals were identified by the researchers and invited to take part in an interview via email. Written or audio-recorded verbal consent was obtained prior to each interview. The interview topic guide explored experiences of the pES service, care pathways, challenges for service delivery, goals for the service, education needs and parental experiences. Of 134 professionals invited to participate, 63 agreed, including clinical geneticists (*n*=24), genetic counsellors (*n*=6) fetal medicine clinicians (*n*=21), fetal medicine midwives (*n*=6) and clinical scientists (*n*=5) (response rate: 57%). Interviews were conducted between November 2020 and December 2022 and lasted between 23 and 80 minutes (median duration 44 minutes). Interviews were audio-recorded and transcribed verbatim. Analysis followed the principles of thematic analysis[38] and used a team-based codebook approach.[39] Rapid assessment procedure sheets (RAP sheets)[40] framed around the MSC Framework[35] domains were populated for each of the 17 sites and used to develop a summary of themes and subthemes that informed codebook development. Coding used both inductive and deductive approaches.[41] Analysis was facilitated by NVivo 13 (Lumivero, Denver, CO, USA).

Surveys with professionals

Professionals from genetics, fetal medicine and obstetric backgrounds involved in offering pES were identified by the clinical leads for the R21 service at the 17 clinical genomics services. These potential participants were emailed a study invitation, participant information

sheet and a link to the online survey (hosted by SurveyMonkey). Three reminder emails were sent. The survey was open from 21/03/2022 until 4/05/2022. From 280 invitations, 159 surveys were completed by genetics (*n*=73) and fetal medicine (*n*=86) professionals (response rate: 57%). Closed-text items assessed demographic information, views on the pES service, pES impact on administrative and clinical time, awareness of guidelines and policies, eligibility criteria knowledge and educational needs and preferences. Open-ended items allowed detailed feedback. Independent *t*-tests, chi-squared associations of independence and two proportions *z*-tests were used to assess differences between groups. All analyses were conducted using R 4.0.2.[42]

Integration of findings to define implementation models

Data from key documents, interviews and surveys were triangulated by imputing findings from each site into a care pathway spreadsheet that included referral, consent, testing and return of results. These findings were used to develop models of local pES implementation. Models were checked by a local clinician from each site. The models were used to compare factors influencing implementation between sites (Section 3.1), examine service-related factors associated with variation in clinical outcomes (Section 3.6), and explore impacts of staffing on costs (Section 3.8).

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2.3.2 Workstream 2: Parental views and experiences of pES

Objectives:

a. Explore parent experiences and support needs when offered pES
b. Evaluate an animation developed as an information resource for parents offered pES.
c. Explore the reasons parents decline pES

Interviews with parents

Parents over 18 years who had been offered pES were recruited through Antenatal Results and Choices (ARC) and FMUs at six NHS hospitals across five GLHs. Parents were offered a £10 gift voucher to thank them for their time. Written or audio-recorded verbal consent was obtained prior to each interview. Forty-two interviews were conducted with 42 women and

six male partners by telephone (n=17) or video call (n=25) between October 2021 and May 2023. Interviews lasted between 18 and 113 minutes (median duration 46 minutes).

The interview topic guide explored experiences with pES, information and support needs, benefits and concerns and impact of pES results on decisions to continue or terminate the pregnancy. Interviews were audio-recorded and transcribed verbatim. Notes were taken for one interview where the parent declined audio-recording. Analysis and coding were facilitated by NVivo version 13 (Lumivero, Denver, CO, USA). Analysis followed the principles of thematic analysis[38] and used a team-based codebook approach[39] that included inductive and deductive approaches.[41] As the themes from the parent interviews were reviewed and revised, they were compared to themes from the professional interviews (Section 2.3.1) that related to parent experiences of pES.

Development and evaluation of a prenatal sequencing animation

An animation describing prenatal sequencing was developed to support parents' decision-making when offered prenatal sequencing tests. Animation development was collaborative with the PPIAG, parents offered prenatal testing, and clinicians (genetic counsellors, clinical geneticists, clinical scientists, fetal medicine consultants and fetal medicine midwives). There were three development phases: 1) content and script development, 2) script and storyboard development, and 3) animation development (Figure 4).

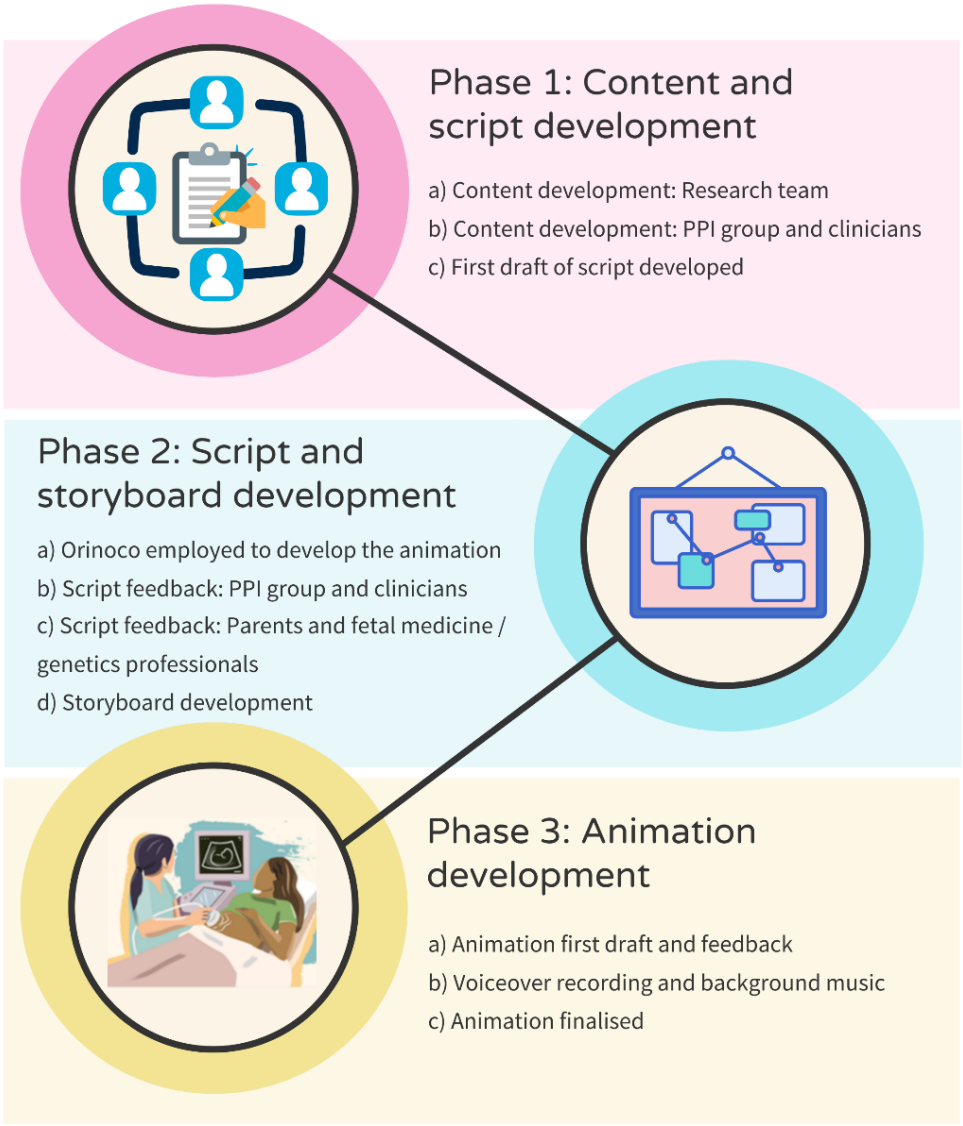

Figure 4 Overview of animation development. Reproduced from the supplementary material in Daniel et al.[43] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/.

The animation was evaluated to: 1) determine if the animation improves parents' knowledge and understanding of prenatal sequencing, 2) compare the effectiveness of the animation against a written leaflet with the same content, and 3) determine satisfaction with and perceived value of the animation and leaflet. Men and women aged over 18 years who had been pregnant in the previous two years were recruited through a market research company

(Dynata). Recruitment targets were set across a range of ethnic backgrounds, genders, and educational levels. Participants (n=428) were randomly assigned to receive one of three interventions: animation (n=153), leaflet (n=130), or animation plus leaflet (n=144). Participants completed a survey before the intervention (T1) and after the intervention (T2). The T1 survey included: demographic information (age, gender, ethnicity and education level), self-perceived knowledge and objective knowledge (12 knowledge questions that could be True, False or Don't know). The T2 survey included: self-perceived knowledge, objective knowledge, and satisfaction and value. Descriptive statistics were calculated and ANOVA, Spearman's correlation, Wilcoxon signed rank tests and ANCOVA and model comparisons were used for comparative analyses. All analyses were conducted using R 4.1.3.[42] Free text responses were grouped into "positive" or "negative" responses.

Case reviews: Exploring the reasons parents decline pES

Case reviews were conducted at three FMUs in England (two in London, one in the North of England) across a six-month period (01/03/2022 – 31/08/2022). Included cases were eligible for pES but this had not been pursued. A standardised data collection spreadsheet was used that included demographics, a brief description of phenotype, reasons pES was not pursued (Parents declined pES but chose an alternative test; parents declined invasive testing, fetal demise, other) and comments. Data were collated into a single anonymised data set for analysis with descriptive statistics.

Deviation from the protocol: we had anticipated that 8-10 FMUs would undertake case reviews, however, this was not possible due to restricted capacity in clinical teams. This limited the analyses undertaken. Furthermore, some demographic data, including ethnicity, was not routinely recorded. Thus any impact of demographic factors in parents declining pES cannot be evaluated.

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

Objectives:

a. Describe the number and characteristics of women giving birth in each GLH area,

b. Examine service (referral rate, diagnostic yield and sources of referral) and pregnancy outcomes of the pES service in each GLH area
c. Identify individual or service-related factors associated with variation in outcomes

Data description

The study period was 01/10/2021 to 30/06/2022. pES test data from the two testing GLHs was linked with data from the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)[44] and the Maternity Services Data Set (MSDS)[45] from NHS England and the clinical care pathway models identified in Workstream 1 (Section 3.1). In addition, data on all women who gave birth in England during the study period were obtained from MSDS to describe the number and characteristics of women giving birth in each GLH area annually and as the denominator for the computation of referral rate. Data linkage is described in Ramakrishnan et al.[46]

Individual-level characteristics included: woman's age, ethnicity, IMD quintiles (derived using the Lower Layer Super Output Area 2011 as reference and based on postcode of the woman at booking), complex social factors indicator (defined based on NICE guidance (CG110))[47] and gestational age (weeks) at pregnancy outcome.

Service-level characteristics included: sources of referral (who leads the service – fetal medicine only, genetics only or fetal medicine or genetics - based on service delivery models identified in Workstream 1 (Table 2)), turn-around time in days (number of days between sample receipt at the testing laboratory and issuing the final report) and gestational age (weeks) when the final report was issued.

Outcomes were: diagnosis (yes - at least one pathogenic or likely pathogenic variant reported or no - no pathogenic variant found or VUS reported) and pregnancy outcomes (termination (at any gestation), miscarriage (fetal loss under 24 weeks' gestation), stillbirth (fetal loss over 24 weeks' gestation), or live birth).

Analysis

The number of women giving birth in the GLH area annually (mapped based on births in referring units and their associated home births), the number of women referred for pES and the number proceeding with testing were calculated and their characteristics described using counts and percentages. Referral rates with 95% confidence interval were calculated. Among women who proceeded with pES, sources of referrals, diagnostic yield and individual- and service-related factors for diagnostic yield and pregnancy outcomes were described overall and by GLH using counts and percentages. Analyses were conducted using Stata v18.0, R 4.4, and DBeaver (for extraction of data from the NCARDRS Congenital Anomaly PostgreSQL database).

