**Implementation of a national prenatal exome sequencing service in England: cost-effectiveness analysis**

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**Running title**: Economic evaluation of a prenatal exome sequencing service

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**Abstract [244/250]**

**Objective**

To evaluate costs and cost-effectiveness to the healthcare system, and costs to families, of a national prenatal exome sequencing (pES) service additional to standard testing, compared to standard testing alone.

**Design**

A cost-effectiveness analysis combining costs, outcomes, parent and professional interview and professional survey data.

**Setting**

The English National Health Service (NHS) Genomic Medicine Service.

**Sample**

413 cases referred for pES testing from 01/10/2021 to 30/06/2022.

**Methods**

We costed the incremental resource required to deliver the pES clinical pathway, synthesising this with unit costs and outcomes data on additional cases diagnosed to analyse cost-effectiveness. We estimated the annual NHS budget requirement based on case numbers. We determined parental costs from interviews.

**Main Outcome Measures**

Incremental costs of pES to the NHS and families, incremental cost per additional diagnosis, NHS budget impact.

**Results**

Of 413 referred cases, 241 were tested, at a cost of £2,331 (95% credibility interval £1,894-£2,856) per referred case, or £3,592 (£2,959-£4,250) per case that proceeded with testing. The incremental cost per diagnosis (yield 35.3%) was £11,326 (£8,582-£15,361). At current demand levels pES costs the NHS approximately £1.7m annually. Family costs could not be separated from other pregnancy related appointments but were not considered burdensome as most appointments were concurrent or remote.

**Conclusions**

pES is more expensive than predecessor prenatal genetic testing technologies, has a higher diagnostic yield and informs pregnancy management and decision making. Further research into potential savings from the foregone diagnostic odyssey resulting from pES may be informative.

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**Keywords:** economic evaluation, prenatal, genomics, exome sequencing, cost-effectiveness, budget impact

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**Introduction [291/400]**

Prenatal exome sequencing (pES) was introduced in the English National Health Service (NHS) Genomic Medicine Service (GMS) in October 20201,2 based on evidence of its potential benefits.3–5 pES is available when there are no informative findings from standard testing (rapid aneuploidy exclusion and chromosomal microarray (CMA)) to families that have anomalies with a suspected genetic cause identified on fetal ultrasound where results have the potential to influence pregnancy management. Testing in the NHS GMS is delivered through seven regional Genomic Laboratory Hubs (GLHs).6 All seven conduct the standard prenatal testing for families in their region, with two GLHs performing pES for the whole country.

pES is ordered following negative aneuploidy testing (via QF-PCR) and in parallel with, or subsequent to, CMA. pES only proceeds to reporting if CMA is negative. It is requested by clinical genetics (CG) professionals following multi-disciplinary team (MDT) discussion involving fetal medicine (FM) professionals. The request is sent to one of the two testing GLHs (depending on geographic region) and reviewed for eligibility. If accepted by the laboratory, the parents are consented by either CG or FM professionals. Parental blood samples are taken, and DNA is extracted as trio sequencing is preferred (fetal DNA already obtained for QF-PCR and CMA testing is used). Results are returned by CG or FM, or jointly. **Figure 1** illustrates the clinical pathway.7

This is the first example of a national pES service globally. Costs and outcomes are yet to be evaluated outside of a research setting.8,9 The aim of this Optimising EXome PREnatal Sequencing Services (EXPRESS)10 study was to identify the incremental costs of delivering pES to the NHS and to families, compared to standard testing only, and to synthesise this with key outcomes data to produce a cost-effectiveness analysis.

**Methods**

**Overview**

We derived costs of pES from the clinical pathway (**Figure 1**), identifying and quantifying the incremental resource to deliver pES in addition to standard testing, compared to standard testing alone. The perspective was the English NHS and costs were calculated in 2021-22 UK pounds. The time horizon was the duration of pregnancy. We also collected outcomes data and present this together with costs as a cost-effectiveness analysis. We sought patient reported costs through interviews and summarise the findings.

**Sample**

The sample was all cases (n = 413) referred for pES to the two testing GLHs during the study period (01/10/2021-30/06/2022). Characteristics of the sample population are reported elsewhere.12

**Costs**

We identified and costed the key stages of the pathway: case identification and referral to the testing GLH, discussion and consent, sample collection, transportation and DNA extraction (parental samples), pES, return of results and administration.