2.3.4 Workstream 4: Ethical analysis

Objective: Identify, characterise, and analyse ethical issues arising in the delivery of pES.

Data sources and analysis

A scoping review, an online workshop (16/04/2021) with participants from clinical genetics (n=11), fetal medicine (n=6) and clinical science (n=2) and a pES-focused UK Genethics Forum meeting (04/07/2022) were used to map likely ethical issues for further investigation. Data sources were qualitative interviews with professionals involved in delivering pES (n=63) (Section 2.3.1) and parents who have been offered pES (n=48) (Section 2.3.2). Thematic analysis was conducted as described in Section 2.3.2, with theme development focused on ethical issues arising in the pES service.

2.3.5 Workstream 5: Economic analysis

Objective: Assess the costs and cost-effectiveness of pES versus standard tests.

NHS costs

We identified the key processes of the "typical" clinical pathway to deliver pES based on the most common staffing model as identified by Workstream 1 (Table 2). We used data from the professional survey to calculate the average incremental resource used in each process including extra time spent discussing and taking consent for pES, number of additional

appointments and additional administration time. We applied unit staff costs based on published sources of NHS costs[48, 49] and estimated overheads. The cost of the pES test was calculated using costings obtained from the two testing GLHs that were prepared for the purpose of establishing reimbursement. We calculated (in 2021-22 UK pounds) the incremental cost to the NHS of delivering pES by applying the cost per case for each stage of the pathway to the number of cases proceeding through each stage (Section 2.3.3). We calculated the mean cost per pES referral by dividing total cost by total number of referred cases.

Families' costs

Interviews with parents (Section 2.3.2) included a section on the financial costs of pES to themselves and their family. Questions covered the format of appointments (i.e. in person or video/telephone consultation), travel, childcare arrangements and time off work. Findings are summarised.

Outcomes

Outcome data were used to identify the diagnostic yield, defined as identification of at least one pathogenic (or likely pathogenic) variant (Section 2.3.3). Additional analysis was performed using data from the two testing GLHs to look at additional outcomes including impact on clinical management, implications and/or affected parents' decisions regarding pregnancy continuation. We did not include pregnancy outcomes in our analysis because it was not possible to obtain data for a comparator cohort.

Cost-effectiveness analysis

We divided the incremental NHS cost by the number of cases that received a diagnosis and by the number of cases with reported changed management to ascertain the cost per outcome for each measure. We accounted for uncertainty in our model using probabilistic sensitivity analysis and calculated 95% credibility intervals. We conducted scenario analysis by modelling the costs and diagnostic yields of two alternative service delivery models, sub-categorising other models (Section 2.3.1), and for a high and low diagnostic yield.

Budget impact analysis

We obtained pES case numbers from the testing GLHs (01/10/2022 to 30/09/2023) to estimate the total annual incremental cost to the NHS of the pES service based on recent demand levels.

Threshold analysis comparing pES and pGS

Prenatal genome sequencing (pGS) may have additional benefits compared to pES including reduced turnaround time, more even sequencing coverage, ability to perform copy number variant (CNV) analysis and ability to detect disease-causing variants in non-coding regions.[50-52] We calculated the maximum cost at which pGS would be no more expensive overall than pES, taking account of the saving from ceasing parallel chromosomal microarray analysis (CMA) testing which would no longer be required if CNV analysis is performed. The mean cost of a prenatal CMA was calculated based on costings obtained from four GLHs.

3 Results

3.1 Evaluating the implementation of the pES service in England (Objectives A, C and H)

Evaluation of pES service implementation (Section 2.3.1),[37] used the first four domains of the MSC framework[34, 35] to explore the links between implementation approaches and implementation outcomes using data from documents, surveys and interviews with professionals (Figure 3).

Decision to change – "I think we were ready": Implementation of a national pES service was driven by: research evidence demonstrating the diagnostic yield and clinical utility of pES, rapid turnaround of results, benefits for clinical care and empowering parent decision making, knowledge, expertise and infrastructure from previous research in the UK (e.g. PAGE[1] and pES for skeletal dysplasia[3]) and key people driving it forward. In addition, many participants saw the pES service as an obvious next step from offering prenatal CMA in clinical practice.

Decision on which model to implement - Development of the national pathway: The national pathway and guidelines for the pES service were informed by research evidence, national and international guidance from professional bodies, and clinical and laboratory expertise. The national pathway and guidelines evolved over time (e.g. additions to the eligibility criteria, introduction of non-urgent pES pathway).

Implementation outcomes – Variation at the local level: Many aspects of local implementation were consistent across all sites: collaborative working across fetal medicine, genetics and laboratory teams, MDT meetings and the pathway processes of referral, consent, testing and return of results. We did observe local variation and identified seven models of pES service delivery across the 17 sites (Table 2). Key differences across models included whether genetics, fetal medicine or both led the initiation of the local pES pathway and the core staff involved in delivering the service. Most sites had adopted genetics led models, however, in more recent interviews it was noted that some sites were shifting to more active fetal medicine involvement in leadership. The minimum staffing model included a fetal medicine consultant, clinical geneticist, and clinical scientist. Some models also included fetal medicine midwives and/or genetic counsellors.

Table 2 Models of rapid pES services identified across England. Reproduced from Walton et al.[37] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/.

Model	Who takes consent (initiating and leading the process)	Which staff are involved in service	Number of sites (number of GLHs) in which model used
1	Genetics	Fetal medicine consultant Clinical geneticist Clinical scientist	N=1 (1 GLH)
2	Genetics [Fetal medicine rarely or only recently]	Fetal medicine consultant Clinical geneticist Clinical scientist	N=3 (3 GLHs)
3	Genetics [Fetal medicine rarely or only recently]	Fetal medicine consultant Clinical geneticist Clinical scientist Genetic counsellor	N=5 (4 GLHs)
4	Fetal medicine	Fetal medicine consultant Clinical geneticist Clinical scientist Genetic counsellor	N=2 (2 GLHs)
5	Fetal medicine or Genetics	Fetal medicine consultant Clinical geneticist Clinical scientist	N=1 (1 GLH)
6	Fetal medicine or Genetics	Fetal medicine consultant Clinical geneticist Clinical scientist Midwife	N=2 (2 GLHs)
7	Fetal medicine or Genetics	Fetal medicine consultant Clinical geneticist Clinical scientist Genetic counsellor Midwife	N=3 (3 GLHs)

Note.

- *Models were defined by who initiates/leads the process (who takes consent) and which staff are involved in the service (core staffing throughout).*
- *"Genetics" refers to Clinical Geneticists and Genetic Counsellors.*

Implementation approach - Factors influencing implementation: Local pES implementation was influenced by staff factors (e.g. time and capacity, staff knowledge and experience and

views, attitudes and interest), service factors (e.g. communication and collaboration across fetal medicine, genetics and laboratory teams and logistics), organisational factors (e.g. sufficient staffing, infrastructure to support collaborative working and previous experience of offering pES), parent factors (e.g. parent involvement in service development, ability to engage with pES testing and access to services) and societal factors (e.g. impact of COVID, availability of funding and geographical location).

Links between implementation approaches and implementation outcomes: Factors influencing the implementation of all seven service models included ensuring collaborative strategies were in place, staff have time and capacity to provide services, clear and specific national guidance and strategies to improve staff knowledge, education, confidence and interest.

3.2 Delivering the pES service: professional viewpoints (Objectives B and C)

Professional views were gathered in interviews (Section 2.3.1).[15] Overall, professionals were positive about the pES service. They noted that pES provides increased opportunity for receiving actionable results during a critical period to support parental decision-making. Professionals also welcomed the improved equity of access to genomic testing, particularly as it was integrated to mainstream care. Despite initial apprehension about whether newly aligned clinical departments and laboratories would successfully collaborate, professionals reported that they were working well together and valued the opportunity for knowledge exchange between fetal medicine and genetics. Offering pES also brought some challenges. For instance, some professionals reported a perceived lack of autonomy in decision-making that left them frustrated at having to seek approval for pES referrals despite their own expertise. In addition, extra administrative processes and clinic time to counsel parents impacted professionals from all disciplines, especially genetics professionals. Many interview participants felt that greater education of fetal medicine professionals about genomics and pES was needed to optimise the service, with a particular focus on targeting midwives as 'a priority'. It was also felt that some genetics professionals would benefit from education in recognising and managing prenatally diagnosed genetic conditions. Looking to the future, professionals envisioned a service with more trust and autonomy in their decision-making,

and many felt that the service would eventually devolve to fetal medicine with genetics oversight. There was hope that the eligibility criteria would widen to improve access and that information for parents would be made available in different formats and languages. Other suggestions included improved communication and case sharing across the service as well as upgrades to pathways, IT systems, and additional staffing to manage the increased workload.

3.3 Experiences of parents offered pES (Objectives B, C and H)

To explore the experiences and support needs of parents when pES was offered[53] we drew on findings from interviews with parents (Section 2.3.2) and professionals (Section 2.3.1). Our findings fell under three overarching themes (Figure 5).

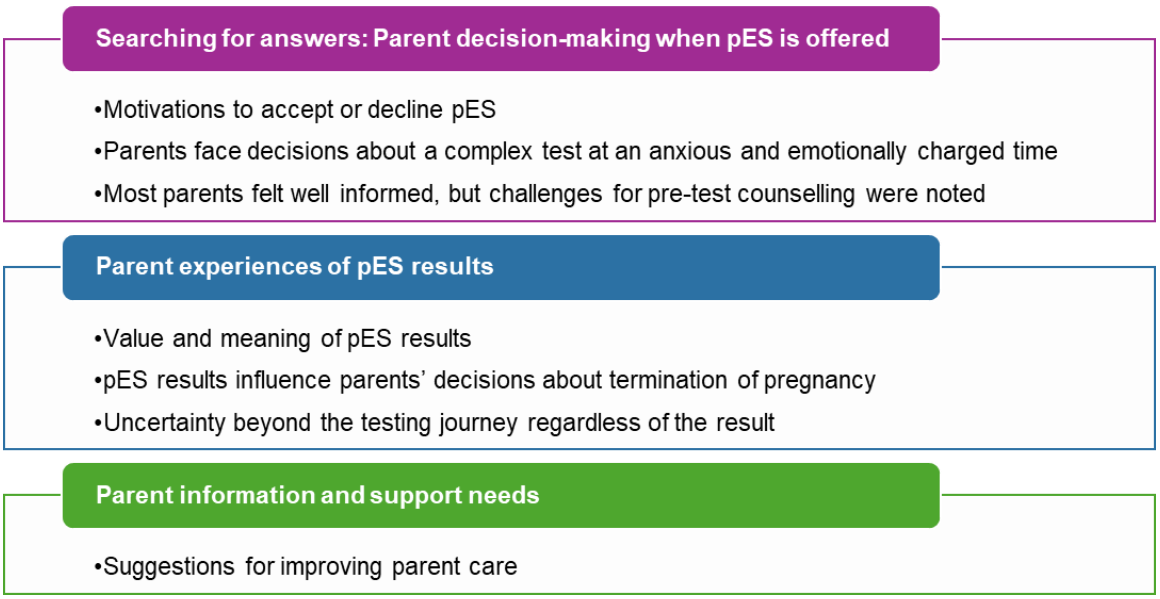

Figure 5 Summary of themes relating to the experiences and support needs of parents.