We collected data on resource use through surveys with CG and FM professionals (methodology reported elsewhere7). Professionals were asked to identify incremental resources to deliver pES including extra time spent discussing and taking consent, number of additional appointments and time spent on associated administration. They were also asked to identify which staff groups were usually responsible for undertaking each process. For our base case we aggregated the survey data from the five (out of 17) sites identified as using the modal service delivery model delineated by Walton et al.11 The core staff were a fetal medicine consultant, clinical geneticist, clinical scientist and genetic counsellor.

We calculated the mean incremental staff time for each stage and applied unit staff costs using the NHS Agenda for Change pay scale and (for consultant grades) the Personal Social Services Research Unit Costs Database of Health and Social Care Professionals,13,14 with on-costs (national insurance and NHS pension) at prevailing rates and overheads at 25%. We calculated a weighted average cost by applying the percentage of each staff group delivering each part of the pathway, from the survey data. For administration, which was estimated by respondents for the pathway as a whole, we applied the same weighting as for discussion and consent. The laboratory cost of pES was the mean of costings prepared by the two testing GLHs for the purpose of establishing reimbursement. We supplemented costs with published data where appropriate. We calculated the incremental cost to the NHS of pES (compared to no pES) by applying the cost per case for each pathway stage to the number of cases proceeding through that stage. We calculated the mean incremental cost per pES referral by dividing the total cost by the total number of cases referred.

Our semi-structured interviews with parents15 included a section on the financial costs of pES to themselves and their family. Questions covered appointment format (i.e. in person or video/telephone consultation), travel, childcare arrangements and time off work. Responses were analysed as described elsewhere15.

**Outcomes**

Outcomes data were collected from the two testing GLHs and referring CG services. These were linked to data collected by the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) and the national Maternity Services Data Set (MSDS) (linkage methodology described elsewhere12). The key outcome was identified as diagnostic yield, defined as at least one pathogenic (or likely pathogenic) variant reported as a result of pES. This was used to calculate the incremental cost per additional diagnosis.

Additional analysis was performed using data from the two testing GLHs to consider whether the result had changed clinical management or pregnancy continuation decision, and the frequency of incidental findings. We did not include pregnancy outcomes in our analysis because it was not possible to obtain linked pregnancy outcome data for our entire sample.

**Scenario and sensitivity analysis**

We conducted probabilistic sensitivity analysis, running 1,000 simulations with gamma distributions for costs and beta distributions for probabilities. We drew a cost-effective acceptability curve (CEAC) showing the probability pES is cost-effective, versus no pES, at different willingness-to-pay (WTP) levels for an additional diagnosis. We calculated 95% credibility intervals using the 2.5th and 97.5th percentiles of the simulations.

To assess the impact of using different service delivery models we identified two most common sub-types from the seven models described11; those with only consultant grade core staff (“scenario 1”) and those that included a midwife within core staff (“scenario 2”). We aggregated the survey responses relating to each of these model types and calculated the mean resource use, applying costs as described above. We also calculated the mean diagnostic yield for each scenario using outcome data by referral centre and applied this to calculate the cost per diagnosis. Two further scenarios (three and four) examined the impact of the highest and lowest diagnostic yield recorded across all seven GLH regions.

**Budget impact analysis**

We obtained pES case numbers from the testing GLHs for a recent 12-month period (01/10/2022 to 30/9/2023) representative of current demand as our study period was soon after roll-out, when referrals may not have reached steady state. We multiplied case numbers by the mean cost per case to estimate the annual incremental cost to the NHS of the pES service.

**Threshold analysis comparing pES and prenatal genome sequencing (pGS**)

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.16–18 We calculated the maximum cost at which pGS would be no more expensive overall than pES, taking account of the saving from cessation of CMA testing on the assumption CNV analysis would replace this. The mean cost of a prenatal CMA was calculated using costings obtained from four GLHs.