Parents were grateful to have access to the test and professionals appreciated being able to offer parents an additional pathway to try and find a diagnosis. A key challenge was the need to support parents with decision-making around a complex test during an anxious and time pressured period. It was noted that information about pES is complex to convey and for parents to take in, so clinicians need a good understanding of the test and the possible results and limitations. An anxious wait for results was common, often associated with the need to make decisions before 24 weeks in pregnancy after which there are more stringent

legal restrictions for abortion. Participants emphasised the value of pES results, highlighting that a diagnosis was helpful for pregnancy and neonatal management. Some parents felt relief when there were no informative findings, others expressed disappointment and frustration as they had pinned their hopes on finding a diagnosis.

pES results influenced parents' decisions around termination of pregnancy and often helped them come to terms with their choices. Of 16 parents with a diagnosis from pES, 13 opted for termination and three chose to continue their pregnancy, noting the value of the information to prepare for the future. Of 23 parents who received a non-informative result, 16 continued their pregnancy, describing the result as offering *"peace of mind"*. The remaining seven parents who chose to terminate their pregnancy were primarily guided by the findings of other tests such as MRI or ultrasound and pES was viewed as one part of a bigger picture. Some professionals were concerned that a non-informative result could be overly reassuring, highlighting need for individualised counselling to ensure parents understand what the result means for their pregnancy.

Parents were generally very positive about the care they had received. Emotional support from professionals was valued, although some parents felt that post-test support was lacking. The need for continuity of care was highlighted and having a point of contact for follow-up questions and support was particularly welcomed. Other suggestions to improve care included making information available in different languages and formats and clear signposting so that parents know where to find appropriate information.

Views were mixed about including "looked for" additional findings (eg cancer susceptibility genes) alongside pES in the future. The value of the information was noted by both parents and professionals. Some professionals raised concerns about the legal implications of not offering additional findings. In addition, some parents and professionals held concerns that this was not the right setting to offer additional findings as *"it's quite a lot to take in"*.

3.4 Exploring reasons why parents decline pES (Objective B)

Findings draw on interviews with parents (Section 2.3.2) and professionals (Section 2.3.1) and a review of eligible pES cases not referred for testing (Section 2.3.2).

Most parents we interviewed had chosen to proceed with pES (40 of 42 pregnancies). One parent that declined pES felt that while the information from pES would have been welcomed, they did not want to put the pregnancy at risk of miscarriage with an invasive test and preferred to wait for post-natal testing. The other parent had already had an invasive test and described declining pES to avoid waiting for results when they had already decided to end the pregnancy. In addition, some parents who accepted pES described being *"slightly hesitant"* when making this choice, due to the potential to receive results about their own or their family's health as incidental findings with implications for parental health are reported.

These findings link with thoughts from professionals, who described two main reasons that parents decline pES: 1) parents that would not put the pregnancy at risk with an invasive test, and 2) parents prepared to end the pregnancy because other investigations indicate a poor prognosis and who do not feel they can wait 2-3 weeks for pES results. Professionals noted that on rare occasions parents had declined because of concerns around introducing further uncertainty.

Between March and August 2022, three tertiary FMUs (two in London, one North England) recorded 57 cases eligible for pES where no referral for pES was made. The median gestation at the time the fetal anomaly was identified was 22 weeks (range = 14 – 35 weeks). In 18 cases parents chose termination of pregnancy, in 36 parents declined invasive testing, in one there was fetal demise and in one the anomaly was identified at 35 weeks and further testing was declined as the results would not be available before birth.

3.5 Development and evaluation of the prenatal sequencing animation (Objective C)

A prenatal sequencing animation was developed and evaluated using an online survey (Section 2.3.2).[43] Across all respondents (n=428), self-perceived understanding and knowledge of genetics was greater at T2 than at T1 (Table 3). For example, significantly more

respondents described themselves as having 'Good' understanding ($p<0.05$) and significantly more respondents reported knowing the meaning of 'genome' ($p<0.05$) and 'sequencing' ($p<0.05$) after the intervention. Objective knowledge at T2 [mean score 8.38 (*SD*=2.97, median=9.00, range=0–12)] was significantly higher [*V*=7849, $p<0.001$] than T1 [mean score 5.69 (*SD*=2.59, median=6.00, range=0–12)]. No statistical difference in improvement in objective knowledge was found across the three interventions between T1 and T2.

Table 3 Self-perceived and objective knowledge across T1 and T2 for all respondents.

	Self-perceived understanding of genetics		Self-perceived understanding of genetics terms		Self-perceived knowledge of genetics		Objective knowledge of prenatal sequencing	
	T1	T2	T1	T2	T1	T2	T1	T2
n	427	427	428	428	428	428	427	427
Mean	1.33	1.41	3.36	3.64	12.11	12.18	5.69	8.38
SD	0.57	0.55	0.87	0.76	2.75	3.28	2.59	2.97
Median	1	1	4	4	12	12	6	9
Range	0-2	0-2	0-4	0-4	4-16	4-16	0-12	0-12

Most respondents reported that the intervention they received was "Very easy" or "Quite easy" to understand (leaflet (59%), animation (78%) and leaflet plus animation (72%)). Most respondents reported the explanation of prenatal sequencing was too technical (leaflet (88%), animation (88%) and leaflet plus animation (90%)), while around half thought the information was too limited (leaflet (55%), animation (47%) and leaflet plus animation (58%)). Just over half reported feeling overwhelmed with information (leaflet (63%), animation (50%) and leaflet plus animation (53%)). Most respondents reported that they liked the way the information was presented (leaflet (83%), animation (89%) and leaflet plus animation (88%)) and the majority would have found the information helpful if they had been offered prenatal sequencing (leaflet (92%), animation (89%) and leaflet plus animation (92%)). Preferred information formats across all respondents were: 52% for video 42% for written and 6% for audio.

3.6 Factors associated with variation in outcomes (Objective D)

pES service outcomes and possible factors influencing local variation in outcomes were considered across the seven GLHs (Section 2.3.3).[46] During the study period, 475,089 births were recorded in England and 409 women were referred for pES, giving a referral rate of 8.6 (95% CI 7.8, 9.4) per 10,000 maternities. Referral rates varied from 4.3 to 11.9 between GLHs. Of those referred, 75.3% (308/409) were accepted by the testing laboratories and 58.9% (241/409) proceeded to pES tests (Figure 6). The overall characteristics of women who were referred or who proceeded did not differ substantially from the population of women who gave birth. Of 241 pES tests performed, 85 (35%) of women received a diagnosis (pathogenic or likely pathogenic). Diagnostic yield varied between the GLH regions, ranging from 28.6% to 45.5%. Median turnaround time between the sample arriving at the laboratory and the results report was 15 days. Of 85 women with a pES diagnosis, 67% were of White ethnicity and 18% had at least one complex social factor compared to 82% and 8% among the 135 women without a diagnosis following pES. Furthermore, 40% of women with a diagnosis chose termination, 18% had a stillbirth, and 42% a live birth. For women with no diagnosis, 18% chose termination, 5% had a stillbirth and 78% a live birth. For women who had a termination the median gestational age at final report was 24.9 weeks and at termination was 26.2 weeks. There was variation in some of the characteristics and outcomes between GLHs but low numbers prevented robust comparisons. No substantive differences were observed for sources of referral (who initiates and leads the process – fetal medicine, genetics or fetal medicine and genetics – see Table 2) across the 17 genetics services in England.

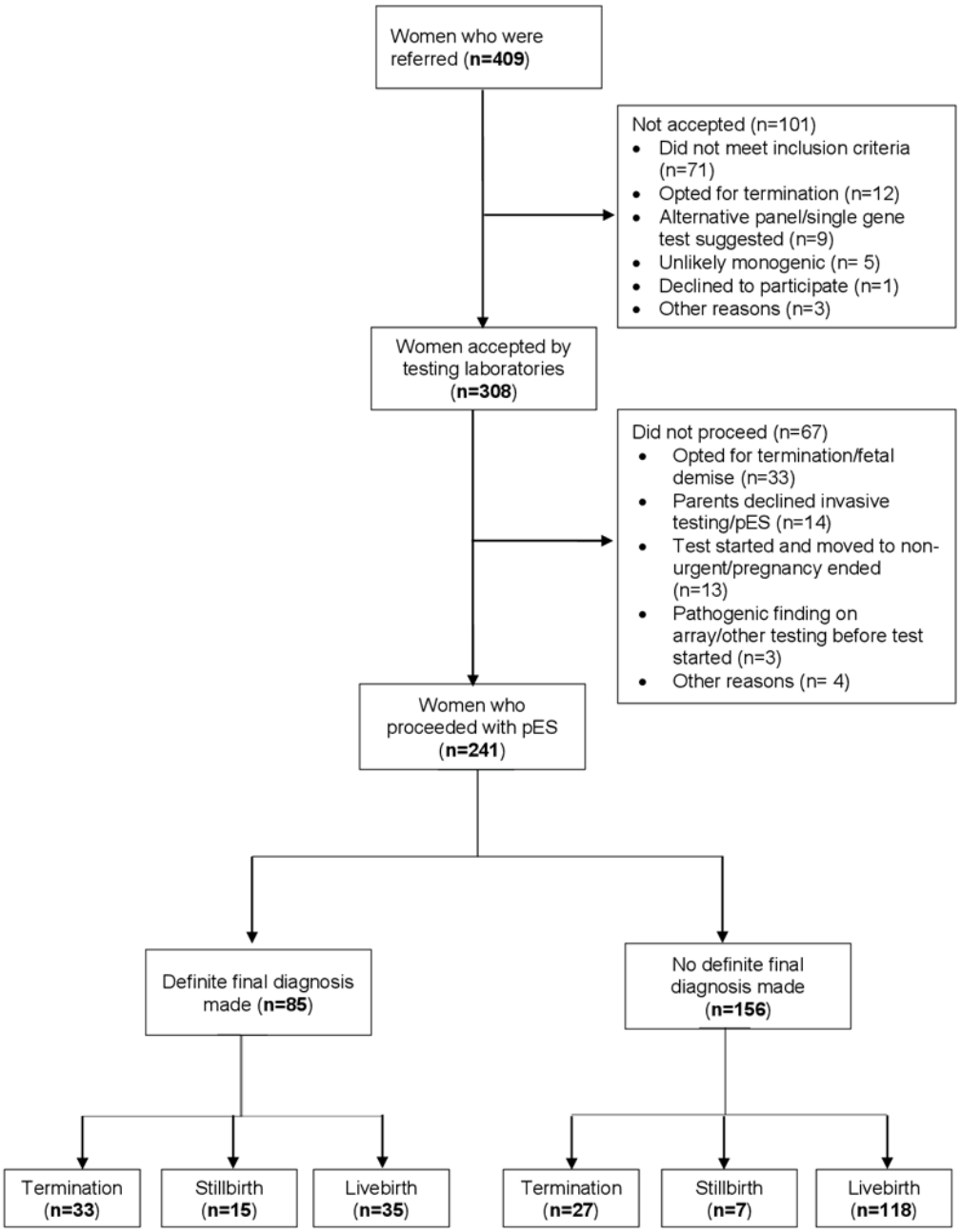

Figure 6 Summary of outcomes of women referred for pES between 01/10/2021 – 30/06/2022. Pregnancy outcomes total 235 (Definite final diagnosis: 83 and No definite final diagnosis: 152) as 6 women were excluded (miscarriage: 2 and missing data: 4). Reporduced from Ramakrishnan et al.[46] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/.

3.7 Ethical issues in the pES service: Equity and timeliness (Objective E)

Our ethical analysis (Section 2.3.4) draws on interviews with professionals (Section 2.3.1) and parents (Section 2.3.2).[54] We focused our analysis on the structural ethical issues of "equity of access" and "timeliness and its impact on parental decision making in pregnancy" as these were issues of particular concern for both parents and professionals that have not been explored in previous empirical work. Themes and sub-themes are presented in Figure 7.

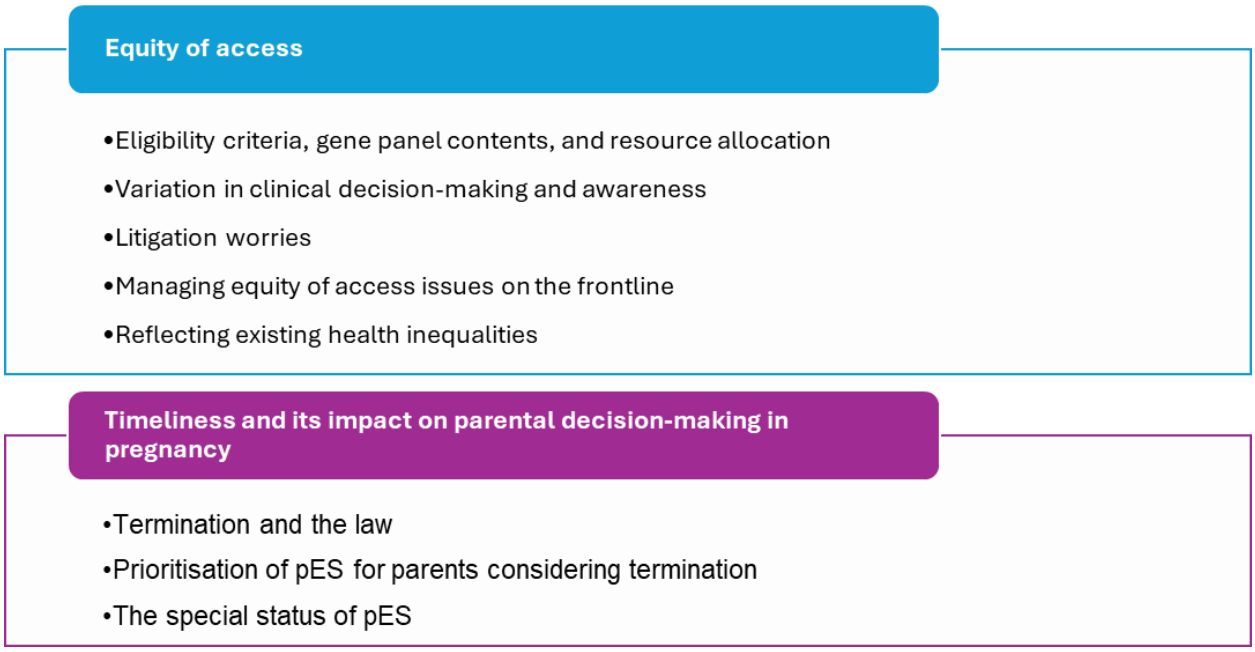

Figure 7 Summary of themes describing ethical issues in the pES service

Equity of access

Equity questions arose in several ways with many participants focussing on decisions around eligibility criteria and test scope. Whilst the current eligibility criteria were viewed positively by some as *"a good starting point"*, many professionals felt these were too conservative and should be widened to make pES more accessible. Several parents also felt that pES should *be "offered to as many people as possible"*. It was also recognised that decisions about the scope of the technology, which as a panel test specifically targets a set number of genes (~1300) make it inevitable that some conditions will not be identified. Several participants highlighted that decisions to "ration" services via eligibility criteria and test scope are

necessary in publicly funded healthcare systems where resources are limited. Referral practices were another issue for equity as the individual judgements of clinicians and varying level of awareness of pES could delay or prevent referrals. Worries about possible litigation impacted the potential to influence willingness to refer. Furthermore, social and health inequalities including language barriers, geography and social deprivation could impact access to pES for many parents.

Timeliness and its impact on parental decision making in pregnancy

Parents and professionals described ethical questions that arose from the interrelationships between the timelines of pregnancy, the pES service, the decision-making needs of parents and abortion law in England, whereby termination is only permitted after 24-weeks when doctors decide there is 'substantial risk' of serious disability after birth. Referrals for pES are most often made at the routine 20-week fetal anomaly scan, bringing the time the testing is performed close to the 24-week limit. This timing was viewed as 'incredibly tight' and was thought to place pressure on decisions around termination. In addition, these timelines resulted in some parents making decisions about termination before pES results were returned. Timelines and decision making also contributed to the ethical question arising from the rapid pES service only being offered if it will impact pregnancy management. Parents who have already decided to continue or terminate the pregnancy are not eligible for pES and are instead offered non-urgent pES. From the perspective of parents, this prioritisation of pES for those whose termination decision will be informed by the result can seem distressing and unjust. From the perspective of a health system, however, the prioritisation of an "expensive test" for parents whose decisions will be impacted by the result makes sense. Another issue that arose was the special status that some parents and professionals could give to pES, which is just one source of information. Scan findings can be key for decision-making and may be overlooked.

3.8 Costs of delivering the pES service in England (Objectives F and G)

Costs were explored (Section 2.3.5), using data from observed local care pathways and service models (Table 2) and parent interviews (Section 2.3.2).[55] For our base case the incremental cost to the NHS to deliver pES for all 413 cases was £962,727 (95% credibility interval £775,454 to £1,204,027) (Table 4). Of the total cost, £865,699 (90%) related to proceeded cases (*n*=241) and £97,028 (10%) to non-proceeded cases (*n*=172). The pES test was £2,931 (£2,373 to £3,499) per case and accounted for the majority of overall cost (76%). The average additional clinical time spent in existing appointments counselling about pES was 32 minutes at a total cost of £9,935 (1% of overall cost). There were on average an additional 1.9 genetics appointments needed at a cost of £36,498 (4% of total cost) which, for simplicity, we assumed related to return of results (pre-test discussion and counselling generally took place in existing FMU appointments). Non-proceeded case costs included case discussion and selection (via MDT meeting) and eligibility review by testing GLHs (£59,881). The mean cost per referred case was £2,331 (£3,592 for a proceeded case, £564 for a non-proceeded case). Diagnoses were obtained for 85 cases, therefore the incremental cost per additional diagnosis was £11,326 (£8,582 to £15,361).

Table 4 Cost of delivering pES**.** Reproduced from Smith et al.[55] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/.

Process	Cost per case (£)	No. of cases	Total cost (£)
Case identification and referral to GLH (MDM)	338	413	139,543
Eligibility review by GLH (rejected/non-proceeded)*	11	163	1,766
Discussion and consent**	40	250	9,935
Sample collection, transport and DNA extraction**	76	250	18,887
Prenatal exome sequencing (pES)**	2,931	250	732,733
Return of results	151	241	36,498
Administration (throughout)	57	413	23,366
Total cost			**962,727**

Mean cost:

Referred pES case	2,331	413
Proceeded pES case	3,592	241
Non-proceeded pES case	564	172

* For accepted cases this cost is included in pES

**241 proceeded pES cases, 9 cases started then subsequently transferred to non-urgent pathway

Alternative staffing models (Table 2) had a negligible impact on diagnostic yield and costs. For scenario one – delivery models that did not include either a genomic counsellor or a midwife within the core team – the total cost was estimated to be £963,625, 0.1% higher than the base case. The diagnostic yield was 35.7% (vs 35.3% in the base case) resulting in a cost per diagnosis of £11,205. For scenario two – delivery models including a midwife in the core team – the total cost was £955,289, 0.8% lower than the base case. Diagnostic yield was 34.9% resulting in cost per diagnosis of £11,372. Taking the base case cost and using the highest (45.5%) and lowest (28.6%) diagnostic yields of the GLHs the cost per diagnosis was £13,953 and £8,752 respectively.

Based on data collected for 42% of proceeded cases for the "changed management" outcome (i.e. influenced decision to continue or end pregnancy, influenced medical management during pregnancy, prenatally or neonatally) 82% of pES cases that received a diagnosis reported a change in management whilst 51% of pES cases without a diagnosis reported a change in management. Taking only the former, the cost per outcome increases to £13,753. Across all proceeded cases (it could be argued the data demonstrates utility even without a diagnosis) the cost per outcome was £6,334.

In the 12 months to 30 September 2023 the testing GLHs received 760 referrals, 442 of which proceeded with pES testing. Applying average costs per case the annual incremental cost to the NHS of delivering a pES service was estimated to be £1,716,595. pGS could cost up to £3,283 per case for this testing approach to be no more expensive overall than pES, assuming CMA is no longer required (the mean cost of a prenatal CMA was £352), assuming pGS costs using technology available in 2023.

It was difficult to identify the costs associated with pES for parents as parents were frequently attending hospital for scans and monitoring for the identified fetal anomaly and did not distinguish between these appointments and pES related appointments. Therefore, we could not confidently ascribe disclosed costs to pES. Pre-test discussion mostly took place in person whilst already attending hospital for a scan, with bloods taken at the same time (though some had separate phlebotomy appointments) and most reported results being returned via remote consultation, minimising travel costs and time off work. Some specifically commented that they did not have any additional expenses specific to pES.

3.9 Integration of findings (Objective G)

By drawing on findings from the implementation evaluation (Section 3.1), parent experiences (Sections 3.3), variation in outcomes (Section 3.6) and costs (Section 3.8) we can start to look at the relationship between implementation outcomes and intervention outcomes (Figure 3). Implementation was not uniform, with variation observed within and between GLHs. Seven different models of implementation were identified based on leadership and types of staff

involved in pES pathways (Section 3.1 – Table 2). Parent experiences of the pES service were largely positive and pES results informed decision making in pregnancy (Section 3.3). The experiences of parents and their support needs were largely consistent across our parent interviews. Some parents did, however, have differing experiences of signposting and follow-up care which may be linked to local variation in how pES pathways are delivered. When looking at variation in outcomes (Section 3.6), differences diagnostic yield were seen at the GLH level. These differences were not related to the service models in terms of who leads the service, which may be explained by qualitative findings that indicated that the service models sometimes differed within individual GLHs (Table 2). More research is needed to explore these differences further. When considering the costs of delivering the pES service, the most common service model based on staffing (model 3 – fetal medicine consultant, clinical geneticist and genetic counsellor – Table 2) was costed and then compared to other models with different staffing. Impact on overall costs of these different staffing models was minimal (Section 3.8).

4 Discussion

4.1 Interpretation of findings

4.1.1 A national pES service was welcomed, with support for parents key to optimal care

Parents and professionals welcomed the introduction of pES into clinical practice, valuing the increased likelihood of obtaining a diagnosis and the additional information for guiding management in current and future pregnancies. Professionals further highlighted the importance of a national service to deliver equity of access across England. These findings align with studies exploring parent and professional experiences when pES was offered in a research setting.[10, 11, 21, 22, 56, 57]

Supporting parental decision-making at a time of high anxiety and the tight timelines of pregnancy was a key challenge for offering pES in clinical practice (Section 3.3). Similar findings have also been seen in studies where pES was offered in a research setting.[10, 11, 56, 57] In our study, parents described making quick decisions to have pES and the time pressures

of pregnancy could make decisions feel rushed. To support parental decision-making, pre-test counselling should be delivered by clinicians with a good understanding of the possible results and limitations of pES. Consideration for culturally sensitive approaches to counselling are also needed to support parents across a range of education levels and with different language requirements.