**Patient and public involvement (PPI)**

PPI involvement in the design of this analysis was via the participation of a PPI Advisory Group in all aspects of EXPRESS, including the development of the recruitment strategy and study materials for parent interviews from which we have analysed data.10

**Results**

During the 9-month study period 413 cases were referred to the testing GLHs for pES. Of these, 241 cases proceeded with pES and had a result returned. Reasons for not proceeding included failure to meet eligibility criteria (n = 73) or alternative testing suggested (n = 10), pregnancy ended due to fetal demise or termination (n = 52), and parents declining invasive testing or pES (n = 16). For nine cases testing was started but subsequently transferred to the non-urgent pathway (outcomes are excluded from our data).

In our base case the incremental cost to the NHS to deliver pES for all 413 cases was £962,727 (95% credibility interval [CI] £775,454 to £1,204,027) **(Table 1/S1)**. Of the total cost, £865,699 (90%) related to proceeded cases and £97,028 (10%) to non-proceeded cases. The pES test was £2,931 (range £2,845 to £3,009) per case and accounted for the majority of overall cost (76%). The average additional clinical time spent in existing appointments providing counselling about pES was 32 minutes per case at a total cost of £9,935 (1% of overall cost). There were on average an additional 1.9 CG 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 FM appointments). Non-proceeded case costs included discussion and selection (via MDT) and eligibility review by testing GLHs (£59,881). The mean cost per referred case was £2,331 (95% CI £1,894 to £2,856), £3,592 (£2,959 to £4,250) for a proceeded case, £564 (£154 to £774) for a non-proceeded case. The diagnostic yield was 35.3% (n = 85 cases) therefore the incremental cost per additional diagnosis was £11,326 (£8,582 to £15,361) (**Table 2**).

The CEAC (**Figure 2**) shows that for WTP thresholds of £8,000, £12,000 and £14,000 per additonal diagnosis, 0%, 66% and 94% respectively of the 1,000 simulations were cost-effective.

**Scenario analysis**

Given that pES made the largest contribution to additional costs, the alternative staffing scenarios had a negligible impact on diagnostic yield and costs (**Table 2**). For our first scenario – 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 unit staff costs were higher due to the greater proportion of consultant level staff used but less additional time was required for existing appointments (29 compared to 32 minutes) and there were slightly fewer additional appointments (1.8 versus 1.9). 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 involving a midwife in the core team – the total cost was £955,289, 0.8% lower than the base case. Additional time in existing appointments was slightly higher at 34 minutes whilst the number of additional CG appointments to return results was lower at 1.4, possibly due to a greater proportion of results being returned and support given by FM. Diagnostic yield was 34.9% resulting in cost per diagnosis of £11,372. Taking the base case cost and applying the highest (45.5%) and lowest (28.6%) diagnostic yields found across GLHs, the incremental cost per additional diagnosis was £8,752 and £13,953, respectively.

**Alternative outcomes**

We collected outcomes data from clinicians on the impact of pES on clinical management. “Changed management” was defined as: influenced decision to continue or end pregnancy, influenced medical management during pregnancy, prenatally or neonatally, more than one of these factors or other (with comments). Responses were obtained for 42% of proceeded cases. Of the cases that received a diagnosis 82% reported a change in management. Applying this percentage to total diagnosed cases the cost per outcome increases to £13,753. However responses showed that for 51% of pES cases without a diagnosis (i.e. no findings or a variant of uncertain significance) there was also a change in management. Across all proceeded cases management was reported to have changed for 63%; by this measure the cost per outcome is £6,334.

Incidental findings were reported in 2.9% (n = 7) of proceeded cases including a variety of rare conditions warranting clinical review in the parent(s) or impacting future reproductive risks. Incremental costs and benefits would be expected to accrue from downstream standard clinical follow-up, but we have not included these in our analysis.

**Annual incremental NHS cost**

In the 12 months to 30/09/2023 the testing GLHs received 760 referrals, 442 of which proceeded to pES testing. It was assumed all remaining 318 cases were rejected or discontinued (data on numbers started then moved to the non-urgent pathway was unavailable). Applying the average cost per proceeded and non-proceeded case the total annual incremental cost to the NHS of delivering a pES service was estimated to be £1,716,595 (**Table S2**).