Support across the pES testing journey was valued by parents. In addition to support during pre- and post-test counselling, parents also benefit from a contact point for questions during the period between having the test and receiving results. Supportive follow-up care after results are received is also needed, regardless of the type of result. Notably we found that access to follow-up care and signposting to specialist support services varies widely. Resolving the gap in follow-up care is particularly important as ongoing uncertainty after results disclosure is a common feature of prenatal testing[58-60] that was also seen in our study.

4.1.2 pES informs parental decisions about termination of pregnancy

Among 241 women who proceeded with pES testing there was a higher proportion of terminations amongst women who had a diagnosis compared to women without a diagnosis (40% vs 18%) (Section 3.6). Similar findings have been seen in other studies of pregnancy outcomes following pES.[9, 61] In our study 42% of women with a diagnosis continued the pregnancy and had a live birth, highlighting that findings from pES also lead to decisions to continue the pregnancy and can be used to inform pregnancy management and neonatal care. The parents we interviewed (Section 3.3) reported that information from pES was often a key factor in decision making about whether to continue or terminate the pregnancy. When pES found a diagnosis, parents reported having more confidence in their decision to terminate. For parents with a no findings result, the information from pES was considered as part of a bigger picture that included findings from scans and other tests. Professionals did, however, raise concerns that parents sometimes saw a no findings result as good news irrespective of the information from scan findings. It is important that counselling is individualised and clinicians highlight that a no findings result from pES does not rule out the possibility of a genetic condition.[17]

4.1.3 Delivering a national pES service

Collaboration and good communication between fetal medicine, genetics and clinical scientists has been central to the successful delivery of pES (Section 3.2). This finding aligns with previous studies where pES was offered in a research setting.[3, 11] Some of the challenges for service delivery faced by professionals included impacts on clinical and administrative workloads, perceived lack of autonomy in referrals for pES, difficulty engaging with regional units, limitations on resources and variation in knowledge about pES. We also identified gaps in genomics knowledge for some fetal medicine professionals and a need for more clinical geneticists with expertise in prenatal conditions. The importance of giving professionals protected time to participate in educational opportunities was highlighted, noting that the key to mainstreaming genomics in the NHS requires genomics education to begin at undergraduate level. A recent survey with medical students across the UK has highlighted variation in the amount and type of genomics teaching students currently receive.[62] In addition, previous research reported that midwives and nurses are underrepresented in the genomics education courses run by Health Education England and while genomics is valued, knowledge and confidence is lacking for many.[63]

4.1.4 Variation in pES implementation across England

Our evaluation of pES implementation (Section 3.1) indicated that while local pES services had similar pathway components (multidisciplinary working, referral, testing, analysis, return of results), there was variation in implementation approaches. Variation included how MDTs work together, and seven models of service delivery were identified that included differences in staffing and the leadership roles genetics and fetal medicine teams take on across the pES pathway (Table 2). Variation was observed both within GLHs and across GLHs (Table 2). Many factors influenced variation, such as the time, capacity and attitudes of local staff, communication, collaboration and logistics, existing infrastructure and previous experience. It is possible that variation in service delivery can lead to differences in patient care. Parents did describe differences in experience that could result from variation in service delivery, such as their experiences of follow up care after pES testing (Section 3.3). Differences in diagnostic yield between GLHs were also identified that may in part be explained by variation

in service delivery (Section 3.6). Our findings align with previous research from the UK and internationally that demonstrates that multiple factors influence implementation of clinical genomics services.64-68 Some variation is expected, however, as there is a need for balance between adapting services to local contexts and adherence to service specifications to ensure successful implementation.65, 69, 70 Best et al65 also emphasise that when scaling up clinical genomics services there is a need to highlight the components of the service that should be standardised and those where flexibility and local adaptation are acceptable.

4.1.5 Delivering an ethical pES service

Previous work has highlighted several practical ethical issues that require consideration when offering pES, including achieving valid consent, interpretation and disclosure of variants, management of uncertain findings, professional responsibilities, privacy and confidentiality, dealing with incidental findings, impact on family members and duties towards the future child.[17, 58, 71-75] Professionals and parents described structural ethical issues linked to the pES service that centred on challenges for equity of access and timeliness and its impact on decision-making (Section 3.7). Participants linked setting eligibility criteria and gene panel content to equity of access, as they determine which parents can access pES and what conditions are tested for. The need to consider resource availability was, however, recognised. Other factors that had the potential to impact equity of access were variation in clinician referral practices, lack of awareness or pES at peripheral units and concerns about litigation. The issues around the timeliness of pES and its impact on decision-making were linked to the change in abortion law at 24 weeks gestation. Other issues for timeliness were decision making in the absence of a result, and the special status perceived for pES results which can override information from other sources, such as ultrasound scans and MRIs. Personalised post-test counselling is essential to help parents understand the implications of their pES results. To mitigate against parents being overly reassured by a no informative findings result,[53, 56] additional information about the pregnancy from scans and other tests must be considered.

4.1.6 Variation in pES service outcomes

From 01/10/2021 to 30/06/2022 the diagnostic yield of pES was 35%, with a mean turnaround time to final report of 15 days (Section 3.6). Previous research has shown that when pES is offered diagnostic yield in any pregnancy with a structural anomaly, the diagnostic yield is 8-10%.[1, 2] A key component of the eligibility criteria for the pES service is to offer pES in pregnancies with a structural anomaly where that the fetus is also considered likely to have a monogenic aetiology following MDT review. The diagnostic yield of 35% aligns with findings from a recent systematic review comparing studies using similar approaches to the pre-selection of cases versus unselected cases, where pre-selection achieved higher diagnostic yields (45% versus 15%).[5] Diagnostic yield varied between GLHs, which may be due to differences in how the eligibility criteria are applied locally and by the two testing laboratories. To ensure equity of access for parents, further education and review of local process is needed to ensure the eligibility criteria are applied in a similar way across all GLHs.

The turnaround time between samples arriving at the laboratory and issuing the final report was 14 days for a no findings results and 16 days for a diagnosis. Possible reasons for this difference are the necessity for validation of pathogenic/likely pathogenic variants before reporting,[61, 76] the challenges of variant interpretation which requires close communication between the laboratory and referring clinicians, and occasional consideration of evolving phenotypes or additional examination of fetus or parents.[77] Turn-around time is critical because parents and clinicians use test results for decisions around termination, pregnancy management, delivery planning, and neonatal treatment. Local audits of consent processes, sample collection and transfer may identify areas that could be streamlined to reduce the time taken for samples to reach the testing laboratories.

4.1.7 The intersection of pES timelines, termination and the law

Findings from several workstreams have highlighted how the timelines of pES intersect with the change in abortion law at 24 weeks gestation (Sections 3.3, 3.6 and 3.7). We found that for women who had a termination, the median time for results to be returned and for termination was 25 weeks and 26 weeks gestation, respectively. These timelines are

consistent with referrals for pES being most common after the routine 20 week fetal anomaly scan which, when combined with the time required for pre-test counselling, sample transfer, laboratory testing, returning results and decision making, can push termination beyond 24 weeks. In addition, some anomalies are not detectable until later in pregnancy.

For many parents waiting for pES results when close to 24 weeks was a very stressful experience and clinicians also find this scenario challenging. Accordingly, timely referral and efficient return of results were essential requirements for an effective and ethical pES service. Where possible we need to find ways to improve the timeliness of both pES referrals and the processes of pES testing. Some researchers have discussed how an earlier assessment of fetal anatomy may allow earlier referral for pES for some fetal anomalies, but note that this will not resolve the issue of late presentation of some anomalies, such as those associated with brain malformations or movement disorders.[61] Further research is needed to understand the support needs of parents having pES who face decisions about termination late in pregnancy. Moreover, it is important that guidance is developed that outlines the roles and responsibilities of professionals so that standardised care can be offered.

4.1.8 Costs and cost effectiveness

The cost to the NHS to deliver pES from 01/10/2021 to 30/06/2022 was £962,727 for 413 referred cases. The mean cost per case was £2,331 and the cost per diagnosis was £11,326. For comparison, prior to its implementation prenatal CMA testing was found to have a mean incremental cost of £113 with a cost of £4,703 per additional pathogenic result compared to karyotyping (the previous standard test).[78] In 63% of proceeded cases (including 51% of undiagnosed cases) pES influenced clinical management and/or pregnancy continuation decision, supporting our interview findings that parents derive utility from pES even when there is no diagnosis. Taking this into account, the cost per outcome reduces to £6,334. However, the potential for harm from misunderstanding a no findings result, as highlighted by professionals, should be considered.

We analysed the impact of different core staffing delivery models and found negligible variances, because the bulk of the costs associated with pES are due to the cost of the test

itself, which does not depend on the delivery model. Therefore, there is no preferred delivery model on the basis of cost or outcomes. There is a more significant impact when diagnostic yield varies, with the cost per diagnosis ranging from £8,752 to £13,953. We have highlighted the need to ensure consistent application of eligibility criteria across GLHs to help reduce variability in outcomes. Standardisation may increase overall diagnostic yield which would reduce the mean cost per diagnosis (assuming there were no significant additional costs to implement). There may be further benefits from a move to pGS.[45-47] If CMA is no longer required and the service delivery model otherwise remains unchanged then, using pGS costs from 2023, a pGS cost of up to £3,283 would be no more expensive overall than pES.

Findings from our parent interviews suggest that the incremental costs of pES to families are negligible as parents are already frequently at hospital for scans and monitoring and many additional appointments were remote, minimising travel costs and time away from work or caring responsibilities.

There are potential downstream savings from the foregone (often lengthy) diagnostic odyssey as a result of obtaining a genomic diagnosis prenatally.[79] EXPRESS was not funded to explore further costs and savings beyond birth and further research to quantify this may be informative to policy makers.

4.1.9 Animation increases understanding of prenatal sequencing

The development and evaluation of an animation describing prenatal sequencing (Section 3.5) was added to our protocol in response to the findings from our systematic review of information resources for pES,[80] that highlighted a scarcity of information for parents about pES, and suggestions to provide information in different formats from parents and professionals (Section 3.3). In line with other studies, we found that information about genomic tests presented in either an animation or written format can increase objective knowledge and self-reported understanding.[81-83] The majority of participants who viewed the animation reported that it was easy to understand, they liked the way the information was presented and that it would be helpful if they were offered testing. Our animation expands the available information resources for parents offered pES and can be used to complement

the discussions parents have with professionals. The animation is freely available to view on the ARC website (https://www.arc-uk.org/) and has been translated (voiceover and captions) into 11 languages. Future research should include a formal evaluation of the animation in the clinical setting and explore the value of the translated versions. Exploration of appropriate information formats and resources for parents with learning disabilities is also needed.

4.2 Study strengths and weaknesses

Overall strengths

This is the first study to evaluate the implementation of a national pES service. Our research commenced at the same time as the pES service, affording a unique opportunity to capture service development and experiences of parents and professionals during the first years of implementation. Our mixed-methods evaluation has been broad in scope, considering implementation processes, patient and professional experiences, ethical issues, clinical outcomes and costs for the NHS and for parents. Our final data-set was extensive and we have been able to draw on national level data that include interviews with parents (n=48), professionals (n=63), surveys with professionals (n=159) from across England, as well as national data from the testing laboratories on pES testing (413) and data on all women giving birth in England obtained through collaboration with NCARDRS. Study design was theoretically informed by the MSC framework[35, 36] which has guided data collection, analysis and interpretation of findings. Finally, it is important to recognise that a major strength of this work has been our approach to PPI, which has been integral to the conception, planning and delivery of EXPRESS (Section 4.3). The PPI members of our research team and our PPI Advisory Group have worked closely with the wider research team on study design, development of materials and, crucially, interpretation of findings, helping us to deliver an evaluation with the potential to benefit parents offered pES across England.

Evaluating pES service implementation

The evaluation of pES service implementation was multi-site, used a parallel convergent mixed-methods design and was guided by the MSC framework.[35, 36] This work has enabled a comprehensive understanding of how the pES service was implemented at a local and national level and the factors influencing implementation. A limitation of this work was that

some pES service pathways will not have been captured, for example we did not rigorously examine the pathways that would cover pES referral from obstetric teams working in District General Hospitals. In addition, pathways will continue to evolve over time and the pathways described can only represent one point in time. There was also variation in the numbers of interviews, surveys and documents available from each site and some staff groups, such as midwives, were under-represented.

Professional views and experiences

The key strengths of this work were that both quantitative and qualitative information has guided our understanding of professional experiences and that participants were from a range of professional backgrounds, with representation across all GLH/GMSA regions in England. A limitation was that interviews were conducted over a two year period and individual experiences may have evolved as the service became more established. A further limitation is that respondents were self-selecting and there may be a bias towards those with strong views about the pES service.

Experiences of parents offered pES

Our exploration of parent experiences of pES combined the individual perspectives of parents who reflected on their own personal experiences with the wider perspective of professionals who were able to draw on the experiences of parents in their care. A limitation was that most parents we interviewed were women who chose to have pES, reported being White/White British and were educated to degree level or above. As a result, our findings are not representative of the full range of parental views and experiences. Recruitment of parents from diverse backgrounds could have been improved by recruiting from a greater number of FMUs located in diversely populated areas and placing a greater emphasis on the importance of recruiting parents from diverse backgrounds by asking the FMUs at the outset of recruitment to specifically recruit women from diverse backgrounds and supporting them to do this by providing a script. Other potential limitations were selection and recall bias as participants were self-selecting and the interviews were not necessarily conducted close in time to being offered pES.

Reasons parents decline pES

We drew on the findings from interviews and a review of cases at three hospitals over a 6-month period. The interview recruitment limitations of self-selection bias and a non-diverse sample of parents described above apply here. In addition, only two families in our participants group had declined pES. This limitation was partially redressed by professionals reflecting on their wider experiences of why parents might decline pES. In addition, fewer FMUs took part in our case reviews than originally anticipated, limiting the types of analyses we could do.

Evaluation of the prenatal sequencing animation

The strength of this work was the large sample of parents (n=428), with diversity in gender, ethnicity and education levels. Whilst the animation was evaluated with parents with a recent pregnancy, a limitation was that participants did not include parents offered pES whose needs may differ to those of the parents included in this study.

Service outcomes and variation across the GLH regions

The key strength of this work is the linkage of data from multiple sources, including national data sets from NHS Digital (i.e. NCARDRS and MSDS). The main limitation was the small number of pES tests performed within the study time frame, which has prevented a more detailed exploration of differences at the GLH or individual service-level. Another limitation is missing values in the laboratory data, especially for ethnicity and gestational age at outcome.

Ethical issues in the pES services

In this study we explored the experiences of health professionals and parents through an ethical lens. The analysis was conducted with the qualitative interviews with parents and professionals, and as such are impacted by the limitations of self-selection bias and a non-diverse sample of parents as described above.

Economic analysis

This is the first economic analysis of pES in a live clinical service.[84] Costs were based on survey data from a range of professionals involved in delivering the service across England, and both testing laboratories, providing robust estimates and taking account of local variation in resource use. A limitation is that we were unable to identify a comparator cohort

from the national dataset with sufficient granularity to enable inclusion of incremental pregnancy outcomes and costs in our analysis. In addition, our analysis was limited to pregnancy and excludes potential costs and benefits for diagnosed cases such as the savings and health benefits that may arise from early diagnosis. EXPRESS was not funded to study costs beyond birth. Future research could consider cost-effectiveness in the longer term.

Triangulation and integration of findings across workstreams

A limitation for triangulation and integration of findings was that implementation (Workstream 1) was evaluated at the level of clinical genetics services, while analysis of variation in outcomes (Workstream 3) and some costs (Workstream 5) was at the GLH level. In addition, overall sample numbers and approaches to the recruitment of parents for qualitative interviews (Workstream 2) that included recruitment from support organisations meant that experiences could not be linked to specific service models.

Study timing

The COVID pandemic impacted on several aspects of the study. Clinical practices changed significantly with the restricrions imposed on face-to-face consultations and staff time was limited as resources were neede elsewhere. Our ability to collect data was impacted and services may have evolved in new ways when restrictions were lifted.

4.3 Patient and Public Involvement

To ensure that our research is of real benefit to parents, PPI has been integral to the planning and delivery of EXPRESS. Two core members of the research team and funded co-applicants are from patient support groups: KLB – Chief Executive Officer, Breaking Down Barriers and JF – Director, Antenatal Results and Choices (ARC). JF has led the PPI elements of the research. One of the social science researchers (HMD) in our EXPRESS team was based at ARC and received training to work on the charity's helpline to gain in-depth understanding of what parents face while having to make decisions around testing, diagnosis and termination of pregnancy. This dual role provided an active link between the research team

and the patient organisation, which helped the wider research team to maintain a focus on parent priorities.

A PPIAG was established at the study outset. Members include representatives from support organisations (ARC, Breaking Down Barriers, Genetic Alliance UK and Unique), and a researcher with relevant experience. The PPIAG met quarterly and members were paid for their time. The PPIAG worked closely with the research team on study design and development of parent-facing documents, such as participant information and interview topic guides (Section 2.3.2). In addition, we have drawn on the PPIAG, and in particular, KLB's experience with Breaking Down Barriers, for the development of interview questions for parents and professionals that are aimed to draw out issues related to equity of access and inclusivity of services offering pES (Section 2.31. and Section 2.3.2). The PPIAG also highlighted potential ethical issues for consideration (Section 2.3.4). The PPIAG contributed to the development and evaluation of the animation describing prenatal sequencing (Section 2.3.2). The PPIAG helped to interpret interview findings and to develop the implications for practice (Section 4.6). They also helped create a newsletter about EXPRESS for parents, which has been circulated through the networks of the organisations represented on the PPIAG. Other formats for sharing the research include a recorded interview with HMD that is available to watch on the EXPRESS website and MPeter gave a presentation about parent experiences of pES at the ARC conference in 2023.

We had PPI input into the systematic review of pES patient information where HMD was equal first author and JF a co-author.[80] As the first step of the review we surveyed ARC members to ask about what search engines and search terms they would use when researching genetic testing and used this information to guide our systematic searches.

The PPIAG's contribution to EXPRESS has significantly benefited the study as recognised by co-authorship here and on several papers.[4, 43, 53, 54] A description of the PPIAG's role in EXPRESS was included as a case study in a paper examining approaches to PPI in genomic research in the UK.[85] Our approach to PPI and the development of the animation was selected as an oral presentation at the International Society for Prenatal Diagnosis meeting in June 2023.

4.4 Equality, Diversity and Inclusion (EDI)

Equality, diversity and inclusion was built into EXPRESS, and we adopted an inclusive approach to our research in a number of ways.

Research conducted with parents

1. Our PPIAG provided valuable input into the study documents and our analysis of the parent interviews. They ensured that the language used was appropriate for parents, that interview questions were framed sensitively and that our interpretation of the findings was measured.
2. A telephone interpreter was available for any parent who wished to conduct the interview in a language other than English.
3. We were flexible when arranging interviews, making sure to book them around parents' work and childcare schedules.
4. All parents were remunerated with a gift voucher as an acknowledgement of their contribution.

Through this inclusive approach and by recruiting parents from across England through the parent charity ARC and FMUs in London and the North and South of England, we had hoped to include the views of a wide range of parents. However, most parents we spoke to identified as coming from a white ethnic background, having a degree or higher, and speaking English as their main language. We acknowledge that the views expressed by these parents will not reflect those of the wider population and recognise the lack of ethnic, religious, cultural, and socioeconomic diversity as a limitation to this work. To address this, MPeter secured funding from the Great Ormond Street NIHR Biomedical Research Centre and ARC to conduct a series of focus groups with Black and South Asian parents, exploring their views and attitudes towards genetic and genomic testing in pregnancy.[86] Black and South Asian women are amongst the most significantly impacted by maternal health inequalities[87] and yet under-represented in research,[22, 56, 88] so including their views in this work was vital for understanding how to offer equitable and culturally sensitive care and support. MPeter, whose interest is in racial health inequalities, took a different approach to

recruitment to reach these groups by working actively with advocates trusted in local South Asian communities and grassroots organisations developed specifically for Black parents. Groups were run in-person and online to accommodate parents' travel needs, parents could bring their children, and the in-person group with South Asian parents was held entirely in Bengali so that parents could share their views in their native language. Having a shared ethnic and cultural identity with these parents (MPeter identifies as Black British), MPeter was able to provide a space in which parents felt comfortable to share their experiences.

These groups extend the findings from EXPRESS: we have gathered valuable insight into the factors that influence decision-making for Black and South Asian parents when they are offered prenatal tests like pES, such as family views and religious and cultural beliefs around termination. MPeter's expertise in engaging with parents from underrepresented groups has better equipped our research team to work with more ethnically and culturally diverse communities in the future. Importantly, the groups have had an ongoing impact:

1. MPeter has maintained the relationship with the local South Asian parent group and, together with JF, hosts regular drop-in sessions for parents where they discuss issues around prenatal testing and work together to develop ways that ARC can tailor its support to these communities.

2. The insights from Black parents have shaped the priorities for MPeter's newly awarded fellowship project which builds on EXPRESS and explores the experiences of Black women offered prenatal genetic screening and testing. Suggestions to include fathers, involve faith leaders in conversations around support and ensure avenues for post-interview signposting to culturally appropriate organisations have been incorporated into the project's design.

Improving equity through accessible parent information

Our prenatal sequencing animation has addressed a need for accessible parent information about pES. The animation was developed with significant PPIAG and parent input to ensure that the language and images used were inclusive to parents from different backgrounds.

The animation benefits those who prefer a visual format over written text, includes closed captions for those with hearing loss, and is available in multiple languages.

When evaluating the animation, we put in place *a priori* quotas regarding participant gender, ethnicity, and education level to ensure that responses from people who are underrepresented in research studies would be included.

4.5 Impact and learning

Evaluating the pES service as it was rolled out across the country will benefit the NHS and patients by identifying good practices and facilitators and barriers to optimal service delivery, thereby highlighting ways to promote delivery of pES in an equitable manner across England. Accordingly, findings are informing ongoing work in the national rapid pES group to improve equity of access to testing, expert fetal phenotyping and genetic counselling. As the pES service is still relatively new and evolving post-pandemic, findings can be used to inform ongoing implementation though strategies to ensure collaborations and MDT working are in place and addressing practical issues such as infrastructure and staffing.

As lessons are taken into clinical practice, improved equity of access to all aspects of pES and its optimised clinical use should allow more parents to receive a genetic diagnosis in pregnancy and subsequently provide valuable information about the cause and prognosis of their baby's problems to inform pregnancy and neonatal management and future reproductive decisions. Findings will benefit healthcare professionals in fetal medicine and genetics as training needs have been identified. A key outcome has been the development and positive evaluation of an animation for parents describing prenatal sequencing that is freely available online and has been translated into 11 different languages. The animation has been recognised by clinicians as a resource to share with parents when discussing pES and for inclusion in local e-learning packs.

Through publications and presentations of our findings at international conferences (Appendix 1), healthcare services in other countries may also benefit from our research findings as they implement and refine their own pES services.

Our study has also led to additional research.