**Prenatal genome sequencing (pGS**)

The mean cost of a prenatal CMA was £352. On the assumption this would be replaced by CNV analysis in every pGS case, the cost of pGS could be up to £3,283 for this testing approach to be no more expensive overall than pES.

It is possible there would be a higher number of cases that proceed with pGS compared to pES in the absence of CMA testing; in our sample, one case was declined by the testing GLH and three were accepted but subsequently discontinued due to a pathogenic finding from a CMA (or other) test. Under a pGS approach it is possible that all four cases (accounting for 1% of referrals) would have proceeded. This would have resulted in additional costs of £12,791 (1.3% of the total base case cost).

**Patient costs**

Responses from semi-structured interviews with parents (42 women and 6 male partners) about the financial cost of pES were analysed. It was difficult to identify the costs associated with pES specifically as, due to having anomalies identified in pregnancy, this group was already frequently attending hospital for scans and monitoring and respondents did not necessarily distinguish between these and pES related appointments. Consequently, it was not possible to quantify the cost to families as we could not confidently ascribe disclosed costs to pES.

When talking about travel expenses, childcare and time off work related to pregnancy appointments in general, there was a lot of variability in costs that were disclosed based on parents’ proximity to the hospital and job flexibility. The pES pre-test discussion mostly took place in person while already attending hospital for a scan,with bloods taken at the same time. Two people described a remote pre-test discussion (via video/telephone call) followed by attending the local hospital for phlebotomy. Most pES results were returned remotely: phone call (n = 22), in person (n = 8), virtual (n = 4), letter (n = 1) (n = 4 unknown, n = 3 not applicable). Several parents noted that they did not think they had any additional expenses specific to pES.

**Discussion [1,107/1,200]**

**Main findings**

We estimated the incremental cost to the NHS to deliver pES during the period 1 October 2021 to 30 June 2022 to be £962,727 for a total of 413 referred cases, 241 of which proceeded with pES and 85 received a diagnosis. The mean cost per case referred was £2,331 and the incremental cost per additional diagnosis was £11,326. We also considered an alternative outcome measure – whether or not pES changed the clinical management and/or pregnancy continuation decision – and found that it did in 63% of proceeded cases (82% of cases with a diagnosis and 51% without). The cost per “changed management” outcome was £6,334.

We analysed the impact of different pES service delivery models based on core staffing. There were some cost variances due to the relative salaries of staff involved and incremental time/appointments to deliver pES, however as the majority (76%) of the cost was attributable to the pES test itself (which does not depend on the delivery model) these differences had a negligible impact on overall cost. There was also a negligible difference in diagnostic yield, and consequently cost per diagnosis, between the models. There was a more significant impact when the diagnostic yield was varied (which it did across GLHs, from 28.6% to 45.5%) with the cost per diagnosis ranging from £8,752 to £13,953.

Applying more recent steady state pES referral numbers, the total annual incremental cost to the NHS of delivering a pES service is estimated to be £1.7m. If pES were replaced with pGS (similarly to rapid paediatric sequencing1,19) the cost of the test would need to be no more than £3,283 per case to require no additional NHS budget, assuming clinical pathways would otherwise remain unchanged and CMA testing would not be required alongside.

We were unable to quantify the average cost of pES to families as interview respondents did not always differentiate expenses from existing pregnancy-related appointments. However responses indicated that counselling and phlebotomy did not usually require an additional hospital visit, and results were mostly delivered remotely, thus additional costs were minimal or nil for most families.

**Strengths and limitations**

This is the first economic analysis of pES in a live clinical service.8,9 Costs were sourced directly from health-professionals from across England and from the laboratories conducting pES, providing robust estimates of resource use and taking account of local variation in service delivery models.

There were some limitations relating to the laboratory and health professional survey data collected. Our database only captured pES cases that were referred to GLHs, thereby excluding costs for cases assessed by FM but not subsequently referred. Only CG professionals were asked to estimate the number of extra appointments for pES, potentially leading to an underestimate of costs where results were returned by FM (though this may have been done in existing appointments). There was also a low (42%) response rate to the request for CG professionals to provide pregnancy outcome data, including “changed management” data, and while constraints on clinician time is a factor, clincians that felt pES impacted upon patient care or decision making may have been more likely to respond, potentially biasing this outcome measure.