- A fellowship exploring needs of parents from ethnic minority groups when offered genetic tests. (MPeter was awarded a This Institute Themed Fellowship: Research to strengthen equity, diversity and inclusion in healthcare improvement).
- Several members of the EXPRESS research team (LSC, JF, MPeter, MK, LB and MH) are collaborating on the Prenatal Genomic Diagnosis NHS Genomic Networks of Excellence (2023/2024) where one arm of the work will build on findings from EXPRESS to address widening the eligibility criteria for pES, improving access to expert fetal ultrasound and genetic counselling, improving diagnosis of conditions with neonatal treatment options and exploring the ethics and mechanisms for consent and feedback of incidental findings to parents.

4.6 Implications

4.6.1 Implications for services

1. *Close collaboration and communication within and across fetal medicine, genetics and laboratory teams is essential for effective service delivery.*

Collaboration and communication can be facilitated through a range of strategies including joint appointments, regular MDT meetings, strategic use of virtual meetings, regular communication, clear roles and responsibilities and embedding of genetic expertise within fetal medicine teams. Funding is essential to support effective collaboration and communication (Section 3.1).

2. *Further education of professionals from both fetal medicine and genetics backgrounds is needed to support pES implementation.*

Some fetal medicine and obstetric professionals require further education in genomics (Section 3.2). Genomics education strategies for fetal medicine midwives should be a priority, as the involvement of fetal medicine midwives in delivering pES varied widely across services, but was highly valued when in place (Section 3.1). There is also a need to have more clinical geneticists available who have expertise in prenatal genomics (Section 3.2).

3. *Increased staffing is needed to successfully deliver pES.*

We found that pES impacted the workloads of clinicians and laboratory staff and there was a need for more staffing across all disciplines (Section 3.1). Offering pES required increased administrative time, particularly for professionals from genetics backgrounds and for fetal phenotyping by experts in ultrasound. Greater involvement of other staff groups, such as genomics associates, to take on administrative tasks may be beneficial. Additional time in consultant job plans is also needed to support service delivery by allowing time for MDTs as well as ultrasound and pre- and post-test counselling. Funding is needed to support these changes, but this is likely to be modest in terms of the total costs of delivering pES.

4. *Streamlined logistics and processes are needed to support effective service delivery*

Professionals suggested that streamlining care pathways and improvements to IT systems at both local and national levels would allow the delivery of the pES service to be more efficient. Improvements to IT systems could also facilitate the various processes involved in sharing documentation with the labs and monitoring test status (Section 3.1). Funding will be needed to facilitate these changes. In addition, streamlining pathways has the potential to shorten time-frames for receiving results which will benefit parents having pES testing close to the change in abortion law at 24 weeks (Section 3.7).

5. *The national guidance for the pES service should be expanded*

a. We found variation in how the pES service had been implemented locally (Section 3.1). National guidance should clarify which parts of the pathway should not vary (eg information and consent, MDT meetings to discuss eligibility, access to expert fetal phenotyping and genetic counselling) and which parts could be flexibly adapted to suit local systems and infrastructure (e.g. training background of staff involved, modality of appointments).

b. Some professionals were concerned about the limitations of the current eligibility criteria and the use of a restricted gene panel for testing (Section 3.2). A process for the regular review and updating of the eligibility criteria and the gene panel should be established and outlined in the guidance.

c. The roles and responsibilities of professionals throughout the different parts of the pES pathway were not always clear and it may be beneficial to set these out in local guidance for delivering the pES service.

4.6.2 Implications for supporting parents

1. *Detailed pre-test counselling is essential to support parents who are offered pES*

a. Detailed pre-test counselling is particularly important as pES is offered at a stressful and anxious time, decision making could feel rushed and parents may not fully consider the potential for pES findings related to their own health (Section 3.3).

To supporting decision making about pES parents need:

- Clear expectation setting about the likelihood of diagnosis
- Information about what genes are being tested and what could be reported
- Multiple opportunities for questions and discussion
- Information available in languages other than English
- Signposting to appropriate written or visual information and websites
- Emotional support alongside information giving throughout the testing journey

b. Pre-test counselling should be undertaken by clinicians who have a good understating of pES, the range of possible findings and the limitations of the test. pES can be offered by clinicians from a range of clinical backgrounds, as long as they are appropriately trained (Section 3.3).

c. Clinicians need regular updates on eligibility criteria and care pathways to mitigate against discussing pES with parents who ultimately find out they are not eligible (Section 3.3).

2. *Parents need ongoing access to ongoing support*

Parents would benefit from having a clear point of contact in the clinical team or a routine "check in" for test-related queries and support across their testing journey (Section 3.3). Fetal medicine midwives and genetic counsellors with pES training have key knowledge and counselling skills suited to this anchoring role in the service. Signposting to specialist parent support services was also valued by parents.

3. *Interpretation of results and post-test counselling should be personalised and draw on both pES findings and other information sources*

a. Some professionals raised concerns that parents may be overly reassured by a no findings result from pES as these results do not rule out the presence of a genetic condition (Section 3.3). It should be highlighted to parents that information from scans and other tests are key for interpreting the implications of pES.

b. Our ethical analysis highlighted that parents and clinicians can give pES a special status that sometimes overrides other available information (Section 3.7). It is important to raise awareness amongst clinicians around the limitations of pES and the need to interpret pES results in the context of other available information to improve personalised post-test counselling and support for parents. It must be remembered that all fetuses undergoing pES have sonographic abnormalities that may in themselves be prognostic.

4. *Clear care guidelines for post 24-week terminations are needed*

Most referrals for pES are made following the routine fetal anomaly scan at 18-20 weeks and the median timing for return of results was 26.4 weeks gestation (Section 3.6). The intersection of these timelines with the change in abortion law at 24 weeks, is a source of additional anxiety for parents and is challenging for the professionals who care from them (Section 3.3). Clinicians supporting parents through pES need to prepare parents for the fact that the change in law may mean they cannot have a termination after 24 weeks and acknowledge the distress this may cause. In addition, clear care guidelines for later termination of pregnancy which include the provision of psychosocial support are needed. Psychosocial support could come from specialised midwifery, perinatal mental health and signposting to other NHS or external services.

5. *Follow-up care after results are returned is important regardless of the result*

Uncertainty continues and questions arise for parents after pES results are returned (Section 3.3). It is important that care pathways are in place to follow-up parents, regardless of the type of result they receive.

6. *Information about pES in a range of formats will benefit parents*

Information about pES should be available in a range of formats as parents differ in their preferences for how information is presented (Section 3.3 and Section 3.5). Information about pES presented as an animation or in a written leaflet were successful in improving parents' self-reported and objective knowledge (Section 3.5).

4.6.3 Recommendations for future research

Gather views and experiences from parents from diverse backgrounds

The majority of parents interviewed in this study were women from a White background, who were educated to a degree level or higher, and spoke English as their main language. The views expressed by these parents will not reflect those of the wider population. To ensure the pES service meets the needs of all parents, future research should seek the views of parents from a wider range of ethnic, religious, cultural, and socioeconomic backgrounds. It will also be important to include more partners in future research so that we can understand their support needs when pES is offered.

Evaluate the prenatal sequencing animation in clinical practice

The animation was an effective tool to increase parents' knowledge and understanding of pES. The evaluation was, however, undertaken outside of a clinical setting and future research should evaluate the value of the animation for supporting decision making in a clinical practice where parents whose pregnancy has a fetal anomaly are being offered pES. In addition, whilst we have translated the animation into 11 different languages to be inclusive towards more pES service users, its value to non-English speakers in clinical settings needs to be explored.

Build on EXPRESS to identify and agree optimal care pathways that will ensure equity of access for all parents regardless of where they live

We identified considerable variation in local pES service delivery across England, including staff numbers, roles and responsibilities and professional backgrounds of those involved, and access for parents to expert prenatal genetic counselling and fetal phenotyping by expert sonography. Through our interviews with parents, we also identified that some parents who had pES lacked access to signposting and follow-up care. Consequently, it is important that future research builds on the work in EXPRESS to delineate the optimal pES pathway and mechanisms for equity of access across the country as well as determining workforce requirements. All GLH/GMSA regions should be involved in pathway development to ensure equity of access to high quality care across the country.

Explore the use of a national MDT system with remote IT to improve equity of access to expert opinion

MDT working was an essential component of service delivery that allowed teams to access expert opinion from genetics and fetal medicine. Many local teams had introduced virtual MDT meetings to improve accessibility for clinicians from other departments or hospitals. However, concerns remained that in some regions clinicians, particularly those in peripheral units, may not have a standard process to gain timely access to expert genetics or fetal ultrasound opinions. We suggest future research explores the use of a national MDT system with MDT meetings held virtually so that there is equal access to expert opinion from both disciplines across England to inform decisions on eligibility and interpretation of findings. A key component of this future research should be testing IT systems that can support sharing fetal images for expert review for fetal phenotyping.

Explore acceptability and feasibility of offering looked for additional findings as part of prenatal sequencing

Interviews with parents and professional asked for their thoughts on offering looked for additional findings when pES is offered. Views were mixed and more work is needed to explore ethical implications and determine if offering additional findings in clinical practice is acceptable. This is particularly important as changes to testing are being considered which

would allow the identification of more incidental or looked for additional findings with implications for fetal and parental health. Future research should explore the views of parents and professionals around which findings should be looked for in parents and the fetus, approaches for test consent and feeding back results and where in the pathway consent and return of results is optimally delivered.

4.7 Conclusions

The EXPRESS study explored the implementation of the national pES service in England. Parents and professionals welcomed the introduction of pES and key areas for improvement have been highlighted. The implications for supporting parents and for improving service delivery will 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.

Additional Information

Disclosure of Interest Statement

LSC has received technical support and consumables for her laboratory from Illumina Inc and Oxford Nanopore Technologies.

NF is an NIHR Senior Investigator and was a member of the following: NIHR Health Services and Delivery Research (HS&DR) Programme Funding Committee (2013-2018), HS&DR Evidence Synthesis Sub Board (2016), the UKRI and NIHR College of Experts for Covid-19 Research Funding (2020); she is the UCL-nominated non-executive director for Whittington Health NHS Trust (2018-2024), a non-executive director of Covid-19 Bereaved Families for Justice UK, and was a trustee of Health Services Research UK (2019-2022).

KLB holds leadership or fiduciary roles with Alström Syndrome UK; England Rare Disease Framework Delivery Group; Breaking Down Barriers; Patient Engagement Group Genetic Alliance UK; Ciliopathy Alliance; and Patient Safety Communication Panel, Bayer.

SM was a member of the following: NIHR HTA Commissioning Board (2009-2013), NIHR HTA Clinical Trials Board (2007), NIHR HS&DR Commissioning Board (2014-2016), NIHR HS&DR Evidence Synthesis Sub Board (2016), NIHR PHR Research Funding Board (2011-2017), NIHR HS&DR Funding Committee (2014-2019), NIHR HS&DR Sub-Committee Unmet Need (November 2019-present), Murray Edwards College, University of Cambridge – Member of

Council and Trustee (October 2022 – present), NIHR RfPB Funding Committee – under-represented disciplines and specialisms highlight notice: methodologist (2023-2024) and was an NIHR HS&DR Workforce Research Partnership funding awards interview panel member (May 24).
SW is a trustee at Genetic Alliance UK.

Disclosure of interest for all other authors: None declared

Patient Data Statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data is used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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- Professor Jenny Hewison, Professor of the Psychology of Healthcare, University of Leeds (Chair)
- Professor Anneke Lucassen, Professor of Genomic Medicine, University of Oxford
- Professor Edward Johnstone, Head of Department University of Manchester Maternal and Fetal Health Research Centre, University of Manchester
- 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
- Ms Jane Fisher, Director, Antenatal Results and Choices (ARC)
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- Professor Zarko Alfirevic, University of Liverpool
- Ms Annette McHugh, Fetal Anomaly Screening Programme, NHS Fetal Anomaly Screening,

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- Ms Jane Fisher, Director, Antenatal Results and Choices (ARC) (Chair)
- Ms Asya Choudry, Project Manager in Patient & Public Involvement and Engagement, Manchester University NHS Foundation Trust Manchester
- Professor Caroline Lafarge, Professor of Psychology, University of West London
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5). She contributed to quantitative data collection and analysis (Workstream 1, Workstream 2). She contributed to the development of study materials (Workstream 1, Workstream 2) and the animation (Workstream 2). She led reporting of the professional views and experiences (Workstream 1) and the ethical issues in the pES service (WP4). She is senior author for the reporting of experiences of parents (Workstream 2) and the evaluation of the animation (Workstream 2). She contributed to the interpretation of findings and reporting of the evaluation of pES service implementation (Workstream 1) and the economic analysis (Workstream 5).

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CRediT statement

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Ethics statement

Ethical approval to conduct the interviews with parents was given by the Health Research Authority (HRA) and the East of Scotland Research Ethics Service REC 1 (21/ES/0073) on 09/08/2021. Interviews conducted by RM as part of her PhD project were approved by the London Bromley Research Ethics Committee (20/LO/0987) on 30/09/2020. The HRA classified the interviews and surveys with professionals as Service Evaluation and research ethics committee approval was not required. The service evaluation was registered with Research and Development at Great Ormond Street Hospital for Children NHS Foundation Trust. Clinical audits for data collection of pregnancy outcomes were registered for North Thames GLH (GOSH: Reference Number: 3082) and Central and South GLH (Clinical Audit Registration and Management System (CARMS) at Birmingham Women's Hospital (CARMS-31001).

Information Governance Statement

Great Ormond Street Hospital for Children NHS Foundation Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, Great Ormond Street Hospital for Children NHS Foundation Trust is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (https://www.gosh.nhs.uk/our-research/our-research-infrastructure/joint-research-and-development-office-rd/gdpr-and-research/).

Department of Health and Social Care disclaimer

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Appendices
Appendix 1 – Further information
Dissemination approach and plans

Dissemination has involved active engagement with stakeholders (parents, clinicians, policy makers) from the study outset and includes both formative and summative approaches to sharing findings.

Formative dissemination

EXPRESS started in line with the launch of the national rapid pES service, which has allowed us to provide formative feedback as the service was implemented and procedures and pathways evolved. Engagement with stakeholders and formative dissemination describing our research plans, opportunities to get involved, progress and preliminary findings has occurred throughout the study. We have developed positive relationships with the clinical teams who deliver pES across England, raising awareness of the EXPRESS study, sharing findings and inviting them to contribute to the study as both research participants and collaborators.

Formative dissemination includes:

- LSC works closely with the NHSE Genomics Unit and has regularly shared findings to relevant to national delivery of pES.
- Newsletters summarising findings that were circulated to relevant professionals and shared via social media.
- Presentation at the ARC Case Café for professionals on December 20th, 2020. JF and HMD gave an overview of EXPRESS and how ARC will be involved.
- EXPRESS Study Webinar held on October 28th, 2021. The webinar gave an overview of EXPRESS and summarised the findings from the first year. The webinar was attended by professionals from clinical genetics, fetal medicine and clinical science.
- Presentation by MPeter and HMD at the Genethics Forum held on July 4th, 2022.
- Presentations on May 19th, 2022 (LSC), and March 11th, 2024 (MP, HW and MD) at the rapid prenatal exome sequencing service (R21) Educational MDT – a national MDT attended by professionals from clinical genetics, fetal medicine and clinical science.

- Presentation by MPeter on parent views and experiences at the East Region Prenatal Genomics Forum on June 14th 2024.

Summative dissemination

Our summative dissemination includes publications, conference presentations, a policy report and a final dissemination event. Our existing and planned publications are listed in Table 1 and our conference abstracts are listed below in Appendix 1, Table 5.

Summative dissemination includes:

- The EXPRESS team at the PHG Foundation (MK and LB) have prepared a high-level report on the integrated findings of the study, that can be used to guide best practice and inform policy decisions on service delivery. The report has been circulated widely through professional networks such as the Fetal Anomaly Screening Programme, the British Maternal and Fetal Medicine Society (BMFMS), the Joint Committee on Genomics in Medicine, the Association for Clinical Genomic Science (ACGS) and relevant Royal Colleges. The report is available here: https://www.phgfoundation.org/publications/reports/optimising-exome-prenatal-sequencing-services/
- The final dissemination event was a one-day hybrid meeting held on March 21st 2025. The meeting was attended by health care professionals, policy makers and parent support organisations representatives. Members of the EXPRESS team (LSC, MH, JF and MPeter) presented the findings of the research and an interactive discussion was held with meeting participants.
- We have utilised social media and the EXPRESS website to summarise and highlight our findings as they are published.

Dissemination for parents and the wider community

We have engaged with parents and patient organisations in a number of ways, including close working with our PPI Advisory Group and presentations by LSC and MPeter at the ARC annual conference where participants include parents and clinicians. Summaries of our research findings for parents and the wider community that have been shared through patient organisation websites and social media networks.

A key output for parents has been the animation describing prenatal sequencing that was developed with ARC. The animation is available on the ARC website(https://www.arc-uk.org/). The animation has been translated (voiceover and captions) into 11 languages (https://www.youtube.com/playlist?list=PL4w_rCr2JXuKWYhtC9QuS_HS-Ibq5c5kX). The links have been circulated to the pES service leads at the 17 clinical genetics services in England.

Conference presentations

Table 5 Conference presentations

Presentation	Conference
Chitty LS, Expanding prenatal screening and diagnosis in the NHS Genomic Medicine Service. Invited lecture.	UK Clinical Genetics Society, June 2021
Chitty LS, The impact of sequencing on prenatal diagnosis. Invited lecture.	European Cytogenomics Society, July 2021.
Chitty LS, Prenatal genomic testing in England: Current state of play. Invited lecture.	British Maternal and Fetal Medicine Society, September 2021.
Chitty LS, The management of fetal anomalies using exome sequencing. Invited lecture.	The XXIII World Congress of Gynecology and Obstetrics, October 2021.
Chitty LS, Rapid fetal exome sequencing. Invited lecture.	Italian Society of Obstetric and Gynecological Ultrasound and Biophysical Methodologies 22nd national meeting, October 2021.
Chitty LS, Prenatal diagnosis in the genomics era. Invited lecture.	The 8th World Congress on Controversies in

	Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGEN), November 2021
Chitty LS, Rapid sequencing for the diagnosis of monogenic conditions in the fetus with structural abnormalities. Invited lecture.	Taiwan Maternal Fetal Medicine Society, November 2021.
Chitty LS, Prenatal genomic testing – how are we doing? Working together to provide high quality care through prenatal screening and diagnosis. Invited lecture.	Antenatal Results and Choices Annual Meeting, May 2022.
McInnis-Dean et al., Professionals' and parents' views and experiences of prenatal exome sequencing offered nationally in England through the NHS Genomic Medicine Service. Poster presentation.	International Society for Prenatal Diagnosis, June 2022.
Chitty LS, Genomics and cfDNA testing for monogenic conditions: Where are we and where are we going. Invited lecture.	International Society of Ultrasound in Obstetrics and Gynaecology, September 2022.
Chitty LS, Prenatal sequencing: How should we be using this powerful diagnostic tool? Invited lecture.	The 10th World Congress on Controversies in Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGEN), June 2023.
Peter M, Prenatal exome sequencing in England's NHS Genomic Medicine Service: What do parents and healthcare professionals think? Poster presentation.	International Society for Prenatal Diagnosis, June 2023.
Peter M, Ensuring PPIE in service evaluation of prenatal exome sequencing. International Society for Prenatal Diagnosis, Edinburgh, UK, June 2023. Lightning Oral Poster presentation	International Society for Prenatal Diagnosis, June 2023.

Hill M, Decision making around prenatal genomic tests. Invited oral presentation.	European Society for Human Genetics Conference, June 2023
Daniel M, Prenatal exome sequencing in England's NHS Genomic Medicine Service: What do parents and healthcare professionals think? Poster presentation.	Genomics England Research Summit, September 2023.
Chitty LS, Fetal Sequencing in the English Genomic Medicine Service. Invited lecture	Festival of Genomics, January 2024.
Chitty LS, National implementation of rapid fetal sequencing in a public health setting: Benefits and challenges. Invited lecture.	International Society for Prenatal Diagnosis, July 2024.

Appendix 2 – Regional Map of the NHS Genomic Medicine Service

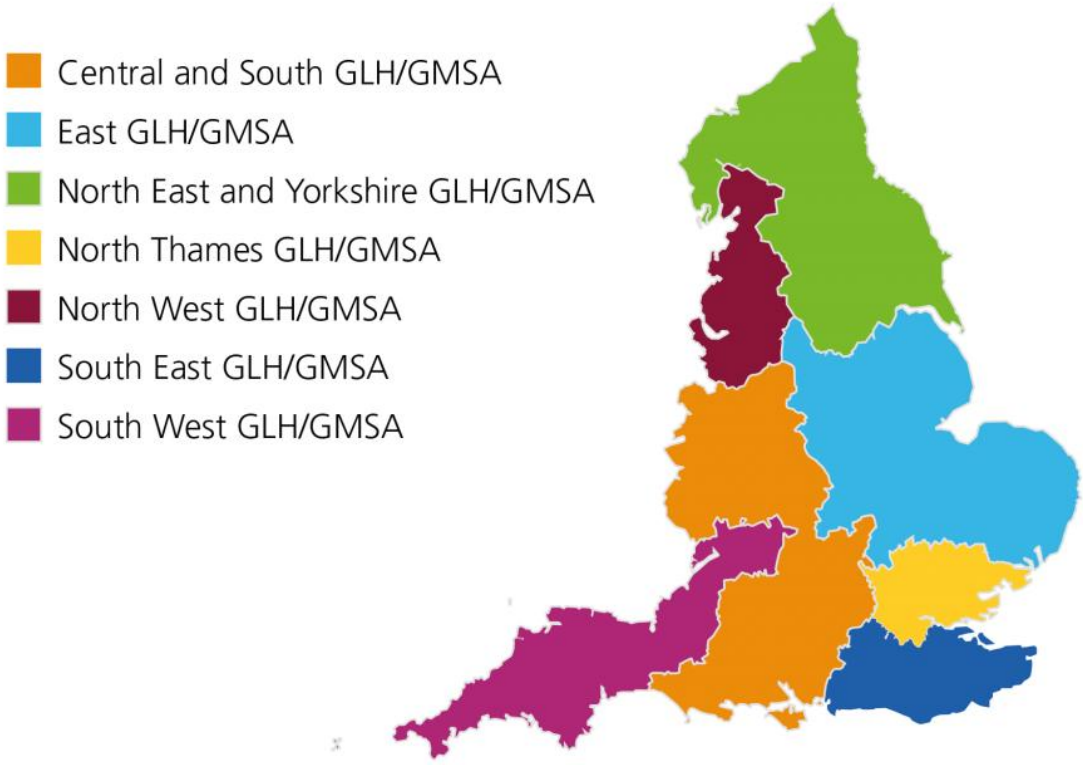

Figure 8 Map of the Genomic Laboratory Hub (GLH) / Genomic Medicine Service Alliance (GMSA) Regions in England. Obtained from https://www.genomicseducation.hee.nhs.uk