We did not take into account the costs of pregnancy outcomes as it was not possible to identify a comparator cohort from the national dataset due to insufficient granularity in clinical phenotype descriptors. Our analysis also excludes downstream costs and benefits from incidental findings (identified in 2.9% of cases) and, for diagnosed cases with a live birth outcome, the savings and health benefits that may arise from avoiding a lengthy diagnostic odyssey.

**Interpretation**

We have found implementation of pES in a live clinical service to be more cost-effective than previously shown in a research setting, where the cost per additional diagnosis for pES in addition to CMA was found to be £25,581.8 The difference is mainly due to the lower diagnostic yield in the previous study (12.1%) in which broader testing eligibility criteria were applied. Costs additionally included pregnancy outcomes however the overall incremental cost was lower, likely driven by the lower pES cost (£2,100 versus £2,931).

Compared to other, previously commissioned genetic diagnostic technologies pES is more expensive. 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) at 2012-13 prices.21 Based on annual case numbers22 CMA also impacted less on the NHS budget at approximately £416k per annum (2021-22 prices) compared to £1.7m for pES.

Our findings do not indicate a preferred service delivery model among those in use in the NHS GMS; alignment of models would not significantly impact upon costs. However there is variability in diagnostic yield across GLHs and consistent application of eligibility criteria and access to expert prenatal genetic and fetal medicine services may help reduce variation. Policy makers should consider that more or less stringent application of the eligibility criteria would impact upon the mean cost per diagnosis.

The “changed management” outcome we captured is, arguably, a more encompassing measure of utility than diagnostic yield alone. This is supported by our parent interviews which indicated that pES informs decision-making irrespective of result, however consideration of potential misunderstanding a negative result is needed, as cautioned by health professionals.15 pES can also inform future reproductive choices and, for live births with a pES diagnosis, there are likey to be downstream savings and health benefits resulting from a foregone, potentially lengthy diagnostic odyssey. This has been demonstrated for children and adults following a genome sequencing diagnosis23; the benefits from a prenatal diagnosis could be even greater. Policy makers may wish to consider that benefit may be derived from pES beyond simply the diagnosis.

Qualitative responses from our parent interviews suggested that the incremental costs of pES to families are negligible; they were often at hospital anyway and additional appointments specific to pES were usually remote, minimising travel costs and time away from work or caring responsibilities. Remote consultations for other genetic testing services have been found to be an acceptable modality and more convenient to patients.24,25

**Conclusion**

The incremental cost of the pES service to the NHS is estimated to be £1.7m annually, with a mean cost of £11,326 per diagnosis. There is no preferred core-staffing delivery model among those in use within the NHS GMS on the basis of cost. Additional costs to families are difficult to differentiate from those already incurred for other pregnancy related appointments and were therefore found to be negligible. Further research into the potential savings and health benefits arising from the foregone diagnostic odyssey resulting from a prenatal genomic diagnosis may be informative to policy makers.

**Disclosure of interests**

The authors have no conflicts to declare

**Contribution to authorship**

EJS: Data curation, Formal analysis, Methodology, Writing–original draft.

MH: Conceptualization, Data curation, Methodology, Funding acquisition, Project administration, Supervision, Writing–review and editing.

MP: Data curation, Formal analysis, Writing–review and editing.

WHW: Data curation, Project administration, Writing–review and editing.

SH: Data curation, Methodology, Writing–review and editing.

CM: Data curation, Methodology, Writing–review and editing.

LSC: Conceptualization, Funding acquisition, Data curation, Formal Analysis, Methodology, Supervision, Writing–review and editing.

SM: Conceptualization, Funding acquisition, Data curation, Formal Analysis, Methodology, Supervision, Writing–review and editing.

**Ethics approval**

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). 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): Birmingham Women's Hospital: CARMS-31001).

**Table/figure caption list**

Figure 1 – Overview of the pES pathway. Local pathways can vary in which staff groups are involved in taking consent and return of results (from Peter et al.)7

Figure 2 – Cost-effective acceptability curve showing probability pES is cost-effective for different willingness-to-pay levels for an extra diagnosis

Table 1 - Cost of delivering prenatal exome sequencing (pES)

Table 2 - Cost per outcome and scenario analysis

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